

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 62055/S-034

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

Sponsor: ANI Pharmaceuticals, Inc.

Approval Date: November 2, 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

APPROVAL LETTER



ANDA 062055/S-034

**PRIOR APPROVAL SUPPLEMENT
APPROVAL**

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) received for review on December 22, 2016, 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 the complete response letter issued by this office on May 25, 2018, and to any amendments thereafter.

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

- A new manufacturing and testing facility, ANI Pharmaceuticals Inc., located in Baudette, MN.

(b) (4)

We have completed the review of this sANDA, as amended, and it is approved.

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 Office of Generic Drugs 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 Office of Generic Drugs 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.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions ¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs

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 09:09:52AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

OTHER ACTION LETTERS



ANDA 062055/S-034

COMPLETE RESPONSE

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 December 22, 2016, 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.

We acknowledge receipt of the February 14, 2018 submission, which constituted a complete response to our September 20, 2017 action letter, and to any amendments thereafter.

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

- A new manufacturing and testing facility, ANI Pharmaceuticals Inc., located in Baudette, MN.

(b) (4)

We have completed our review of this sANDA, as amended, and have determined that we cannot approve this sANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The Product Quality deficiencies have been classified as MAJOR because the DMF was found inadequate with Major deficiencies.

The Drug Master File (DMF) (b) (4) for Erythromycin Ethylsuccinate has been reviewed and found inadequate. The DMF holder, (b) (4) was notified of the deficiencies on April 13, 2018. Please consult with your DMF holder, and provide the updated relevant drug substance sections. Do not respond to this ANDA CR letter until you have confirmed that the DMF holder has responded to the DMF CR letter cited above or your amendment will not be considered a complete response.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please submit updated stability data from long-term stability studies as data becomes available.

**BIOPHARMACEUTICS/BIOEQUIVALENCE/LABELING/FACILITY
INSPECTION/EVALUATIONS**

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

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

It is also your responsibility to ensure that your sANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR AMENDMENT**, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

**RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY**

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the sANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission

must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain 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 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

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

If you have any questions, call Lisa Oh, Regulatory Project Manager, Division of Project Management, at (240) 402-3690.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

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



Andrew
Kim

Digitally signed by Andrew Kim

Date: 5/25/2018 09:48:03PM

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ANDA 062055/S-034

COMPLETE RESPONSE

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

Dear Madam:

This letter is in reference to your supplemental abbreviated new drug application (sANDA) dated and received December 22, 2016, 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 supplemental ANDA, submitted as “Prior Approval Supplement,” provides for:

- A new manufacturing and testing facility, ANI Pharmaceuticals Inc., located in Baudette, MN.

(b) (4)

We have completed our review of this sANDA, as amended, and have determined that we cannot approve this sANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. The Drug Master File (DMF) (b) (4) has been reviewed and found inadequate. The DMF holder, (b) (4) was notified of any deficiencies on May 16, 2017 and they have responded with an amendment to their DMF on July 31, 2017. The DMF, as amended, is currently under review. Please be aware that the quality review of the supplement 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 reviews. Please acknowledge this in your response.

2.

(b) (4)

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please submit updated stability data from long-term stability studies as data become available.

BIOPHARMACEUTICS

The submitted in vitro dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facilities. The critical evaluation is between the “pre-change” and “post-change” products. This evaluation provides FDA with the information needed to assess whether product quality has been adversely impacted as a result of the proposed change. Because you are not able to provide comparative dissolution testing between your “pre-change” drug product and your “post-change” drug product, please conduct a fasting bioequivalence (BE) study comparing your “post-change” test product, Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL to the corresponding strength of the reference product, Arbor Pharmaceuticals LLC’s EryPed®/E.E.S.® (erythromycin ethylsuccinate) Oral Granules, Eq 200 mg base/5 mL. Please refer to the Product-Specific Guidance for Erythromycin Ethylsuccinate Oral Granule for more information regarding study design, analytes to measure, and bioequivalence criteria (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM506882.pdf>).

BIOEQUIVALENCE

Please refer to Biopharmaceutics comment above.

LABELING, FACILITY INSPECTIONS/EVALUATIONS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

Additionally, please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep sANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER Web site at the following address:
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

OTHER

Your resubmission in response to this complete response letter will be considered a **MAJOR AMENDMENT**, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

**RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY/BIPHARMACEUTICS/BIOEQUIVALENCE**

Upon review of your amendment, FDA may identify information in the amendment that requires a change in classification.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

This drug product may not be marketed without final agency approval under section 505 of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

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

If you have any questions, call Lisa Oh, Regulatory Project Manager, Division of Project Management, at (240) 402-3690.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs



Aaron
Sigler

Digitally signed by Aaron Sigler
Date: 9/20/2017 02:53:26PM
GUID: 508da6fa0002827f1a9f2526d1b2cc69



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

LABELING

NDC 62559-440-01

**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, at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

DIRECTIONS FOR PREPARATION: Slowly add 70 mL of water and shake vigorously to make 100 mL of suspension.

After mixing, refrigerate and use within ten days.

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. 9855 Rev 01/18

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



2"

4 1/4"

Label size: 2" x 4 1/4"

(b) (4)

NDC 62559-440-02

Erythromycin Ethylsuccinate

for Oral Suspension USP

**Erythromycin activity
200 mg per 5 mL**

when reconstituted



Rx only
200 mL
(when mixed)

Store granules, prior to mixing, at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

DIRECTIONS FOR PREPARATION: Slowly add 140 mL of water and shake vigorously to make 200 mL of suspension.

After mixing, refrigerate and use within ten days.

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 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.

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

9856 Rev 01/18



3"

5"

Label size: 3" x 5"

(b) (4)

Erythromycin Ethylsuccinate for Oral Suspension USP

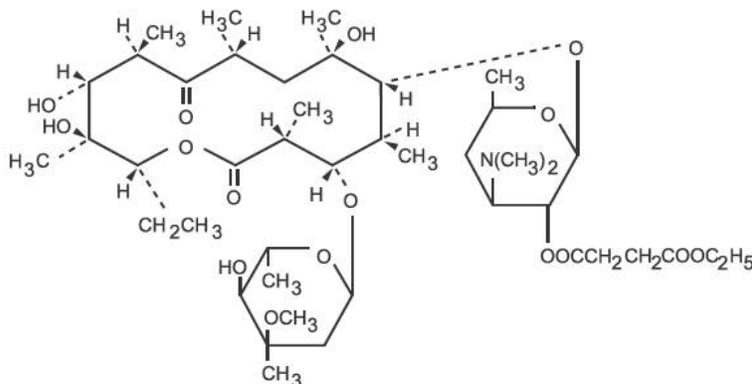
Rx only

9857 Rev 06/18

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'-(ethylsuccinate). The molecular formula is $C_{43}H_{75}NO_{16}$ and the molecular weight is 862.06. The structural formula is:



The granules are intended for reconstitution with water. Each 5 mL teaspoonful of reconstituted palatable cherry-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin.

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

Inactive Ingredients: artificial cherry flavor, lactose anhydrous, methylparaben, polysorbate 80, povidone, simethicone, sodium citrate anhydrous, and sucrose.

CLINICAL PHARMACOLOGY

Orally administered erythromycin ethylsuccinate suspension is readily and reliably absorbed. Comparable serum levels of erythromycin are achieved in the fasting and nonfasting states.

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

Mechanism of Action

Erythromycin acts by inhibition of protein synthesis by binding 50S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

Resistance

The major route of resistance is modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity while efflux can also be significant.

Interactions with Other Antimicrobials

Antagonism exists *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Antimicrobial Activity

Erythromycin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections (See **INDICATIONS AND USAGE**).

Aerobic bacteria

Gram-positive bacteria:

Corynebacterium diphtheriae

Corynebacterium minutissimum

Listeria monocytogenes

Staphylococcus aureus (*resistant organisms may emerge during treatment*)

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative bacteria:

Bordetella pertussis

Haemophilus influenzae

Legionella pneumophila

Neisseria gonorrhoeae

Other microorganisms

Chlamydia trachomatis

Entamoeba histolytica

Mycoplasma pneumoniae
Treponema pallidum
Ureaplasma urealyticum

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for erythromycin against isolates of similar genus or organism group. However, the efficacy of erythromycin in treating clinical infections caused by these bacteria has not been established in adequate and well controlled clinical trials.

Aerobic bacteria

Gram-positive bacteria:

Viridans group streptococci

Gram-negative bacteria:

Moraxella catarrhalis

Susceptibility Testing

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 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 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 patients allergic to the penicillins. In treatment of 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 have 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 to 14 days and 10% for infants who took erythromycin for 15 to 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.

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.

Verapamil

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

Digoxin

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

Anticoagulants

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, pimozone, 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/QT_c 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 is co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes, most likely due to 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 about 500 mg/kg/day (approximately 1 to 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 to 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 the 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 granules contain 16.7 mg (0.7 mEq) of sodium per individual dose.

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** section.)

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 suspension 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 to 50 mg/kg/day 15 to 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 those recommended above (1.6 to 4 g daily in divided doses.)

Directions for Mixing Erythromycin Ethylsuccinate for Oral Suspension

100 mL

Add 70 mL water and shake vigorously. This makes 100 mL of suspension.

200 mL

Add 140 mL water and shake vigorously. This makes 200 mL of suspension.

HOW SUPPLIED

Erythromycin Ethylsuccinate for Oral Suspension USP is available as:

200 mg/5 mL: 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, at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. After mixing, refrigerate and use within ten days.

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



9857 Rev 06/18

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

LABELING REVIEWS

SUPPLEMENT LABELING REVIEW

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

Date of this Review	8/16/2018
Review Cycle Number	4
ANDA(s) and Supplement Number(s)	062055/S-034
Applicant Name	ANI Pharmaceuticals, Inc.
Proprietary Name, Established Name, and Strength(s)	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL
Current Received Date	8/7/2018
Previous Received Date(s) of Proposed Supplement	12/16/2016, 3/9/2017, 2/14/2018
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Theresa Liu
Review Conclusion	
<input type="checkbox"/> ACCEPTABLE - No Comments. <input checked="" type="checkbox"/> ACCEPTABLE - Include Post approval comments. <input type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant <input type="checkbox"/> 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 <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Acceptable for Filing <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	

For labeling supplement(s):

This Changes Being Effected supplemental abbreviated new drug [CLICK HERE](#)

We have completed the review of this supplemental application. Choose an item. effective on the date of this letter. Choose an item.

OR

We have completed the review of your [CLICK HERE](#) [CLICK HERE](#).

1. GENERAL COMMENTS
 - a. Subheading/Comment
 - i. Comment
 - ii. Comment
 - iii.
 2. CONTAINER LABEL
 3. CARTON LABELING
 4. PRESCRIBING INFORMATION
 5. MEDICATION GUIDE
 6. STRUCTURED PRODUCT LABELING (SPL)
-
-

For combined supplement(s):

The Division of Labeling Review has no comments. Labeling is acceptable. However, please make the following revision to the labeling and submit it in your next Annual Report, provided the change is described in full.

PRESCRIBING INFORMATION:

PRECAUTIONS; General: Please revise the last paragraph to read as, "When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy. (b) (4)

(b) (4)

Contents

<u>1.</u>	<u>ANDA REGULATORY INFORMATION:</u>
<u>2.</u>	<u>MATERIAL ANALYSIS</u>
<u>2.1</u>	<u>MATERIALS REVIEWED</u>
<u>2.2</u>	<u>MODEL LABELING</u>
<u>2.3</u>	<u>PATENTS AND EXCLUSIVITIES</u>
<u>2.4</u>	<u>UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)</u>
<u>2.5</u>	<u>HISTORY OF ANDA</u>
<u>3.</u>	<u>ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING</u>
<u>3.1</u>	<u>CONTAINER AND CARTON LABELS</u>
<u>3.1.1</u>	<u>PRESCRIBING INFORMATION AND PATIENT LABELING</u>
<u>3.1.2</u>	<u>DESCRIPTION AND HOW SUPPLIED SECTIONS</u>
<u>4.</u>	<u>SPECIAL CONSIDERATIONS</u>

1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS	
Are there any pending issues in DLR's SharePoint Drug Facts?	YES
If Yes, please explain: Microbiology consult response from OND for Erythromycin Ethylsuccinate tablets and oral suspension, dated 3-26-2013 for ANDA 61639.	
Is the drug product listed in the Policy Alert Tracker on DLRS SharePoint?	NO
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: This Prior Approval Supplement is proposing a new manufacturing, packaging, and testing facility, ANI is also requesting an EXPEDITED REVIEW of this supplemental application based on CDER's Policy and Procedures, MAPP 5240.3; Prioritization of the Review of Original ANDAs, Amendments and Supplements, effective 03/11/16, suggesting the drug product from this ANDA currently meets the criteria for "sole-sourced". Labeling was found to be acceptable. This amendment provides 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. Labeling was found to be acceptable. This amendment was submitted to align with the current labeling from the RLD, NDA 050207-S074, approved April 23, 2018.	
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 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 and 200 mL when mixed	Final	Satisfactory	2/14/2018
Blister	NA			

Carton	NA			
(Other - specify)				
Table 2 Review Summary of Prescribing Information and Patient Labeling				
	Revision Date and/or Code	Draft or Final	Recommendation	Received Date
Prescribing Information	June 2018	Draft	Satisfactory	8/7/2018
Medication Guide	NA			
Patient Information	NA			

2.2 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:	4/23/2018	Proprietary Name:
				E.E.S.®
Description of Original or Supplement:	<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:

2.3 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:

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

The [USP](#) was searched on 8/16/2018.

Table 2: 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	Click here to enter text	Click here to enter the date when the monograph becomes official.	Click here to enter text	Click here to enter text

Reviewer Assessment:

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

Comment:

2.5 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	4/25/2014	<p>Please make the following changes when and if you resume marketing of the product</p> <p>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>
Are there any Pending Labeling Supplements for this ANDA that impact labeling? YES		
Supplement	Submission Date	Labeling Impact
S-035	5/25/2018	PAS provides for two new strengths: Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use).

3. ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING

3.1 CONTAINER AND CARTON LABELS

Reviewer Assessment:

Were container or carton labels submitted in this supplement? **NO, skip to 3.1.2**

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

APPEARS THIS WAY ON ORIGINAL

Comment: Container labels were found to be acceptable in C3 review.

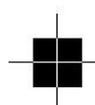
NOTE: The reconstitution instructions on the container labels are same as the reconstitution instructions on the container labels approved in the original application, approved 2/25/1992.

Previously submitted

(b) (4)

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

Model container/carton/blister labels [Source: ANRPT-25 received 5/31/2013]



Exp. Lot
04-A906-R1 (List 6369)
May be taken without regard to meals. Shake well before using. Oversize bottle provides shake space. Keep tightly closed. After mixing, store in the refrigerator and use within 10 days.

[UPCA Code]
FPO

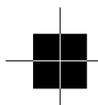
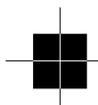
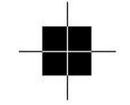
NDC 24338-134-02
100 mL (when mixed)
For Oral Suspension

E.E.S.® Granules

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

Rx only  Arbor Pharmaceuticals, Inc.
Atlanta, GA 30328

Before mixing, store below 86°F (30°C).
DIRECTIONS FOR MIXING: Add 77 mL water and shake vigorously. This makes 100 mL of suspension.
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 erythromycin200 mg in a buffered, cherry-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 adult dose and full prescribing information.



Exp. Lot
04-A907-R1 (List 6369)
May be taken without regard to meals. Shake well before using. Oversize bottle provides shake space. Keep tightly closed. After mixing, store in the refrigerator and use within 10 days.

FPO

3 2433813610 2

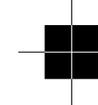
NDC 24338-136-10
200 mL (when mixed)
For Oral Suspension

E.E.S.® Granules

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

Rx only  Arbor Pharmaceuticals, Inc.
Atlanta, GA, 30328

Before mixing, store below 86°F (30°C).
DIRECTIONS FOR MIXING: Add 154 mL water and shake vigorously. This makes 200 mL of suspension.
Contains erythromycin ethylsuccinate equivalent to 8 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 erythromycin200 mg in a buffered, cherry-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 adult dose and full prescribing information.



3.1.2 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

Post-approval comment:

PRECAUTIONS; General: Please revise the last paragraph to read as, “When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy. (b) (4)

(b) (4)

3.1.3 DESCRIPTION, HOW SUPPLIED, MANUFACTURING BY STATEMENT sections [for OTC products, please include the inactives in table 8; package sizes being marketed in table 9; and drug product manufacturing/distributing statement in table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **YES**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED section or OTC package sizes? **YES**
 Are there changes to the manufacturing/distributing statements? **YES**
 If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section		
Previously Approved	Currently Proposed	Assessment
(b) (4)	Inactive Ingredients: artificial cherry flavor, lactose anhydrous, methylparaben, polysorbate 80, povidone, simethicone, sodium citrate anhydrous, and sucrose.	(b) (4) (b) (4) This is acceptable.

Table 9: Comparison of HOW SUPPLIED Section		
Previously Approved	Currently Proposed	Assessment
(b) (4)	Erythromycin Ethylsuccinate for Oral Suspension USP is available as: 200 mg/5 mL: 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	NDCs were updated due to change in ownership. The storage temperature was modified to be in accordance with USP recommended storage temperature. This is acceptable.

(b) (4)	Recommended storage 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 ten days.	
---------	--	--

Table 10: Manufactured by Statement		
Previously Approved	Currently Proposed	Assessment
MANUFACTURED BY BARR LABORATORIES, INC. POMONA, NY 10970	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	Change of ownership from Barr to ANI (7/13/2015; DARRTS). This is acceptable.

4. SPECIAL CONSIDERATIONS [PLEASE INCLUDE OTHER INFORMATION THAT MAY PERTAIN TO YOUR DRUG PRODUCT APPLICATION.]

From C2 review



i. Chemist Response:

The applicant states no changes are proposed to the drug product formulation. I also compared the batch formulation submitted in this supplement (S-034) and the formulation submitted in Supplement 030. They are the same.

See ANI's response in ECD letter dated 2/24/2017 for further documentation (b) (4)

(b) (4)



Rita
Lindie

Digitally signed by Rita Lindie
Date: 8/16/2018 03:03:14PM
GUID: 53c570830001639fca7572eedfad43b0



Theresa
Liu

Digitally signed by Theresa Liu
Date: 8/17/2018 02:07:34PM
GUID: 508da70a00028d58911de18a598cda6f

SUPPLEMENT LABELING REVIEW

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

Date of this Review	3/1/2018
Review Cycle Number	3
ANDA(s) and Supplement Number(s)	062055/S-034
Applicant Name	ANI Pharmaceuticals, Inc.
Proprietary Name, Established Name, and Strength(s)	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL
Current Received Date	2/14/2018
Previous Received Date(s) of Proposed Supplement	12/16/2016, 3/9/2017
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Theresa Liu
Review Conclusion	
<input checked="" type="checkbox"/> ACCEPTABLE - No Comments. <input type="checkbox"/> ACCEPTABLE - Include Post approval comments. <input type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant <input type="checkbox"/> 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 <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Acceptable for Filing <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	

For labeling supplement(s):

This Changes Being Effected supplemental abbreviated new drug [CLICK HERE](#)

We have completed the review of this supplemental application. Choose an item. effective on the date of this letter. Choose an item.

OR

We have completed the review of your [CLICK HERE](#) [CLICK HERE](#).

1. GENERAL COMMENTS
 - a. Subheading/Comment
 - i. Comment
 - ii. Comment
 - iii.
 2. CONTAINER LABEL
 3. CARTON LABELING
 4. PRESCRIBING INFORMATION
 5. MEDICATION GUIDE
 6. STRUCTURED PRODUCT LABELING (SPL)
-
-

For combined supplement(s):

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

Contents

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<u>2.</u>	<u>MATERIAL ANALYSIS</u>
<u>2.1</u>	<u>MATERIALS REVIEWED</u>
<u>2.2</u>	<u>MODEL LABELING</u>
<u>2.3</u>	<u>PATENTS AND EXCLUSIVITIES</u>
<u>2.4</u>	<u>UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)</u>
<u>2.5</u>	<u>HISTORY OF ANDA</u>
<u>3.</u>	<u>ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING</u>
<u>3.1</u>	<u>CONTAINER AND CARTON LABELS</u>
<u>3.1.1</u>	<u>PRESCRIBING INFORMATION AND PATIENT LABELING</u>
<u>3.1.2</u>	<u>DESCRIPTION AND HOW SUPPLIED SECTIONS</u>
<u>4.</u>	<u>SPECIAL CONSIDERATIONS</u>

1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS	
Are there any pending issues in <u>DLR's SharePoint Drug Facts?</u>	YES
If Yes, please explain: Microbiology consult response from OND for Erythromycin Ethylsuccinate tablets and oral suspension, dated 3-26-2013 for ANDA 61639.	
Is the drug product listed in the Policy Alert Tracker on <u>DLRS SharePoint?</u>	NO
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	NO
Reason for Submission: This Prior Approval Supplement is proposing a new manufacturing, packaging, and testing facility, ANI is also requesting an EXPEDITED REVIEW of this supplemental application based on CDER's Policy and Procedures, MAPP 5240.3; Prioritization of the Review of Original ANDAs, Amendments and Supplements, effective 03/11/16, suggesting the drug product from this ANDA currently meets the criteria for "sole-sourced". Labeling was found to be acceptable on 3/16/2017. This amendment provides 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.	
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 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 and 200 mL when mixed	Final	Satisfactory	2/14/2018
Blister	NA			
Carton	NA			
(Other - specify)				
Table 2 Review Summary of Prescribing Information and Patient Labeling				

	Revision Date and/or Code	Draft or Final	Recommendation	Received Date
Prescribing Information	January 2018	Draft	Satisfactory	2/14/2018
Medication Guide	NA			
Patient Information	NA			

2.2 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-073	Approval Date:	8/17/2017	Proprietary Name:	E.E.S.®
Description of Original or Supplement:	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				
<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:

2.3 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:

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

The USP was searched on 3/1/2018.

Table 2: 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	Click here to enter text	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

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

Comment:

2.5 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	4/25/2014	Please make the following changes when and if you resume marketing of the product PRESCRIBING INFORMATION/PHYSICIAN INSERT General 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. ii. Please note that the established name of your drug product is "erythromycin ethylsuccinate for oral suspension." Please revise accordingly throughout the package insert. iii. Revise "µg" to "mg." Applicant revised the labeling as requested.
Are there any Pending Labeling Supplements for this ANDA that impact labeling? NO		

Table 7: Labeling History of ANDA

Supplement	Submission Date	Labeling Impact

3. ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING

3.1 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: Container labels were found to be acceptable in C2 review. The container labels were revised to incorporate minor editorial changes and to modify the layout and dimensions. The storage temperature was modified. Container labels are acceptable.

NOTE: The reconstitution instructions on the container labels are same as the reconstitution instructions on the container labels approved in the original application, approved 2/25/1992.

Previously submitted

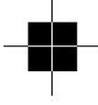
(b) (4)



3.1.1 MODEL CONTAINER LABELS

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

Model container/carton/blister labels [Source: ANRPT-25 received 5/31/2013]



Exp.
Lot

04-A905-R1 (List 6369)

May be taken without regard to meals.
Shake well before using. Oversize bottle provides shake space.
Keep tightly closed. After mixing, store in the refrigerator and use within 10 days.



NDC 24338-134-02
100 mL (when mixed)
For Oral Suspension

E.E.S.[®] Granules

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 77 mL water and shake vigorously. This makes 100 mL of suspension.

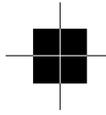
Contains erythromycin ethylsuccinate equivalent to 4 g erythromycin. Child-resistant closure not required; exemption approved by U.S. Consumer Product Safety Commission.

When mixed as directed, each teaspoonful (5 mL) contains: Erythromycin ethylsuccinate equivalent to erythromycin200 mg in a buffered, cherry-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 adult dose and full prescribing information.

Arbor Pharmaceuticals, Inc.
Atlanta, GA 30328



Exp.
Lot

04-A907-R1 (List 6369)

May be taken without regard to meals.
Shake well before using. Oversize bottle provides shake space.
Keep tightly closed. After mixing, store in the refrigerator and use within 10 days.



NDC 24338-136-10
200 mL (when mixed)
For Oral Suspension

E.E.S.[®] Granules

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 154 mL water and shake vigorously. This makes 200 mL of suspension.

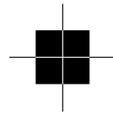
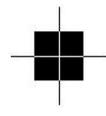
Contains erythromycin ethylsuccinate equivalent to 8 g erythromycin. Child-resistant closure not required; exemption approved by U.S. Consumer Product Safety Commission.

When mixed as directed, each teaspoonful (5 mL) contains: Erythromycin ethylsuccinate equivalent to erythromycin200 mg in a buffered, cherry-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 adult dose and full prescribing information.

Arbor Pharmaceuticals, Inc.
Atlanta, GA, 30328



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

3.1.3 DESCRIPTION, HOW SUPPLIED, MANUFACTURING BY STATEMENT sections [for OTC products, please include the inactives in table 8; package sizes being marketed in table 9; and drug product manufacturing/distributing statement in table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **YES**

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

Are there changes to the manufacturing/distributing statements? **YES**

If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section

Previously Approved	Currently Proposed	Assessment
(b) (4)	Inactive Ingredients: artificial cherry flavor, lactose anhydrous, methylparaben, polysorbate 80, povidone, simethicone, sodium citrate anhydrous, and sucrose.	(b) (4) (b) (4) This is acceptable.

Table 9: Comparison of HOW SUPPLIED Section

Previously Approved	Currently Proposed	Assessment
(b) (4)	Erythromycin Ethylsuccinate for Oral Suspension USP is available as: 200 mg/5 mL: 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, at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. After mixing, refrigerate and use within ten days.	NDCs were updated due to change in ownership. The storage temperature was modified to be in accordance with USP recommended storage temperature. This is acceptable.

Table 10: Manufactured by Statement

Previously Approved	Currently Proposed	Assessment
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MANUFACTURED BY BARR LABORATORIES, INC. POMONA, NY 10970	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	Change of ownership from Barr to ANI (7/13/2015; DARRTS). This is acceptable.
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4. SPECIAL CONSIDERATIONS [PLEASE INCLUDE OTHER INFORMATION THAT MAY PERTAIN TO YOUR DRUG PRODUCT APPLICATION.]

From C2 review



i. Chemist Response:

The applicant states no changes are proposed to the drug product formulation. I also compared the batch formulation submitted in this supplement (S-034) and the formulation submitted in Supplement 030. They are the same.

See ANI's response in ECD letter dated 2/24/2017 for further documentation





Rita
Lindie

Digitally signed by Rita Lindie
Date: 3/01/2018 11:48:18AM
GUID: 53c570830001639fca7572eedfad43b0



Theresa
Liu

Digitally signed by Theresa Liu
Date: 3/02/2018 10:50:09AM
GUID: 508da70a00028d58911de18a598cda6f

SUPPLEMENT LABELING REVIEW

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

Date of this Review	3/13/2017
Review Cycle Number	2
ANDA(s) and Supplement Number(s)	062055/S-034
Applicant Name	ANI Pharmaceuticals, Inc.
Proprietary Name, Established Name, and Strength(s)	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 m
Current Received Date	3/9/2017 (amendment)
Previous Received Date(s) of Proposed Supplement	12/22/2016
Labeling Reviewer	Soon Oh
Labeling Team Leader	Betty Turner

Review Conclusion

- ACCEPTABLE - No Comments.
- ACCEPTABLE - Include Post approval comments.
- Minor Deficiency/ECD - Refer to Labeling Deficiencies and Comments for the Letter to Applicant
- On Policy Alert List

For labeling supplement(s):

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: <input type="text" value="PAS"/>	
Are there any pending issues in <u>DLR's SharePoint Drug Facts</u> ? If Yes, please explain: Microbiology Consult Response dated 3/22/2013 for ANDA 061639 posted 1/5/2016	<input type="text" value="YES"/>
Is the drug product listed in the Policy Alert Tracker on <u>DLRS SharePoint</u> ? If Yes, please explain:	<input type="text" value="NO"/>

Reason for Submission:

ANI Pharmaceuticals, Inc. is submitting this Prior Approval Supplement after receiving FDA letter dated December 22, 2016, (b) (4) ANI is proposing a new manufacturing, packaging, and testing facility, and intends to market the drug product. ANI is also requesting an EXPEDITED REVIEW of this supplemental application on the basis of CDER's Policy and Procedures, MAPP 5240.3; Prioritization of the Review of Original ANDAs, Amendments and Supplements, Effective 03/11/16, suggesting the drug product from this ANDA currently meets the criteria for "sole-sourced".

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 and 200 mL when mixed	Final	Satisfactory	12/22/2016
Blister				
Carton				
Pouch				

Table 2 Review Summary of Prescribing Information and Patient Labeling

	Revision Date and/or Code	Draft or Final	Recommendation	Received Date
Prescribing Information	9857 Rev 03/17	Draft	Satisfactory	3/9/2017
Medication Guide				
Patient Information				

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-071	Approval Date:	2/2/2012	Proprietary Name:	E.E.S®
Description of Original or Supplement:	This "Prior Approval" supplemental new drug application was submitted in response to an Agency supplemental request letter dated November 15, 2011 to add wording concerning QT prolongation to the WARNINGS section of the label.				
<input type="checkbox"/> BPCA TEMPLATE					
<input checked="" type="checkbox"/> OTHER (Describe)	Microbiology Consult Response for ANDA 061639 dated 3/26/2013.				
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: Review for Microbiology subsection based on the Microbiology Consult Response for the ANDA 061639 dated 3/22/2013 (3/26/2013 DARRTS). The review for the ANDAs 061639/S-032 (now discontinued) and 062304/S-032 was based on this consult response. The sponsor for the NDA 050207 did not submit the supplement for this updates but included the updates in the labeling found in the Annual Report-28 dated 5/25/2016.

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")
NA					

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")
NA				

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:

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

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 6.

Table 6: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Copy of pertinent information from USP or PF
USP	3/14/2017	YES	Erythromycin Ethylsuccinate for Oral Suspension	Packaging and storage —Preserve in tight containers. (b) (4)
PF	3/14/2017	NO	NA	NA

Reviewer Assessment:

Are there any updates needed to the labeling based on the USP monograph? **NO**

Comment:

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: History of ANDA		
Last approved <u>labels and labeling</u> addressed the following:		
Supplement	Approval Date	What post approval changes requested and were the changes addressed?
S-032	4/25/2014	Please make the following changes when and if you resume marketing of the product. PRESCRIBING INFORMATION/PHYSICIAN INSERT General 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. ii. Please note that the established name of your drug product is “erythromycin ethylsuccinate for oral suspension.” Please revise accordingly throughout the package insert. iii. Revise “µg” to “mcg.” ASSESSMENT: Applicant revised the prescribing information as requested.
Are there any Pending Supplements for this ANDA that impact labeling? NO		

Table 7: History of ANDA

Supplement	Submission Date	Labeling Impact

3. ASSESSMENT OF CURRENT SUPPLEMENT’S LABELING

3.1 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: Re-marketing the product under the new ownership. Transfer of ownership from Barr Laboratories, Inc., an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA, Inc. to ANI Pharmaceuticals, Inc. (7/13/2015; DARRTS).

NOTE: The reconstitution instructions on the container labels are same as the reconstitution instructions on the container labels approved in the original application, approved 2/25/1992.

3.1.1 MODEL CONTAINER LABELS

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

Model container/carton/blister labels [Source: AR-28 submitted 5/25/2016]

Exp. Lot 04-A907-R1 (List 6369)
 May be taken without regard to meals. Shake well before using. Overuse bottle provides shake space. Keep tightly closed. After mixing, store in the refrigerator and use within 10 days.

3 2433813610 2

NDC 24338-136-10
200 mL (when mixed)
For Oral Suspension

E.E.S.® Granules

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

Before mixing, store below 86°F (30°C).
DIRECTIONS FOR MIXING: Add 154 mL water and shake vigorously. This makes 200 mL of suspension.
 Contains erythromycin ethylsuccinate equivalent to 8 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 buffered, cherry-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 adult dose and full prescribing information.

Rx only **Arbor Pharmaceuticals, Inc.**
 Atlanta, GA, 30328

3.1.2 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** (e list ANDA numbers).

Comment:

3.1.3 DESCRIPTION, HOW SUPPLIED, MANUFACTURING BY STATEMENT sections [for OTC products, please include the inactives in table 8; package sizes being marketed in table 9; and drug product manufacturing/distributing statement in table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **YES**

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

Are there changes to the manufacturing/distributing statements? **YES**

If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section		
Previously Approved	Currently Proposed	Assessment
(b) (4)	artificial cherry flavor, lactose anhydrous, methylparaben, polysorbate 80, povidone, simethicone, sodium citrate anhydrous, and sucrose .	Acceptable: (b) (4)

Table 9: Comparison of HOW SUPPLIED Section		
Previously Approved	Currently Proposed	Assessment
(b) (4)	Erythromycin Ethylsuccinate for Oral Suspension USP is available as: 200mg/5mL: Each 5 mL teaspoon of	Acceptable: NDC number changed due to the change of ownership

	<p>(b) (4)</p> <p>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</p> <p>Recommended storage Store granules, prior to mixing, below 86°F (30°C). After mixing, refrigerate and use within ten days.</p>	
--	--	--

Table 10: Manufactured by Statement		
Previously Approved	Currently Proposed	Assessment
<p>MANUFACTURED BY BARR LABORATORIES, INC. POMONA, NY 10970</p>	<p>Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623</p>	<p>Acceptable: Change of ownership from Barr to ANI (7/13/2015; DARRTS)</p>

4. SPECIAL CONSIDERATIONS [PLEASE INCLUDE OTHER INFORMATION THAT MAY PERTAIN TO YOUR DRUG PRODUCT APPLICATION.]

a. This product is currently not being manufactured or marketed and is listed in the discontinued section of the Orange Book. ANI Pharmaceuticals, Inc. intends to implement the changes proposed in this supplement and market the drug product.

b. Manufacturer

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

c. (b) (4)

Applicant re-submitted the proposal as a PAS in the S-034.

d. (b) (4)

i. Chemist Response:

The applicant states no changes are proposed to the drug product formulation. I also compared the batch formulation submitted in this supplement (S-034) and the formulation submitted in Supplement 030. They are the same.

ii. ANI's Response made to the Easily Correctable Deficiency (ECD) letter dated February 24, 2017:





Betty
Turner

Digitally signed by Betty Turner
Date: 3/16/2017 02:06:27PM
GUID: 508da70600028acef381be737f7836a9



Soon
Oh

Digitally signed by Soon Oh
Date: 3/15/2017 08:37:08AM
GUID: 508da70900028d34da321579dc393122

SUPPLEMENT LABELING REVIEW

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

Date of this Review	1/6/2017
Review Cycle Number	1
ANDA(s) and Supplement Number(s)	062055/S-034
Applicant Name	ANI Pharmaceuticals, Inc.
Proprietary Name, Established Name, and Strength(s)	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL
Current Received Date	12/22/2016
Previous Received Date(s) of Proposed Supplement	NA
Labeling Reviewer	Soon Oh
Labeling Team Leader	Betty Turner

Review Conclusion

- ACCEPTABLE - No Comments.
- ACCEPTABLE - Include Post approval comments.
- Minor Deficiency/ECD - Refer to Labeling Deficiencies and Comments for the Letter to Applicant
- On Policy Alert List

For labeling supplement(s):

For combined supplement(s):

Labeling deficiencies determined on January 11, 2017, based on your submission dated December 22, 2016:

1. Please update CLINICAL PHARMACOLOGY, Microbiology subsection and REFERENCES section as follows:



- 2. Revise “µg” to read “mcg” throughout the text, including the tables.
- 3. INDICATIONS AND USAGE

Please revise “erythromycin ethylsuccinate” to read “erythromycin ethylsuccinate for oral suspension, USP” when the text makes reference to the established name of your drug product.

- 4. PRECAUTIONS – Geriatric Use

Contents

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1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS	
Are there any pending issues in <u>DLR's SharePoint Drug Facts</u>? If Yes, please explain: Microbiology Consult Response dated 3/23/2013 for ANDA 061639 posted 1/5/2016	YES
Is the drug product listed in the Policy Alert Tracker on <u>DLRS SharePoint</u>? If Yes, please explain:	NO
Reason for Submission: ANI Pharmaceuticals, Inc. is submitting this Prior Approval Supplement after receiving FDA letter dated December 22, 2016, (b) (4) ANI is proposing a new manufacturing, packaging, and testing facility, and intends to market the drug product. ANI is also requesting an EXPEDITED REVIEW of this supplemental application on the basis of CDER's Policy and Procedures, MAPP 5240.3; Prioritization of the Review of Original ANDAs, Amendments and Supplements, Effective 03/11/16, suggesting the drug product from this ANDA currently meets the criteria for "sole-sourced".	
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 and 200 mL when mixed	Final	Satisfactory	12/22/2016
Blister				
Carton				
Pouch				
Table 2 Review Summary of Prescribing Information and Patient Labeling				
	Revision Date and/or Code	Draft or Final	Recommendation	Received Date
Prescribing Information	9857 Rev 09/16	Final	Revise	12/22/2016
Medication Guide				
Patient Information				

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/Supplement:	050207/S-071	Approval Date:	2/2/2012	Proprietary Name:	E.E.S®
Description of Supplement:	This "Prior Approval" supplemental new drug application was submitted in response to an Agency supplemental request letter dated November 15, 2011 to add wording concerning QT prolongation to the WARNINGS section of the label.				
<input type="checkbox"/> BPCA TEMPLATE					
<input checked="" type="checkbox"/> OTHER (Describe)	Microbiology Consult Response for ANDA 061639 dated 3/26/2013.				
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: Review for Microbiology subsection based on the Microbiology Consult Response for the ANDA 061639 dated 3/26/2013. The review for the ANDAs 061639/S-032 (now discontinued) and 062304/S-032 was based on this consult response. The sponsor for the NDA 050207 did not submit the supplement for this updates but included the updates in the labeling found in the Annual Report-28 dated 5/25/2016.

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")
NA					

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")
NA				

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:

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

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 6.

Table 6: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Copy of pertinent information from USP or PF
USP	1/9/2017	YES	Erythromycin Ethylsuccinate for Oral Suspension	Packaging and storage —Preserve in tight containers. (b) (4)
PF	1/9/2017	NO	NA	NA

Reviewer Assessment:

Are there any updates needed to the labeling based on the USP monograph? **NO**

Comment:

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: History of ANDA		
Last approved <u>labels and labeling</u> addressed the following:		
Supplement	Approval Date	What post approval changes requested and were the changes addressed?
S-032	4/25/2014	Please make the following changes when and if you resume marketing of the product. PRESCRIBING INFORMATION/PHYSICIAN INSERT General 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. ii. Please note that the established name of your drug product is “erythromycin ethylsuccinate for oral suspension.” Please revise accordingly throughout the package insert. iii. Revise “µg” to “mcg.” ASSESSMENT: Applicant included “USP” appropriately except in the INDICATIONS AND USAGE section and did not revise “µg” to read “mcg”. These issues will be re-addressed in the review.
Are there any Pending Supplements for this ANDA that impact labeling? NO		

Table 7: History of ANDA

Supplement	Submission Date	Labeling Impact

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: Re-marketing the product under the new ownership. Transfer of ownership from Barr Laboratories, Inc., an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA, Inc. to ANI Pharmaceuticals, Inc. (7/13/2015; DARRTS)

3.1.2 MODEL CONTAINER LABELS

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

Model container/carton/blister labels [Source: AR-28 submitted 5/25/2016]

Exp. Lot 04-A906-R1 (List 6369)

May be taken without regard to meals. Shake well before using. Oversize bottle provides shake space. Keep tightly closed. After mixing, store in the refrigerator and use within 10 days.

[UPC-A Code]

FPO

NDC 24338-134-02
100 mL (when mixed)
For Oral Suspension

E.E.S.® Granules

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Erythromycin activity 200 mg per 5 mL

when reconstituted

Rx only  Arbor Pharmaceuticals, Inc. Atlanta, GA 30328

Before mixing, store below 86°F (30°C).
DIRECTIONS FOR MIXING: Add 77 mL water and shake vigorously. This makes 100 mL of suspension.
 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 erythromycin200 mg in a buffered, cherry-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 adult dose and full prescribing information.

Exp. Lot 04-A907-R1 (List 6369)

May be taken without regard to meals. Shake well before using. Oversize bottle provides shake space. Keep tightly closed. After mixing, store in the refrigerator and use within 10 days.



3 2433813610 2

NDC 24338-136-10
200 mL (when mixed)
For Oral Suspension

E.E.S.® Granules

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Erythromycin activity 200 mg per 5 mL

when reconstituted

Rx only  Arbor Pharmaceuticals, Inc. Atlanta, GA 30328

Before mixing, store below 86°F (30°C).
DIRECTIONS FOR MIXING: Add 154 mL water and shake vigorously. This makes 200 mL of suspension.
 Contains erythromycin ethylsuccinate equivalent to 8 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 erythromycin200 mg in a buffered, cherry-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 adult dose and full prescribing information.

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))? **NO**

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

Comment: Applicant needs to update Microbiology subsection in accordance with the consult response from OND.

3.1.4 DESCRIPTION, HOW SUPPLIED, MANUFACTURING BY STATEMENT sections [for OTC products, please include the inactives in table 8; package sizes being marketed in table 9; and drug product manufacturing/distributing statement in table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **YES**

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

Are there changes to the manufacturing/distributing statements? **YES**

If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section

Previously Approved	Currently Proposed	Assessment
(b) (4)	artificial cherry flavor, lactose anhydrous, methylparaben, polysorbate 80, povidone, simethicone, sodium citrate anhydrous, and sucrose .	Acceptable: (b) (4)

Table 9: Comparison of HOW SUPPLIED Section

Previously Approved	Currently Proposed	Assessment
(b) (4)	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.	Acceptable: NDC number changed due to the change of ownership

Table 10: Manufactured by Statement

Previously Approved	Currently Proposed	Assessment
MANUFACTURED BY BARR LABORATORIES, INC. POMONA, NY 10970	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	Acceptable: Change of ownership from Barr to ANI (7/13/2015; DARRTS)

4. SPECIAL CONSIDERATIONS [PLEASE INCLUDE OTHER INFORMATION THAT MAY PERTAIN TO YOUR DRUG PRODUCT APPLICATION.]

1. This product is currently not being manufactured or marketed and is listed in the discontinued section of the Orange Book. ANI Pharmaceuticals, Inc. intends to implement the changes proposed in this supplement and market the drug product.

2. Manufacturer

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

3.



Applicant re-submitted the proposal as a PAS in the S-034.

4. The sodium content per individual dose in this supplement labeling is not consistent with sodium content in the last approved labeling. See comment above. Email sent to chemist for FYI.



Chemist Response: The applicant states no changes are proposed to the drug product formulation. I also compared the batch formulation submitted in this supplement (S-034) and the formulation submitted in Supplement 030. They are the same.



Betty
Turner

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Soon
Oh

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Date: 1/11/2017 01:13:46PM
GUID: 508da70900028d34da321579dc393122

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

CHEMISTRY REVIEWS

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):	December 22, 2016		
Amendment(s) Date (from Amendment Cover Letter):	March 9, 2017; September 8, 2017; December 11, 2017; February 14, 2018; August 7, 2018; September 21, 2018		

Note: The assessment below pertains to only those amendments denoted with yellow highlight. Refer to Project associated with the original supplement submission for additional information.

PAS ASSESSMENT FORM

ANDA No./Supplement No.: 62055/S34_AMD 100

Name of applicant and address (from 356h): ANI Pharmaceuticals, Inc.
210 Main Street West,
Baudette, MN 53326

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

Reporting Category: PAS

Supplement provides for: 1. A new manufacturing and testing facility for the drug product Erythromycin Ethylsuccinate for Oral Suspension USP; The new site is ANI Pharmaceuticals Inc., located in Baudette, MN; (b) (4)

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.

The following Type III DMFs have also been referenced in this supplement (b) (4)

Assessment Notes: The firm (Ani Pharmaceuticals, Inc.) submitted the original Prior Approval Supplement for a new manufacturing and testing facility on December 22, 2016. The manufacturing and testing site is

ANI Pharmaceuticals Inc.,
210 Main Street West
Baudette, MN 56623
FEI#: 2111358

(b) (4)

The proposed facilities were found Adequate on August 20th, 2018 per Panorama report.

Note that ANDA 62055 was originally approved in 1978. The ANDA holder was Barr Lab. This product was discontinued for manufacturing since 2003. Ani Pharmaceuticals Inc. acquired the ANDA ownership from Barr on July 2014 and proposed to manufacture the drug product at their facility Ani Pharmaceutical Inc. Minnesota.

The PAS was found Not approvable in the first review cycle, and a major complete response letter was sent to the firm on September 6, 2017. A Complete Response Amendment was submitted on February 14, 2018. In the second review cycle, the Supplement was Not recommended for approval due to the Major deficiency in DMF. Amendment 100 was submitted on August 7, 2018 to address the Deficiencies listed in the Complete Response Letter dated May 25, 2018.

For clarity, the deficiencies are denoted in italics, followed by the firm's response and review assessment.

FDA'S COMMENT #1: *The Drug Master File (DMF) (b) (4) has been reviewed and found inadequate. The DMF holder, (b) (4) was notified of the deficiencies on April 13, 2018. Please consult with your DMF holder, and provide the updated relevant drug substance sections. Do not respond to this ANDA CR letter until you have confirmed that the DMF holder has responded to the DMF CR letter cited above or your amendment will not be considered a complete response.*

The firm's Response:

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

FDA'S COMMENT #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.

ANI's response:

ANI acknowledges that the DMF No. (b) (4) is still pending review and that the ANDA review cannot be fully completed until all DMF deficiencies are adequately resolved. ANI also acknowledges that additional ANDA deficiency comments may be issued based on the outcome of the DMF review. ANI will continue to work with the DMF holder, (b) (4) to expedite the resolution of any forthcoming comments in an effort to expedite the review of this supplement. ANI also commits to providing timely responses to future agency inquiries.

Reviewer's Assessment: Satisfactory

DMF# (b) (4) has been reviewed up-to-date by L. Mu on October 19, 2018 and was found to be Adequate.

There is no further question per Drug Product discipline. The supplement is recommended for approval.

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 Outlaw



Huiqi
He

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Date: 10/22/2018 02:03:52PM
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Kathy
Woodland Outlaw

Digitally signed by Kathy Woodland Outlaw
Date: 10/22/2018 03:04:56PM
GUID: 508da70000028671b774f642ccb12211

cDiscipline 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	Deficient	Bioequivalent	AC
		Biopharm	AC
Microbiology	NA	Facilities	AC
Labeling	AC	DMF	Inadequate
SUBMISSIONS REVIEWED			
Submission Date (from Cover Letter):	December 22, 2016		
Amendment(s) Date (from Amendment Cover Letter):	March 9, 2017; September 8, 2017; December 11, 2017; February 14, 2018		

Note: The assessment below pertains to only those amendments denoted with yellow highlight. Refer to Project associated with the original supplement submission for additional information.

PAS ASSESSMENT FORM

ANDA No./Supplement No.: 62055/S34_AMD 94

Name of applicant and address (from 356h): ANI Pharmaceuticals, Inc.
210 Main Street West,
Baudette, MN 53326

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

Reporting Category: PAS

Supplement provides for: 1. A new manufacturing and testing facility for the drug product Erythromycin Ethylsuccinate for Oral Suspension USP; The new site is ANI Pharmaceuticals Inc., located in Baudette, MN; (b) (4)

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 April 16, 2018 and was found to be **Inadequate**.

The following Type III DMFs have also been referenced in this supplement

(b) (4)

Assessment Notes: The firm (Ani Pharmaceuticals, Inc.) submitted the original Prior Approval Supplement for a new manufacturing and testing facility on December 22, 2016. The manufacturing and testing site is

ANI Pharmaceuticals Inc.,
210 Main Street West
Baudette, MN 56623
FEI#: 2111358

(b) (4)

Note that ANDA 62055 was originally approved in 1978. The ANDA holder was Barr Lab. This product was discontinued for manufacturing since 2003. Ani Pharmaceuticals Inc. acquired the ANDA ownership from Barr on July 2014 and proposed to manufacture the drug product at their facility Ani Pharmaceutical Inc. Minnesota.

The PAS was found Not approvable in the first cycle review, and a major complete response letter was sent to the firm on September 6, 2017. This Complete Response Amendment was submitted on February 14, 2018.

The proposed facilities were found Adequate on April 7th, 2018.

FDA'S COMMENT #1: *The Drug Master File (DMF) (b) (4) has been reviewed and found inadequate. The DMF holder, (b) (4) was notified of any deficiencies on May 16, 2017, and they have responded with an amendment of their DMF on July 31, 2017. The DMF, as amended, is currently under review. Please be aware that the quality review of the supplement cannot be fully completed until all DMF deficiencies are adequately resolved. Therefore, additional ANDA deficiency comments may be used based on the outcome of the DMF reviews. Please acknowledge this in your response.*

The firm's Response:

ANI acknowledges that a quality review of the supplement cannot be fully completed until all DMF deficiencies are adequately resolved. Furthermore, the firm also understands that additional comments to the ANDA may be issued based on the outcome of the DMF review.

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

Deficiencies noted (list deficiencies or record None):

DMF# (b) (4) for Erythromycin Ethylsuccinate has been found Inadequate and the DMF holder, (b) (4) (b) (4) has been notified of the deficiencies. Please be aware that the quality review of the supplement cannot be fully completed until all DMF deficiencies are adequately resolved. Please consult with your DMF holder to address the outstanding deficiencies.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please submit updated stability data from long-term stability studies as data becomes available.

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: 5/14/2018

QAL's Name Kathy Woodland Outlaw



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Date: 5/14/2018 01:03:39PM
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Kathy
Woodland Outlaw

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Date: 5/15/2018 08:34:19AM
GUID: 508da70000028671b774f642ccb12211

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	Deficient	Biopharm	Deficient
Microbiology	NA	Facilities	AC
Labeling	AC	DMF	Inadequate
SUBMISSIONS REVIEWED			
Submission Date (from Cover Letter):	December 22, 2016*		
Amendment(s) Date (from Amendment Cover Letter):	March 9, 2017		

(b) (4)
[Redacted] . The firm resubmitted on December 22, 2016 as noted above.

PAS ASSESSMENT FORM

ANDA No./Supplement No.: 62055/S34

Name of applicant and address (from 356h): ANI Pharmaceuticals, Inc.
210 Main Street West,
Baudette, MN 53326

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

Reporting Category: PAS

Supplement provides for: 1. A new manufacturing and testing facility for the drug product Erythromycin Ethylsuccinate for Oral Suspension USP; The new site is ANI Pharmaceuticals Inc., located in Baudette, MN;

[Redacted]

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) the DMF has been reviewed up-to-date by L. Mu on May 16, 2017 and found to be **Inadequate**. The following Type III DMFs have also been referenced in this supplement

[Redacted]

Assessment Notes: The firm (Ani Pharmaceuticals, Inc.) submitted this Prior Approval Supplement for a new manufacturing and testing facility. The manufacturing and testing site is

ANI Pharmaceuticals Inc.,
210 Main Street West
Baudette, MN 56623
FEI#: 2111358

Note that ANDA 62055 was originally approved in 1978. The ANDA holder was Barr Lab. This product was discontinued for manufacturing since 2003. Ani Pharmaceuticals Inc. acquired the ANDA ownership from Barr on July 2014 and proposed to manufacture the drug product at their facility Ani Pharmaceutical Inc. Minnesota.

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

Deficiencies noted (list deficiencies or record None):

Deficiencies:

1. The Drug Master File (DMF) (b)(4) has been reviewed and found Inadequate. The DMF holder, (b)(4) was notified of any deficiencies on May 16, 2017 and they have responded with an amendment to their DMF on July 31, 2017. The DMF, as amended, is currently under review. Please be aware that the quality review of the supplement 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 reviews. Please acknowledge this in your response.

2. (b)(4)

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please submit updated stability data from long-term stability studies as data become available.

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: 8/30/2017

QAL's Name Kathy Woodland Outlaw



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Date: 8/30/2017 11:35:08AM
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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	Deficient	Biopharm	Deficient
Microbiology	NA	Facilities	PN
Labeling	AC	DMF	Inadequate
SUBMISSIONS REVIEWED			
Submission Date (from Cover Letter):	December 22, 2016*		
Amendment(s) Date (from Amendment Cover Letter):	March 9, 2017		

(b) (4)
. The firm resubmitted on December 22, 2016 as noted above.

PAS ASSESSMENT FORM

ANDA No./Supplement No.: 62055/S34

Name of applicant and address (from 356h): ANI Pharmaceuticals, Inc.
210 Main Street West,
Baudette, MN 53326

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

Reporting Category: PAS

Supplement provides for: 1. A new manufacturing and testing facility for the drug product Erythromycin Ethylsuccinate for Oral Suspension USP; The new site is ANI Pharmaceuticals Inc., located in Baudette, MN; (b) (4)

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), the DMF has been reviewed up-to-date by L. Mu on May 16, 2017 and found to be **Inadequate**. The following Type III DMFs have also been referenced in this supplement (b) (4)

Assessment Notes: The firm (Ani Pharmaceuticals, Inc.) submitted this Prior Approval Supplement for a new manufacturing and testing facility. The manufacturing and testing site is

ANI Pharmaceuticals Inc.,
210 Main Street West
Baudette, MN 56623
FEI#: 2111358

Note that ANDA 62055 was originally approved in 1978. The ANDA holder was Barr Lab. This product was discontinued for manufacturing since 2003. Ani Pharmaceuticals Inc. acquired the ANDA ownership from Barr on July 2014 and proposed to manufacture the drug product at their facility Ani Pharmaceutical Inc. Minnesota.

Deficiencies noted (list deficiencies or record None):

Deficiencies:

1. DMF# (b) (4) for Erythromycin Ethylsuccinate USP, has been found Inadequate and the DMF holder, (b) (4) has been notified of the deficiencies. Please be aware that the quality review of the supplement cannot be fully completed until all DMF deficiencies are adequately resolved. Please consult with your DMF holder to address the outstanding deficiencies.

2. (b) (4)

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please submit updated stability data from long-term stability studies as data become available.

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.

Pending Facility

Reviewer's Name: Huiqi He

Date: 5/16/2017

QAL's Name Kathy Woodland Outlaw



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Date: 5/17/2017 11:14:58PM
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Woodland Outlaw

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

BIOEQUIVALENCE REVIEWS

BIOPHARMACEUTICS REVIEW - ADDENDUM			
Office of New Drugs Products			
Application No.	ANDA 062055 S-34-A-94	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 Granule	Biopharmaceutics Division Director: Paul Seo, Ph.D.	
Indication	Treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria	Date Assigned	2/26/2018
Formulation/strength	Granule for oral suspension, 200 mg/5 ml	Date of Review	4/26/2018
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date(s)	Date of informal/formal consult	GDUFA due date	
February 14, 2018	N/A	June 13, 2018	
Type of Submission	Prior Approval Supplement (PAS)		
Key Review Points	<p>The supplement proposes: Propose a new manufacturing site for the approved ANDA 062055</p> <p>Biopharmaceutics review focuses on: the proposed dissolution method and acceptance criterion for finished product batch release and stability testing.</p>		
Recommendation	ADEQUATE		
<p>Purpose: Correction of a typo in the Biopharmaceutics review for ANDA 062055 S-34-A-94</p> <p>Addendum Date: 8/21/2018</p>			

Under Medium/Temperature in **Table 1**, the sodium dodecyl sulfate (SDS) concentration should be **1%**, not **0.1%** as shown in the original document.

Table 1 Proposed dissolution method and acceptance criterion for finished product batch release and stability testing of the proposed product

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 (Q) % (Q)

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

The above proposed dissolution method and acceptance criterion in **Table 1** is found acceptable.

Signature
8/22/2018
 Jia Yin Ph.D
 Biopharmaceutics Reviewer
 Office of New Drug Products

Signature
08/22/2018
 Poonam Delvadia, Ph.D.,
 Acting Biopharmaceutics Lead
 DB\ONDP\OPQ



Poonam
Delvadia

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BIOPHARMACEUTICS REVIEW Office of New Drugs Products			
Application No.	ANDA 062055 S-34-A-94	Primary Reviewer: Jia Yin, Ph.D.	
Submission Date	2/14/2018		
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 Granule	Biopharmaceutics Division Director: Paul Seo, Ph.D.	
Indication	Treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria	Date Assigned	2/26/2018
		Date of Review	4/26/2018
Formulation/strength	Granule for oral suspension 200 mg/5 ml	Type of Submission	Prior Approval Supplement (PAS)
Type of Review	Proposed a new manufacturing site for the approved ANDA 062055		
Recommendation	ADEQUATE		
<u>SUMMARY</u>			
<i>Background</i>			
<p>Erythromycin ethylsuccinate granule for oral suspension (E.E.S) was developed by Arbor Pharms LLC and was approved in 1965 under NDA 050207. E.E.S serves as the reference listed drug (RLD) for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 ml. The sole generic product 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 planned to relaunch the product at new manufacturing, packaging, and testing facilities.</p>			
<i>Submission</i>			
(b) (4)			

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

(b) (4)² On December 22, 2016, ANI Pharmaceuticals Inc submitted a PAS (Supplement 34) and requested expedited review. On September 20, 2017, FDA provided a Complete Response Letter (CRL) to the PAS submission due to product quality and biopharmaceutics deficiencies.³ Specifically, in vivo bioequivalence study was recommended to support the new manufacturing site due to unavailability of the pre-change product for dissolution comparison with the post-change product. On February 14, 2018, ANI Pharmaceuticals Inc re-submitted the PAS (Amendment 94).

This re-submission contains information on chemistry, manufacturing, and control of erythromycin ethylsuccinate granule for oral suspension 200 mg/5 ml and results from one bioequivalence (BE) study between the proposed product and the RLD. Review of the BE study is completed by the office of generic drugs (OGD) and the BE study is found adequate supporting manufacturing change.⁴ The biopharmaceutics component of the supplemental submission (S34/A94) includes addition of dissolution testing in drug product specification. The dissolution testing was included as drug product specification in (b) (4) S34⁶. However, the approvability decision with regards to dissolution was not made due to multiple reasons.¹

Review Objective

The biopharmaceutics assessment focuses on the evaluation of the proposed dissolution method and acceptance criterion for quality control i.e., finished product batch release and stability testing of the drug product.

Biopharmaceutics Assessment

The proposed in vitro dissolution method is the same as the dissolution method for a similar dosage form of the same drug substance, erythromycin ethylsuccinate oral suspension. Since the proposed oral granule product is reconstituted to create an oral suspension, this dissolution method is acceptable from the biopharmaceutics perspective.

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

Recommendations

²

(b) (4)

³ ANDA-062055-SUPPL-34: [AN62055DPM-SupplementCompleteResponseLetter34.doc](#) (Accessed on 05/04/2018)

⁴ ANDA-062055-SUPPL-34: Bioequivalence Review – [A062055N034DB-SupplementReview01-Amend02142018.docx](#) (Accessed on 05/04/2018)

⁵

(b) (4)

⁶ ANDA-062055-SUPPL-34 dated 12/22/2016. [M 3.2.P.5.6 – Justification of Specification](#). (Accessed on 05/04/2018)

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-34-A-94 for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 ml is recommended for approval.

Signature

Jia Yin Ph.D
Biopharmaceutics Reviewer
Office of New Drug Products

Signature

Poonam R Delvadia, Ph.D.,
Acting Biopharmaceutics Lead
DB\ONDP\OPQ

BIOPHARMACEUTICS ASSESSMENT

This Applicant is planning to relaunch erythromycin ethylsuccinate granule for Oral Suspension USP, 200 mg/5 mL at new manufacturing, packaging, and testing facility. The proposed change is categorized as a Level III site change defined by SUPAC-IR guidance that could be supported by comparative dissolution testing.⁷ However, based on historical information provided above, an in vivo BE study was conducted to support the change and is found adequate by the OGD.

Dissolution method and acceptance criteria

There was no dissolution test when the ANDA was approved. In the FDA Dissolution Method Database, the recommended dissolution method for this drug product (erythromycin ethylsuccinate oral granule) is “develop a dissolution method”. However, there is a recommended dissolution method in the database for a similar dosage form of the same drug substance, erythromycin ethylsuccinate oral suspension, where specific dissolution parameters are provided for evaluation. Since the oral granule product is reconstituted to create an oral suspension, these parameters were studied for adequacy in monitoring the dissolution for this drug product by the Applicant. The dissolution specification (method and acceptance criterion) has also been added to the drug product specifications in (b) (4) S34. **Table 1** shows the proposed dissolution method and acceptance criterion.

Table 1 Proposed dissolution method and acceptance criterion for finished product batch release and stability testing of the proposed product

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 0.1% Sodium dodecyl sulfate (SDS)/ 37°C ± 0.5°C	900 mL	10, 15, 20, 30	20 min – NLT (b) (4) % (Q)
* Dissolution method in the database for oral suspension was adopted for this product which is oral granule for suspension						

Dissolution data

Dissolution data was provided for reference product E.E.S (Lot 1065393) and ANI test batch (Lot MTMW12441) used in the in vivo BE study (Table 2 and 3 respectively). Comparison of mean dissolution profiles between the reference product and test product biobatches provided in Figure 1.

⁷ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070636.pdf>

Based on the data, the proposed drug product dissolves very rapid (b) (4) and reaches complete dissolution (b) (4)

Table 2 Dissolution data for the reference product E.E.S. (Lot 1065393) used in the BE study.

Referenced Data

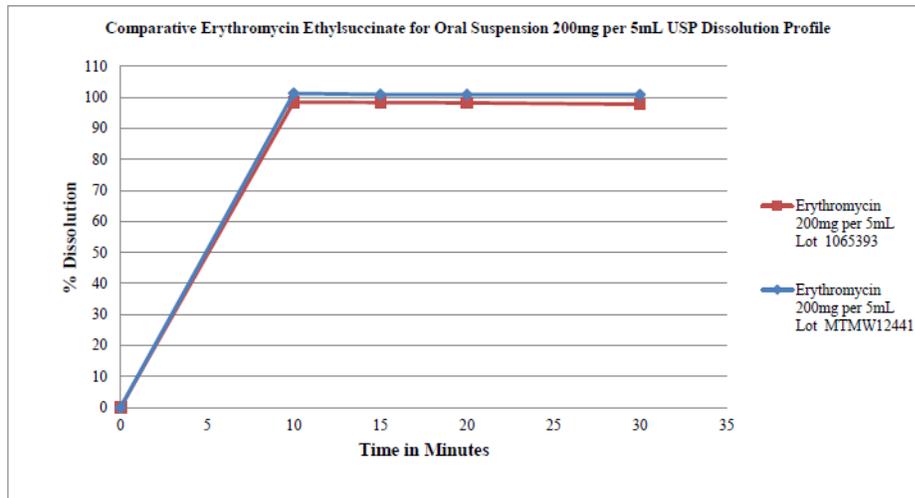
Erythromycin 200mg per 5mL Lot 1065393					
Tablet ↓	% Dissolution				
Min →	0	10	15	20	30
V1	(b) (4)				
V2					
V3					
V4					
V5					
V6					
V7					
V8					
V9					
V10					
V11					
V12					
Min					
Max					
Ave	0	98	98	98	98
RSD%	0	1.1	1.1	1.1	1.1

Table 3 Dissolution data for ANI test biobatch (Lot MTMW12441)

Comparative Data

Erythromycin 200mg per 5mL Lot MTMW12441					
Tablet ↓	% Dissolution				
Min →	0	10	15	20	30
V1	(b) (4)				
V2					
V3					
V4					
V5					
V6					
V7					
V8					
V9					
V10					
V11					
V12					
Min					
Max					
Ave	0	101	101	101	101
RSD%	0	0.6	0.7	0.5	0.6

Figure 1 Comparison of the mean dissolution profiles between the reference product and the ANI biobatch



Dissolution data is also provided for ANI batch No. MTMW11961 for stability evaluation. Up to 12 months, there is no significant change in dissolution of the test product.⁸

Assessment

Dissolution method: Acceptable

The proposed in vitro dissolution method is the same as the dissolution method for a similar dosage form of the same drug substance, erythromycin ethylsuccinate oral suspension. Since the proposed oral granule product is reconstituted to create an oral suspension, this dissolution method is acceptable from the biopharmaceutics perspective.

Dissolution acceptance criterion: Adequate

The proposed dissolution acceptance criterion NLT $\frac{(b)}{(4)}\%$ (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-34-A-94 for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 ml is recommended for approval.

⁸ [Application 062055 - Erythromycin Ethylsuccinate for Oral Suspension USP 200 mg/5 mL \(Lot No. MTGW11961 200 mL\): 18 month CRT](#)



Poonam
Delvadia

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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	062055-SUPP-034		
Drug Product Name	Erythronycin Ethylsuccinate for Oral Suspension, USP		
Strength(s)	Eq 200 mg base/5 mL 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	02/14/2018 (Supplement-034, SD-94 – Response to Complete Response Letter)		
Primary Reviewer	Yibo Wang, Ph.D.		
Secondary Reviewer	Jennifer N. Miller, Ph.D.		
Tertiary Reviewer	N/A		
Study Number(s)	606/17		
Study Type(s)	Fasting		
Strength(s)	200 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 <input type="checkbox"/> N/A (Waiver/Deem Bioequivalent) ²		<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 <input type="checkbox"/> N/A (Waiver/Deem

¹ For the ease of review, “Eq 200 mg base/5 mL” will be referred as to “200 mg/5 ml”.

	Bioequivalent) Error! Bookmark not defined.		
Waiver	<input type="checkbox"/> Granted <input type="checkbox"/> Tentatively granted <input type="checkbox"/> Not granted <input checked="" type="checkbox"/> N/A		
QC Dissolution	<input checked="" type="checkbox"/> Pending <input 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	<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> <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		
Deficiency Classification	<input type="checkbox"/> Major (Deficiencies to be communicated by CR) <input type="checkbox"/> Minor <input checked="" type="checkbox"/> N/A (Review is Adequate)		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
94	Fasting	200 mg/5 mL	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate

1 EXECUTIVE SUMMARY

This is a review of a **study amendment for supplement-034**.

ANDA 062055 for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL was approved on November 27, 1978, and discontinued for manufacturing in 2003. 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 July 10, 2015.³ ANI Pharmaceuticals, Inc.

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

³ DARRTS, ANDA 062055, COR-ANDAACK-01(Transfer of Ownership), dated 10/23/2015.

planned to re-launch the Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL.

(b) (4)

(b) (4).⁴ The firm resubmitted as a PAS on December 22, 2016. This submission is to obtain an approval of new manufacturing, packaging, and testing facilities.

On August 3, 2017, the Division of Bioequivalence (DB) II received a consult from the Division of Biopharmaceutics, inquiring if a new bioequivalence (BE) study is needed for approval of the applicant's proposed changes and to what product should the "post-change" test product be compared – the Reference Listed Drug (RLD) product or the "pre-change" test product. The DB II responded that the "post-change" test product should be compared to the corresponding strength of the RLD product.⁵

ANI Pharmaceuticals, Inc. submitted this amendment on February 14, 2018 in response to the Supplement Complete Response Letter (CRL) dated September 20, 2017.⁶ In the deficiency letter, the applicant was asked to conduct a fasting BE study comparing its "post-change" test product, Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL to the corresponding strength of the Reference Listed Drug (RLD) product, Arbor Pharmaceuticals LLC's EryPed®/E.E.S.® (erythromycin ethylsuccinate) Oral Granules, Eq 200 mg base/5 mL.

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 BE study was designed as a two-treatment, three-period, partially replicate, crossover study in healthy male subjects. The results are summarized in the table below.

4

(b) (4)

(b) (4)

⁵ GDRP, ANDA-062055-SUPPL-34»Biopharmaceutics ECD/IR and Consults, A062055N034DB_ConsultResponse01-Biopharm08032017.docx, dated 8/15/2017. <http://panorama.fda.gov/task/view?ID=59837a3a008a0c2fe95d97d02add234b>

⁶ GDRP, ANDA-062055-SUPPL-34»Final Decision, AN62055DPM-SupplementCompleteResponseLetter34.docx, dated 9/20/2017. <http://panorama.fda.gov/task/view?ID=585e17c500d7a7c481bda29800d4b6df>

Erythromycin Ethylsuccinate for Oral Suspension, USP, Dose (1 x 200 mg/5 mL) Fasting Bioequivalence Study No. 606/17, N=54 (Male=54 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)	2548.71	2940.17	0.87	79.61	94.39			
AUC _∞ (hr *ng/ml)	3011.14	3376.24	0.89	79.70	99.80			
C _{max} (ng/ml)	988.11	1198.64	0.82	75.26	90.29			
Scaled								
Parameter	T/R Ratio	90% CI (%)		s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	0.86	79.61	94.39	0.129945	0.3604789	-0.0374	Scaled/PE	PASS
AUC _∞	0.89	79.70	99.80	0.2152428	0.4639426	-0.0972	Scaled/PE	PASS
C _{max}	0.82	75.26	90.29	0.14228	0.3772003	-0.0179	Scaled/PE	PASS

The applicant conducted the dissolution testing using the following in-house method: 900 mL of Monobasic Sodium Phosphate, pH 6.8 Buffer with 1% SLS, with USP Apparatus II (Paddle) at 75 rpm. The applicant's dissolution method and data will be reviewed separately.

Per GDRP, OSIS recommends accepting data without on-site inspection for the clinical site (QPS Bioserve India Pvt. Limited).⁷ Per the Establishment Inspection Report (EIR), the inspection at the analytical site (b) (4) is classified as No Action Indicated (NAI).⁸ In addition, the study submitted in the current ANDA does 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.

⁷ GDRP, ANDA-062055-SUPPL-34-AMEND-94»Clinical PK/PD Sites, Decline to Inspection_A062055S-034_Clin.pdf, dated 2/28/2018. Link:

<http://panorama.fda.gov/task/view?ID=5a875a3100659fbf4689e3304147a221>

⁸

(b) (4)

(b) (4)

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3 SUBMISSION SUMMARY

3.1 Deficiencies

Biopharmaceutics/Bioequivalence Deficiency:

The submitted in vitro dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facilities. The critical evaluation is between the “pre-change” and “post-change” products. This evaluation provides FDA with the information needed to assess whether product quality has been adversely impacted as a result of the proposed change. Because you are not able to provide comparative dissolution testing between your “pre-change” drug product and your “post-change” drug product, please conduct a fasting bioequivalence (BE) study comparing your “post-change” test product, Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL to the corresponding strength of the reference product, Arbor Pharmaceuticals LLC’s EryPed®/E.E.S.® (erythromycin ethylsuccinate) Oral Granules, Eq 200 mg base/5 mL. Please refer to the Product-Specific Guidance for Erythromycin Ethylsuccinate Oral Granule for more information regarding study design, analytes to measure, and bioequivalence criteria (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM506882.pdf>).

Applicant’s Response:

In accordance with the agency’s request, ANI performed the required fasted bioequivalence study. The following study was conducted according to the recommended FDA’s published Bioequivalence (BE) Recommendation for Erythromycin Ethylsuccinate Granules (Recommended June 2016; RLD NDA 050207):

An open label, balanced, randomized, two-treatment, three-period, three-sequence, single dose, crossover, partial replicate oral bioequivalence study of Erythromycin Ethylsuccinate Granules 200 mg Base/5 mL of ANI Pharmaceuticals, Inc., USA, comparing with that of E.E.S.® (Erythromycin Ethylsuccinate Granules 200 mg Base/5 mL) of Arbor Pharmaceuticals, Inc. Atlanta, GA 30328 in healthy, adult, human subjects under fasting conditions.

The successful BE study report and FDA BE Tables can be found in **Module 5.3.1.2** and **Module 2.7**, respectively. ANI is also providing a *Companion Document for the Assessment of Bioequivalence for Erythromycin Ethylsuccinate Granule (Oral)* as a review aid to assist in explaining ANI’s position on the interpretation of the FDA’s published BE Guidance on the Erythromycin Ethylsuccinate product lines. This companion document is located in **Module 2.7** and **Module 5.2**.

In the Pre-submission Facility Correspondence (SN0017) dated December 14, 2017, supportive information such as the Certificates of Analysis and comparative dissolution profile were sent to FDA. Specifically, the following supportive information was submitted to the Agency for the batches used in the BE study:

eCTD Modules	Supportive Information	Lot Number
2.7.1	Certificate of Analysis – ANI	MTMW12441
3.2.P.5.4	Certificate of Analysis – RLD	1065393
	Dissolution Profile Report	MTMW1441 (ANI) and 1065393 (RLD)

Please note, an administrative change was made to the dissolution profile report submitted in the PFC to include a graphical representation. No changes were made to the dissolution profile data submitted in this correspondence.

Reviewer’s Comments:

Per the Agency’s request, the applicant conducted a fasting BE study (No. 606/17) comparing the test batch (No. MTMW12441) manufactured at the new facility (ANI

Pharmaceuticals, Inc., 210 Main Street, West Baudette, MN 56623) to the RLD product (Lot #1065393). The fasting BE study is acceptable.

The applicant's response to the bioequivalence deficiency is **adequate**. Please refer to [Appendix 4.1](#) for details.

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	606/17			
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 200 mg Base/5 mL of ANI Pharmaceuticals, Inc., USA, comparing with that of E.E.S. [®] (Erythromycin Ethylsuccinate Granules 200 mg Base/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 16.5			
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. Adm. E-mail: dr.sumanlata@qpsbioserve.com			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
Principal Analytical Investigator (Name, Email)				
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)	(a) (November 7, 2017 to December 24, 2017) 48 days (b) -20 °C ± 10°C			
Long-Term Storage Stability (LTSS) Coverage (no. days at temp °C)	Analyte: 65 days at -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.: 41 of 58.
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4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Erythromycin Ethylsuccinate for Oral Suspension, USP 200 mg/5 mL	E.E.S. [®] Granules (Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg per 5 mL)
Manufacturer	ANI Pharmaceuticals, Inc.	Arbor Pharmaceuticals, Inc.
Batch/Lot No.	MTMW12441	1065393
Manufacture Date	April 24, 2017	N/A
Expiration Date	N/A	August 5, 2019
Strength	200 mg/5 mL	200 mg/5 mL
Dosage Form	Suspension	Suspension
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	100.7%	102.2%
Content Uniformity (mean, % CV)	N/A	N/A
Dose Administered	1 × 200 mg/5 mL	1 × 200 mg/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%? If No, please comment	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.1.1.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 54 Dosed: Period I: 54, Period II and III: 53 Completed: 53* Samples Analyzed: 54 Statistically Analyzed: 54#
---------------------------	---

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Single-Dose Fasting Bioequivalence Study Review

No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	7 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, 5.50, 6.00, 8.00, 10.00 and 12.00 hours post dose.
IRB Approval	<input checked="" type="checkbox"/> Yes Date: 04/12/2017 <input type="checkbox"/> No
Informed Consent	<input checked="" type="checkbox"/> Yes Date: 04/12/2017 <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 46 of 176): \\cdsesub1\evsprod\anda062055\0019\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-no-6\fast-report-body.pdf
Safety Monitoring	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

* This is the subject number that completed all three periods.

A total of 54 subjects completed the clinical phase of the study either in complete for all the periods or at least two periods (one test and one reference or two reference).

Comments on Study Design: Adequate

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. 606/17				
		Treatment Groups		
		Test Product (T) N = 54	Reference Product (R) N = 54	
Age (years)	Mean ± SD	30.4 ± 6.5	30.4 ± 6.5	
	Range	18.0 – 44.0	18.0 – 44.0	
Age Groups	< 18	00	00	
	18 – 40	49 (90.74%)	49 (90.74%)	
	41 – 64	05 (09.26%)	05 (09.26%)	
	65 – 75	00	00	
	> 75	00	00	
Sex	Male	54 (100.0%)	54 (100.0%)	
	Female	00	00	
Race	Asian	54 (100.0%)	54 (100.0%)	
	Black	00	00	
	Caucasian	00	00	
	Hispanic	00	00	
	Other	00	00	
BMI	Mean ± SD	24.1 ± 2.9	24.1 ± 2.9	
	Range	18.5 – 29.8	18.5 – 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. 606/17				
Subject ID	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Subject did not turn up for period-III check-in.	III	No	N/A
(b) (6)	Subject did not turn 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. 606/17		
	Test (I) N = 53	Reference (R) N = 54	Post study N = 54
Muscular skeletal and connective tissue disorder			
Left hip joint pain	--	01 (1.85%)	--
Gastrointestinal System			
Nausea	01 (1.89%)	--	--
Pain abdomen	01 (1.89%)	--	--
Abdominal discomfort	--	01 (1.85%)	--
Investigations			
Increased Total Bilirubin	--	--	02 (3.70%)
Increased Potassium	--	--	01 (1.85%)
Decreased Haemoglobin	--	--	01 (1.85%)
Decreased HCT	--	--	01 (1.85%)
Total	02 (3.77%)	02 (3.70%)	05 (9.26%)

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 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

4.1.1.2.4 Protocol Deviations

Study No. 606/17		
Type	Subject #s (Test)	Subject #s (Ref.)
In-house Blood Draw Deviation	Period-I	
	(b) (6)	
Physical Activity Restriction Deviations		

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

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

Comments on Clinical Results: Adequate

4.1.1.3 Bioanalytical Results

4.1.1.3.1 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 A
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)

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	(b) (4)
Limit of quantitation (ng/mL)	6.0128
Average recovery of drug (%)	LQC: 87.78, MQC: 103.69, HQC: 104.69 Average: 98.7
Average recovery of IS (%)	104.3
Standard curve concentrations (ng/mL)	6.0128 to 3002.5
QC concentrations (ng/mL)	LLOQ QC: 6.0259
	LQC: 15.652
	AQC-II: 100.33
	AQC-I: 501.66
	MQC: 1203.0
	HQC: 2282.8
QC Intraday precision range (%)	LLOQ QC: 3.0 to 5.5
	LQC: 1.1 to 2.6
	AQC-II: 0.3 to 1.2
	AQC-I: 0.6 to 2.5
	MQC: 0.7 to 3.1
	HQC: 0.5 to 1.3
QC Intraday accuracy range (%)	LLOQ QC: 99.5 to 108.4
	LQC: 100.8 to 103.5
	AQC-II: 101.3 to 106.3
	AQC-I: 102.4 to 109.0
	MQC: 104.3 to 110.6
	HQC: 101.9 to 108.6
QC Inter day precision range (%)	LLOQ QC: 5.2
	LQC: 2.1
	AQC-II: 2.0
	AQC-I: 2.8
	MQC: 2.8
	HQC: 2.7
QC Inter day accuracy range (%)	LLOQ QC: 104.3
	LQC: 102.1
	AQC-II: 104.3
	AQC-I: 106.6
	MQC: 108.0
	HQC: 106.3
Bench-top stability (hrs)	17 hrs @ bench top (room temperature) condition

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Stock stability (days)	09 days @ -20°C ± 10°C
Processed stability (hrs)	116 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)	65 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Comments on the Pre-Study Method Validation: Adequate

- 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 step 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 measures the total erythromycin, which includes contributions from erythromycin and erythromycin ethylsuccinate present in the plasma sample (after hydrolysis). The applicant also 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.⁹ The applicant argues that the PSG's wording of measuring erythromycin "free base" is incorrect. 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 any erythromycin and erythromycin ethylsuccinate present in the plasma sample. In addition, the PSG for Erythromycin Ethylsuccinate Tablets

⁹ ANDA 062055, EDR, dated 2/24/2018, Sequ 0019 (94), Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods, link: <\\cdsesub1\evsprod\anda062055\0019\m2\27-clin-sum\summary-biopharm1.pdf>

recommends Erythromycin in plasma as analytes to measure and BE is based on 90% CI of Erythromycin. The reviewer agrees that the applicant's bioanalytical method of measuring the total erythromycin is acceptable and BE should be based on 90% CI of the total erythromycin.

- The applicant also conducted a conversion experiment for Erythromycin Ethylsuccinate A to Erythromycin A. The results demonstrated that the analytical method can convert the Erythromycin Ethyl Succinate A to Erythromycin A.

4.1.1.3.2 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
--------------------------------------	---

4.1.1.3.3 Sample Analysis Calibration and Quality Control

Bioequivalence Study No.: 606/17										
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)	6.0167	12.033	30.084	75.209	150.42	300.84	752.09	1803.6	2700.0	3000.0
Inter day Precision (%CV)	1.3	2.5	2.7	1.6	3.0	2.2	3.0	1.6	2.0	2.4
Inter day Accuracy (%)	101.8	98.1	97.2	96.4	98.6	101.7	99.3	100.4	101.4	104.8
Linearity (Range of R ² values)	0.9982 to 0.9998									
Linearity Range (ng/mL)	6.0167 to 3000.0									
Sensitivity/ LLOQ (ng/mL)	6.0167									

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Bioequivalence Study No. 606/17					
Analyte Name: (Erythromycin A)					
Parameter	Quality Control Samples				
	HQC	MQC	AQC-I	AQC-II	LQC
Concentration (ng/mL)	2282.8	1203.0	501.66	100.33	15.652
Interday Precision (%CV)	2.5	3.9	2.2	2.9	2.6
Interday Accuracy (% Actual)	104.7	101.2	100.2	96.9	99.1

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 54 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

4.1.1.3.4 Reanalysis of Study Samples

Study No. 606/17 (Erythromycin A) Additional information in Volume(01 pages), Page(46 of 56 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	00	03	0.00	0.14	00	03	0.00	0.14
Incomplete Analysis	01	03	0.09	0.14	01	03	0.09	0.14
Above Upper Limit of Quantification	00	02	0.00	0.09	00	02	0.00	0.09
Total	01	08	0.09	0.37	01	08	0.09	0.37

Note: Total number of test (T) samples analyzed: 1060
Total number of reference (R) samples analyzed: 2140

Does the reviewer agree with the reanalysis of study samples:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
---	---

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analytical and/or PK repeat?	
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 Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (MF) Type Age: mean (Range))	Mean Parameters +/-SD (%CV)									Study Report Location
					C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-tau} (ng*hr/mL)	AUC _∞ (ng*hr/mL)	T _{1/2} (hr)	K _{el} (hr ⁻¹)	K _{el lower} (hr ⁻¹)	K _{el upper} (hr ⁻¹)	AUC _{9%} Extrap	
Study# 606/17	To assess the bioequivalence of Erythromycin Ethylsuccinate Granules 200 mg Base/5 mL of ANI Pharmaceuticals, Inc., USA, comparing with that of E.E.S. [®] (Erythromycin Ethylsuccinate Granules 200 mg Base/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.	An 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 Granules 200 mg Base/5 mL Administered orally Lot No. MTMW12441	54 (Completed) Healthy, male subjects Age: 30.4 (18.0 – 44.0)										
			Reference product (R): 01 unit dose E.E.S. [®] (Erythromycin Ethylsuccinate Granules 200 mg Base/5 mL) Administered orally Lot No: 1065393		1161.5 ± 616.63 (53.091)	0.50 (0.17 – 10.00)	2943.616 ± 1480.834 (50.307)	3544.726 ± 2106.298 (59.421)	4.48 ± 5.22 (116.58)	0.2295 ± 0.0869 (37.8525)	4.58 ± 2.47 (53.95)	11.88 ± 0.63 (5.28)	10.783 ± 15.074 (139.795)	This information has been extracted from the Clinical Study Report (Pages 84 of 176 and 89 of 176).

4.1.1.4.2 Arithmetic Mean Pharmacokinetic Parameters – Reviewer Calculated

		Test		Reference 1		Reference 2		RatioT1R1	RatioT1R2	RatioR1R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T1/R)	(T1/R)	(T2/R)
AUCT	ng hr/mL	2943.616	50.31	3505.789	56.00	3256.644	38.71	0.84	0.90	1.08
AUCI	ng hr/mL	3544.723	59.42	4532.096	93.49	3652.388	43.07	0.78	0.97	1.24
C _{MAX}	ng/mL	1161.467	53.09	1424.973	52.90	1346.579	42.48	0.82	0.86	1.06
T _{MAX} *	hr	0.500	.	0.500	.	0.500	.	1.00	1.00	1.00
KE	hr ⁻¹	0.230	37.85	0.220	36.56	0.230	28.89	1.05	1.00	0.95
THALF	hr	4.475	116.6	7.105	333.46	3.477	55.59	0.63	1.29	2.04

Composite				
Parameter	Unit	Test	Reference (Ave of R1 and R2)	Ratio T/R
AUCT	ng hr/mL	2943.616	3381.2165	0.87
AUCI	ng hr/mL	3544.723	4092.242	0.87
C _{MAX}	ng/mL	1161.467	1385.776	0.84
T _{MAX} *	Hr	0.500	0.500	1.00
KE	hr ⁻¹	0.230	0.225	1.02
THALF	hr	4.475	5.291	0.85

* T_{max} values are presented as median.

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Erythromycin Ethylsuccinate for Oral Suspension, USP Dose (1 x 200 mg/5 mL) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fasting Bioequivalence Study No. 606/17								
Unscaled								
Parameter (ng)	Test	N	RLD	N	Ratio	90% C.I.		
AUC _{0-t} (hr *ng/ml)	NA	NA	NA	NA	85.74	79.61	94.39	
AUC _∞ (hr *ng/ml)	NA	NA	NA	NA	88.72	79.07	99.80	
C _{max} (ng/ml)	NA	NA	NA	NA	81.56	75.26	90.29	
Scaled								
Parameter	T/R Ratio	90% CI (%)		s2wr	sWR	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	85.74	79.61	94.39	0.12995	0.36048	-0.0375	GLM	Bioequivalent
AUC _∞	88.72	79.70	99.80	0.21524	0.46394	-0.0972	GLM	Bioequivalent
C _{max}	81.56	75.26	90.29	0.14228	0.37720	-0.0179	GLM	Bioequivalent

4.1.1.4.4 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Erythromycin Ethylsuccinate for Oral Suspension, USP								
Dose (1 x 200 mg/5 mL)								
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fasting Bioequivalence Study No. 606/17								
Unscaled								
Parameter (ng)	Test	N	RLD	N	Ratio	90% C.I.		
AUC _{0-t} (hr *ng/ml)	2548.71	53	2940.17	107	0.87	79.61	94.39	
AUC _∞ (hr *ng/ml)	3011.14	50	3376.24	103	0.89	79.70	99.80	
C _{max} (ng/ml)	988.11	53	1198.64	107	0.82	75.26	90.29	
Scaled								
Parameter	T/R Ratio	90% CI (%)		s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	0.86	79.61	94.39	0.129945	0.3604789	-0.0374	Scaled/PE	PASS
AUC _∞	0.89	79.70	99.80	0.2152428	0.4639426	-0.0972	Scaled/PE	PASS
C _{max}	0.82	75.26	90.29	0.14228	0.3772003	-0.0179	Scaled/PE	PASS

4.1.1.4.5 Additional Information for the Study

Root Mean Square Error	AUC _t : 0.3384 AUC _i : 0.4345 C _{max} : 0.3550
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
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)} in Period I (Test) had first measurable concentration as C _{max} . The applicant's sampling scheme (i.e. 0.17, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00 hrs etc.) adequately captured the early sampling time points in each instance.
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

ANDA 062055
Single-Dose Fasting Bioequivalence Study Review

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	50	0.89	0.20	0.99
Reference 1	52	0.90	0.04	0.98
Reference 2	51	0.91	0.52	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.		

SUB	PER	TRT	AUC _t /AUC _i
(b) (6)	2	B	0.80
	1	B	0.75
	3	A	0.71
	3	A	0.79
	1	A	0.20
	2	B	0.65
	3	B	0.79
	3	B	0.75
	1	B	0.57
	2	B	0.52
	2	B	0.63
	1	B	0.70
	3	A	0.68
	2	B	0.04
	3	A	0.38
	3	B	0.70
	1	A	0.72
	3	B	0.70
	2	A	0.68
	3	B	0.73
	1	A	0.80
	2	B	0.78

Comments on PK results: Adequate

4.1.1.5 Overall Comment

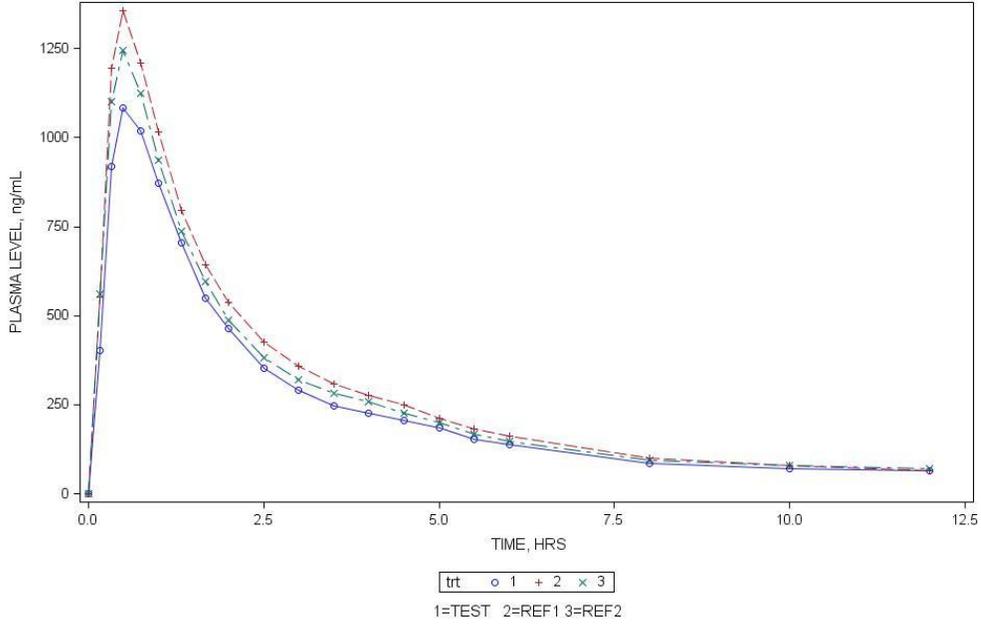
Was the Fasting bioequivalence study acceptable? Yes.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

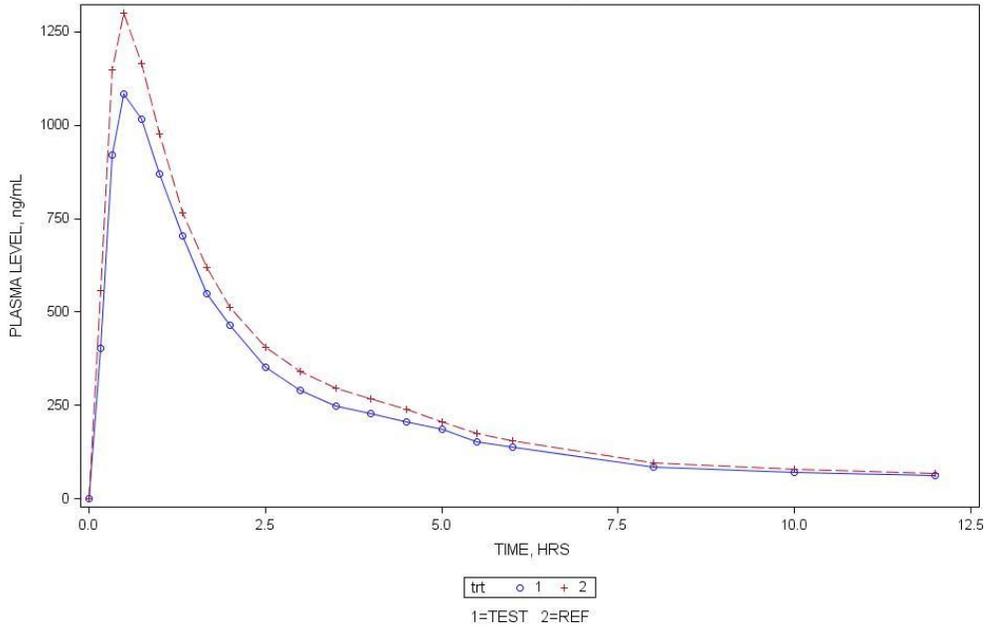
	Test (n=53)		Reference 1 (n=54)		Reference 2 (n=53)		RatioT1R1	RatioT1R2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T1/R1)	(T1/R2)	(R1/R2)
0.00	0.00	.	0.00	.	0.00
0.17	401.75	91.96	552.08	94.58	562.36	74.38	0.73	0.71	0.98
0.33	919.24	67.15	1195.37	64.83	1100.70	57.11	0.77	0.84	1.09
0.50	1082.79	58.58	1356.54	55.29	1245.20	46.68	0.80	0.87	1.09
0.75	1017.31	51.96	1209.17	53.94	1124.16	46.32	0.84	0.90	1.08
1.00	871.19	49.86	1014.51	55.91	937.26	45.48	0.86	0.93	1.08
1.33	703.56	51.32	794.24	58.91	738.14	48.40	0.89	0.95	1.08
1.67	549.91	55.97	641.84	60.43	595.25	48.45	0.86	0.92	1.08
2.00	463.41	54.02	537.59	61.45	488.87	47.69	0.86	0.95	1.10
2.50	352.54	56.17	427.06	60.76	382.84	47.70	0.83	0.92	1.12
3.00	291.33	59.17	357.98	58.51	321.74	43.99	0.81	0.91	1.11
3.50	248.45	58.39	309.38	58.53	281.23	46.19	0.80	0.88	1.10
4.00	227.18	58.52	276.84	58.74	257.61	48.69	0.82	0.88	1.07
4.50	205.39	59.08	250.73	60.02	226.89	43.50	0.82	0.91	1.11
5.00	184.91	59.47	212.29	58.35	198.89	43.72	0.87	0.93	1.07
5.50	152.33	61.67	181.76	61.27	168.31	42.38	0.84	0.91	1.08
6.00	137.20	61.04	161.46	62.93	146.90	44.29	0.85	0.93	1.10
8.00	85.82	64.54	100.24	72.21	93.66	57.65	0.86	0.92	1.07
10.00	70.74	77.98	78.48	91.05	79.24	90.17	0.90	0.89	0.99
12.00	63.70	101.51	64.82	107.92	70.17	118.86	0.98	0.91	0.92

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 200 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 200 mg/5 mL



4.2 Formulation Data

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

Comments on Formulation: Adequate

- The formulation of the test product remains the same as the previous approved formulation in supplement-30 submitted on 03/02/2001.¹⁰

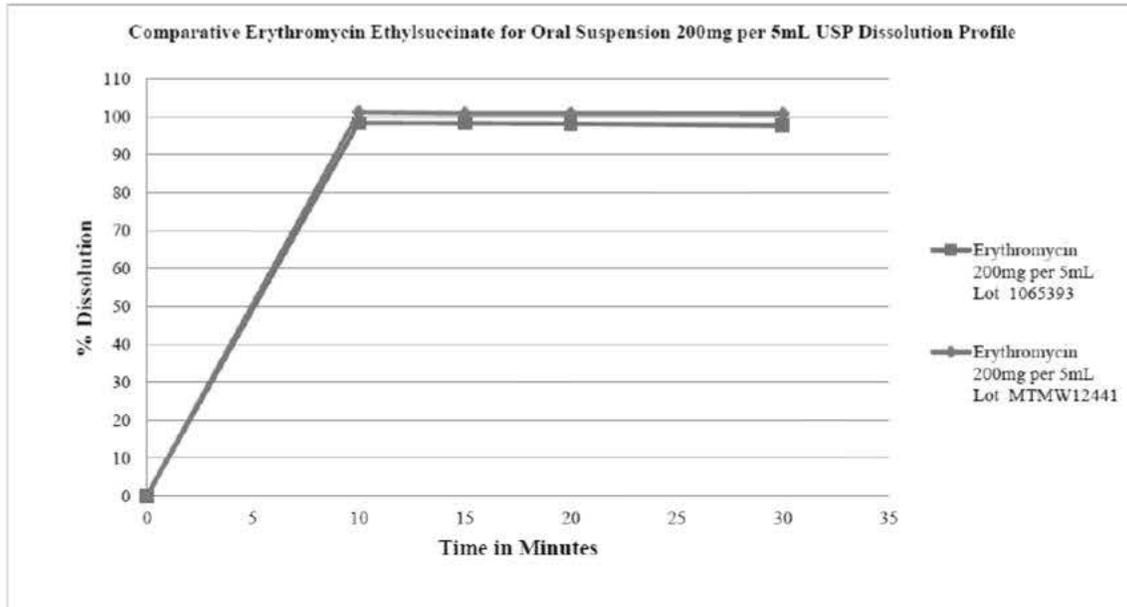
¹⁰ [\\fda.gov\wodc\CDER\OGD\AllOGDS1\FIRMSAM\BARR\LTRS&REV.62055s30r2ap.doc](https://www.fda.gov/wod/cder/ogd/AllOGDS1/FIRMSAM/BARR/LTRS&REV.62055s30r2ap.doc)

4.3 Dissolution Testing

4.3.1 Dissolution Data

Dissolution Conditions		Apparatus:	Apparatus II (Paddles)									
		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 Ng		Collection Times (minutes)					Study Report Location	
						0	10	15	20	30		
Study Report #: N/A	10/25/17	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL Batch No.: MTMW12441 Mfg Date: April 24, 2017	200 mg/5 mL Suspension	12	Mean (%)	0	101	101	101	101	3.2.P.5.4	
					Range (%)	0	^(b) ₍₄₎					
					%CV	0	0.6	0.7	0.5	0.6		
Study Report #: N/A	10/25/17	E.E.S. [®] (Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL) Batch No.: 1065393 Exp. Date: August 2019	200 mg/5 mL Suspension	12	Mean (%)	0	98	98	98	98	3.2.P.5.4	
					Range (%)	0	^(b) ₍₄₎					
					%CV	0	1.1	1.1	1.1	1.1		

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	Only one strength and no waiver request

Overall Comments: pending

- The applicant conducted the dissolution testing using the following in-house method: 900 mL of Monobasic Sodium Phosphate, pH 6.8 Buffer with 1% SLS, with USP Apparatus II (Paddle) at 75 rpm. The UPS monograph for this drug product does not specify a dissolution testing method.¹¹ Per the FDA's external dissolution database, the applicant should develop a dissolution method for this drug product.¹² The applicant's dissolution method and data will be reviewed separately.

4.4 Attachments

4.4.1 Additional Studies

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

¹¹ UPS 40-NF 35 Online, search: Erythromycin Ethylsuccinate for Oral Suspension, accessed on 3/19/2018.

¹² FDA's external dissolution database, search: Erythromycin Ethylsuccinate, accessed on 3/19/2018.

4.4.2 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	 062055DATA.xlsx	 HV-RefScale3Period- ver3-ParamNotConve	N/A	 062055-ANALYSIS.do c
		 BE03-For3PerHVDSu mmaryTables with ne	 062055_FASTING_stat _Erythromycin Ethylsu	 062055_FASTING_tabl e_Erythromycin Ethyls

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 062055

APPLICANT: ANI Pharmaceuticals, Inc.

DRUG PRODUCT: Erythromycin Ethylsuccinate for Oral Suspension, USP, Eq 200 mg base/5 mL

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: 34347

Reviewer: Wang, Yibo

Date

Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Erythromycin Ethylsuccinate for Oral Suspension, USP,
Eq 200 mg base/5 mL

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
34347	2/14/2018	BIO	Supplement Amendments [1]	1	1
34347	2/14/2018	Parallel	Fasting Study (Full template) [1]	1	1
34347	2/14/2018	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	2.25

BIOPHARMACEUTICS REVIEW
Office of New Drug Product

Application No.:	ANDA 062055/S-34	Primary Reviewer: Ge Bai, Ph.D.	
Submission Date:	December 22, 2016		
Division:	Office of Generic Drugs	Secondary Reviewer: Kimberly Raines, Ph.D.	
Applicant:	ANI Pharmaceuticals, Inc.	Acting Branch Chief: Kimberly Raines, Ph.D.	
Trade Name:	None	Acting Division Director: Paul Seo, Ph.D.	
Established Name:	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL	Date Assigned:	January 6, 2017
Indication:	Treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria	Date of Review:	March 10, 2017; August 18, 2017
Formulation/strengths	Oral Suspension, 200 mg/5 mL	Type of Submission: Prior Approval Supplement (PAS)	
Route of Administration	Oral		
Type of Review:	Proposed alternative manufacturing site for the approved ANDA		

SUMMARY:

Background:

ANDA # 062055 was approved on November 27, 1978. The last distribution for the drug product was reported in the Annual Report dated December 08, 2003. The expiration date of the product is 3 years (36 months) and therefore could have been in the market up to the Fourth Quarter (4Q) of 2006. ANI acquired this ANDA (062055) from Barr Laboratories Inc. (an indirect wholly owned subsidiary of Teva Pharmaceuticals USP, Inc. and Teva Pharmaceutical Industry Ltd.), effective July 10, 2015. Teva submitted the transfer of ownership on July 13, 2015 and ANI provided the FDA the acceptance of ownership on July 27, 2015. The FDA provided a letter of Acknowledgement of ANDA transfer dated October 23, 2015. ANI Pharmaceuticals, Inc. planned to re-launch the Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL

Submission:

This prior approval supplement (PAS) was submitted by ANI Pharmaceuticals, Inc. on December 22, 2016 for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL. This submission is to obtain an approval of a new manufacturing, packaging, and testing facility.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of:

1. Whether the submitted dissolution data is sufficient to support the inclusion of the new drug product manufacturing, packaging and testing facility.

RECOMMENDATION:

From a biopharmaceutics perspective, in vitro dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facility. The Division of Biopharmaceutics recommends that an OGD Office of Bioequivalence reviewer is included in the review team to assess the necessity of an in vivo bioequivalence study to support the proposed change. A consult review was completed by Bioequivalence reviewer, Yibo Wang, on 08/15/017. An in vivo bioequivalence study was recommended by Bioequivalence reviewer to support the proposed change. From a biopharmaceutics perspective this post-approval supplement is NOT recommended for APPROVAL at this time.

Signature

Ge Bai, Ph.D.
Biopharmaceutics Primary Reviewer
Office of New Drug Products

Signature

Kimberly Raines, Ph.D.
Biopharmaceutics Secondary Reviewer
Office of New Drug Products

cc. PSeo.

BIOPHARMACEUTICS ASSESSMENT

This prior approval supplement (PAS) was submitted by ANI Pharmaceuticals, Inc. on December 22, 2016 for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL. This submission is to obtain an approval of a new manufacturing, packaging, and testing facility.

The proposed manufacturing site change is categorized as a Level III change defined by the SUPAC-IR guidance. As per the guidance, the Applicant is to demonstrate similarity of dissolution in the application/compendial medium between the old and new drug products at different site. The current drug product specification does not include dissolution testing. Hence, there is no dissolution data of the drug product manufactured at the old manufacturing site available for comparison. In accordance with the Agency and current expectations for this dosage form, the Applicant is proposing an in vitro dissolution test method and specification.

From a biopharmaceutics perspective, in vitro dissolution data is not sufficient to support the approval of the proposed changes of manufacturing, packaging, and testing facility based on the following considerations:

- Suspected BCS Class 4 (low solubility; low permeability) drug substance
- ANDA was acquired and the Applicant has no prior experience with the product
- Product discontinued since 2003 and there is no available “pre-change” product
- New in vitro dissolution testing method with no historical data available for comparison
- There are no approved ANDAs currently on the market

(b) (4)

The Division of Biopharmaceutics recommends that an OGD bioequivalence reviewer is included in the review team to assess the necessity of a bioequivalence study to support the proposed change. Therefore, from a biopharmaceutics perspective this post-approval supplement is NOT recommended for APPROVAL.

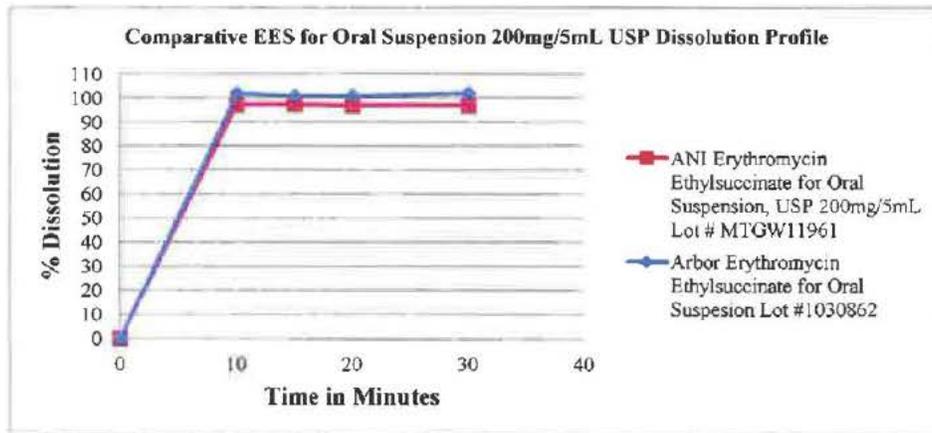
In the FDA’s Dissolution Methods Database the recommended dissolution method for this drug product (Erythromycin Ethylsuccinate for Oral Suspension – Oral Granule) is “develop a dissolution method”. The database also recommends a dissolution method for a similar dosage form of the same drug product (Erythromycin Ethylsuccinate Oral Suspension – Suspension), where specific dissolution parameters are provided for evaluation. Since the oral granule product is constituted to create an oral suspension, these parameters were studied for adequacy in monitoring the rate of release for this drug product by the Applicant. The Applicant’s proposed dissolution method is listed in the table below:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)
Erythromycin Ethylsuccinate	Oral granule	II (Paddle)	75	Monobasic Sodium Phosphate, pH 6.8 Buffer with 1% SLS Buffer w/ 1% SLS	900

The Applicant conducted dissolution testing on both the RLD (ANDA# 050207, Arbor Pharmaceuticals, LLC. Lot# 1030862) and the test product manufactured at the newly proposed manufacturing site. Dissolution data and dissolution profiles are listed in the tables and figure below. Dissolution data demonstrated similarity between the test and RLD, although the f2 comparison cannot be made due to rapid dissolution. Complete dissolution is achieved for both the test product and RLD lots (b) (4) into the analysis. The proposed in vitro dissolution method is not discriminatory for the test or RLD. Evaluation of the acceptability of the dissolution testing method will not be made at this time.

ANI Erythromycin Ethylsuccinate for Oral Suspension, USP 200mg/5mL Lot # MTGW11961						
Vessel ↓	% Dissolution					
	Min →	0	10	15	20	30 (b) (4)
V1						
V2						
V3						
V4						
V5						
V6						
V7						
V8						
V9						
V10						
V11						
V12						
Min						
Max						
Ave	0	97	97	97	97	97
RSD%	N/A	6.0	6.0	6.1	6.1	6.1

Arbor Erythromycin Ethylsuccinate for Oral Suspension Lot #1030862						
Tablet ↓	% Dissolution					
	Min →	0	10	15	20	30
V1						(b) (4)
V2						
V3						
V4						
V5						
V6						
V7						
V8						
V9						
V10						
V11						
V12						
Min						
Max						
Ave		0	102	101	101	102
RSD%		N/A	3.9	3.8	3.9	4.1



The Applicant proposed a dissolution acceptance criterion of “NLT (b) (4)% (Q) in 20 minutes”. Based on available dissolution data, the proposed dissolution acceptance criterion is too permissive. Acceptability of the dissolution acceptance criteria will not be completed at this time. The dissolution acceptance criterion will be recommended based on dissolution data generated with the bio-batch, if applicable.

The Applicant uses a HPLC analytical method to test dissolved drug substance. The Applicant conducted dissolution analytical method validation and provided a detailed method validation report (approved on April 25, 2016). The method was validated against specificity, linearity, precision, accuracy and ruggedness. Solution stability for the Standard has been demonstrated for 7 days when stored at 2-8°C. The sample solution will be analyzed immediately. The use of (b) (4) filters to clarify the solutions was verified.

The OGD Office of Bioequivalence was asked to determine if an in vivo bioequivalence study is necessary in support of the proposed new drug product manufacturing, packaging and testing facility. A consult review was completed by Bioequivalence reviewer, Yibo Wang, on 08/15/017.

An in vivo bioequivalence study was recommended by Bioequivalence reviewer to support the proposed change.

Deficiency 1: The submitted *in vitro* dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facilities. The critical evaluation is between the “pre-change” and “post-change” products. This evaluation provides FDA with the information needed to assess whether product quality has been adversely impacted as a result of the proposed change. Because you are not able to provide comparative dissolution testing between your “pre-change” drug product and your “post-change” drug product, please conduct a fasting bioequivalence (BE) study comparing your “post-change” test product, Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL to the corresponding strength of the reference product, Arbor Pharmaceuticals LLC’s EryPed®/E.E.S.® (erythromycin ethylsuccinate) Oral Granules, Eq 200 mg base/5 mL. Please refer to the Product-Specific Guidance for Erythromycin Ethylsuccinate Oral Granule for more information regarding study design, analytes to measure, and bioequivalence criteria.

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

Primary Biopharmaceutics Reviewer Name and Date: Ge Bai, Ph.D. March 10, 2017; August 18, 2017

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

I concur with the Primary Reviewer assessment.

Kimberly Raines, Ph.D.

03/21/2017



Kimberly
Raines

Digitally signed by Kimberly Raines
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Ge
Bai

Digitally signed by Ge Bai
Date: 8/21/2017 02:09:11PM
GUID: 51df0af000010a3d5c5b684a9a453803

DIVISION OF BIOEQUIVALENCE REVIEW

Consult Review

ANDA #	062055-SUPP-034
Drug Product Name	Erythromycin Ethylsuccinate for Oral Suspension USP
Strength(s)	Eq 200 mg base/5 mL ¹
Applicant's Name	ANI Pharmaceuticals, Inc.
Original Submission Date(s)	07/25/2007
Primary Reviewer	Yibo Wang, Ph.D.
Secondary Reviewer	Jennifer N. Miller, Ph.D.
Tertiary Reviewer	N/A
Consult Requested From	Division of Biopharmaceutics, Chinedu Ebonine
Consult Submission Date	08/03/2017
Consult Question	<p><i>The submitted in vitro dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facility. The critical evaluation is between the "pre-change" and "post-change" products. This evaluation provides FDA with the information needed to assess whether product quality has been adversely impacted as a result of the proposed change. Because you are not able to provide comparative dissolution testing between your "pre-change" drug product and your "post-change" drug product, please conduct a bioequivalence study demonstrating the equivalency between your "pre-change" drug product and your "post-change" drug product.</i>" The Division of Biopharmaceutics wants to communicate the above language to the applicant in a CR letter regarding a proposed change by the applicant, and requests concurrence from the Office of Bioequivalence.</p>
Date of Consult Assigned	08/08/2017
Date of Completion	08/15/2017

¹ For the ease of review, Eq 200 mg base/5 mL will be referred as to 200 mg/5 mL in this review.

Conclusion

The Division of Bioequivalence (DB) II recommends the following comments to be conveyed to the applicant:

The submitted *in vitro* dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facilities. The critical evaluation is between the “pre-change” and “post-change” products. This evaluation provides FDA with the information needed to assess whether product quality has been adversely impacted as a result of the proposed change. Because you are not able to provide comparative dissolution testing between your “pre-change” drug product and your “post-change” drug product, please conduct a fasting bioequivalence (BE) study comparing your “post-change” test product, Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL to the corresponding strength of the reference product, Arbor Pharmaceuticals LLC’s EryPed®/E.E.S.® (erythromycin ethylsuccinate) Oral Granules, Eq 200 mg base/5 mL. Please refer to the Product-Specific Guidance for Erythromycin Ethylsuccinate Oral Granule for more information regarding study design, analytes to measure, and bioequivalence criteria

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

Review of a Consult Request

1. Background

ANDA 062055 for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL was approved on November 27, 1978, and discontinued for manufacturing in 2003. 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 July 10, 2015.² ANI Pharmaceuticals, Inc. planned to re-launch the Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL

(b) (4)

³ The firm resubmitted as a PAS on December 22, 2016. This submission is to obtain an approval of new manufacturing, packaging, and testing facilities.

² DARRTS, ANDA 062055, COR-ANDAACK-01(Transfer of Ownership), dated 10/23/2015.

³

(b) (4)

2. Question Asked

The submitted in vitro dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facility. The critical evaluation is between the “pre-change” and “post-change” products. This evaluation provides FDA with the information needed to assess whether product quality has been adversely impacted as a result of the proposed change. Because you are not able to provide comparative dissolution testing between your “pre-change” drug product and your “post-change” drug product, please conduct a bioequivalence study demonstrating the equivalency between your “pre-change” drug product and your “post-change” drug product.” The Division of Biopharmaceutics wants to communicate the above language to the applicant in a CR letter regarding a proposed change by the applicant, and request concurrence from the Office of Bioequivalence.

3. Reviewer’s Comments

Per the SUPAC-IR guidance,⁴ for manufacturing site change, a Level 3 change consists of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing batch records except for administrative information, location and language translation, where needed. From a Biopharmaceutics perspective, the dissolution profile of the drug product at the current and proposed site should be similar.

However, in this case, the “pre-change” product was discontinued for manufacturing in 2003 and is not available. The firm conducted dissolution testing comparing the “post-change” product to the RLD product. No historical dissolution data are available for comparison of the “pre-change” and “post-change” products. Therefore, the reviewer agrees with the Biopharmaceutics reviewer’s conclusion that the *in vitro* dissolution data are not sufficient to support the approval of the proposed changes of manufacturing, packaging, and testing facilities.⁵ Additional information, including a bioequivalence (BE) study, may be warranted.

As per the SUPAC-IR Questions and Answers about SUPAC-IR Guidance,⁶ the following is noted in the *In Vivo* Bio Studies section:

⁴ <https://www.fda.gov/downloads/drugs/guidances/ucm070636.pdf>

⁵ ANDA-062055-SUPPL-34»Biopharmaceutics Quality Review, [20170306 ANDA062055 S34 Biopharm.pdf](https://www.fda.gov/oc/ohrt/anda062055_s34_biopharm.pdf), dated 5/4/2017.

⁶ <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124826.htm>

Question 5: *When a bio study is required under SUPAC-IR, to what product should a generic product be compared - the Reference Listed Drug or the generic product approved prior to the SUPAC change.*

Answer: *An innovator product should be compared to itself. A generic should be compared to the reference listed drug for that drug product.*

Therefore, in this case, the “post-change” product should be compared to the RLD product in a BE study.

As per the Product-Specific Guidance (PSG) for Erythromycin Ethylsuccinate Oral Granule,⁷ two (2) *in vivo* (fasting and fed) BE studies on the highest strength for this drug product (400 mg/5 mL) are recommended to demonstrate BE between the test and RLD products. Waivers can be granted for the lower strengths, 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.

Since this Supplement-034 is a PAS, and ANDA 062055 only has one strength (200 mg/5 mL), the reviewer recommends the firm to conduct a fasting BE study comparing the “post-change” test product, Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL to the corresponding strength of the reference product, Arbor Pharmaceuticals LLC’s EryPed[®]/E.E.S.[®] (erythromycin ethylsuccinate) Oral Granules, Eq 200 mg base/5 mL. The firm will be referred to the PSG for Erythromycin Ethylsuccinate Oral Granule for more information regarding study design, analytes to measure, and bioequivalence criteria (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM506882.pdf>).

4. Summary and Conclusions

The Division of Bioequivalence (DB) II recommends the following comments to be conveyed to the applicant:

The submitted *in vitro* dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facilities. The critical evaluation is between the “pre-change” and “post-change” products. This evaluation provides FDA with the information needed to assess whether product quality has been adversely impacted as a result of the proposed change. Because you are not able to provide comparative dissolution testing between your “pre-change” drug product and your “post-change” drug product, please conduct a fasting

⁷ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM506882.pdf>

bioequivalence (BE) study comparing your “post-change” test product, Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL to the corresponding strength of the reference product, Arbor Pharmaceuticals LLC’s EryPed[®]/E.E.S.[®] (erythromycin ethylsuccinate) Oral Granules, Eq 200 mg base/5 mL. Please refer to the Product-Specific Guidance for Erythromycin Ethylsuccinate Oral Granule for more information regarding study design, analytes to measure, and bioequivalence criteria (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM506882.pdf>).

5. Additional Attachments

N/A

6. Outcome Page

ANDA 062055

Reviewer: Wang, Yibo

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
32009	8/3/2017	BIO	Consult Review (For Consults to DBs) [1]	1	1
32009	8/3/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
				Total:	2



Yibo
Wang

Digitally signed by Yibo Wang
Date: 8/15/2017 01:35:46PM
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Jennifer
Miller

Digitally signed by Jennifer Miller
Date: 8/15/2017 01:37:11PM
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BIOPHARMACEUTICS REVIEW Office of New Drug Product			
Application No.:	ANDA 062055/S-34	Primary Reviewer: Ge Bai, Ph.D.	
Submission Date:	December 22, 2016		
Division:	Office of Generic Drugs	Secondary Reviewer: Kimberly Raines, Ph.D.	
Applicant:	ANI Pharmaceuticals, Inc.	Acting Branch Chief: Kimberly Raines, Ph.D.	
Trade Name:	None	Acting Division Director: Paul Seo, Ph.D.	
Established Name:	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL	Date Assigned:	January 6, 2017
Indication:	Treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria	Date of Review:	March 10, 2017
Formulation/ strengths	Oral Suspension, 200 mg/5 mL	Type of Submission: Prior Approval Supplement (PAS)	
Route of Administration	Oral		
Type of Review:	Proposed alternative manufacturing site for the approved ANDA		
SUMMARY:			
Background:			
<p>ANDA # 062055 was approved on November 27, 1978. The last distribution for the drug product was reported in the Annual Report dated December 08, 2003. The expiration date of the product is 3 years (36 months) and therefore could have been in the market up to the Fourth Quarter (4Q) of 2006. ANI acquired this ANDA (062055) from Barr Laboratories Inc. (an indirect wholly owned subsidiary of Teva Pharmaceuticals USP, Inc. and Teva Pharmaceutical Industry Ltd.), effective July 10, 2015. Teva submitted the transfer of ownership on July 13, 2015 and ANI provided the FDA the acceptance of ownership on July 27, 2015. The FDA provided a letter of Acknowledgement of ANDA transfer dated October 23, 2015. ANI Pharmaceuticals, Inc. planned to re-launch the Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL</p>			

Submission:

This prior approval supplement (PAS) was submitted by ANI Pharmaceuticals, Inc. on December 22, 2016 for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL. This submission is to obtain an approval of a new manufacturing, packaging, and testing facility.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of:

1. Whether the submitted dissolution data is sufficient to support the inclusion of the new drug product manufacturing, packaging and testing facility.

RECOMMENDATION:

From a biopharmaceutics perspective, in vitro dissolution data is not sufficient to support the approval of the inclusion of the new manufacturing, packaging, and testing facility. The Division of Biopharmaceutics recommends that an OGD Office of Bioequivalence reviewer is included in the review team to assess the necessity of an in vivo bioequivalence study to support the proposed change. Therefore, from a biopharmaceutics perspective this post-approval supplement is NOT recommended for APPROVAL at this time.

Signature

Ge Bai, Ph.D.
Biopharmaceutics Primary Reviewer
Office of New Drug Products

Signature

Kimberly Raines, Ph.D.
Biopharmaceutics Secondary Reviewer
Office of New Drug Products

cc. PSeo.

BIOPHARMACEUTICS ASSESSMENT

This prior approval supplement (PAS) was submitted by ANI Pharmaceuticals, Inc. on December 22, 2016 for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL. This submission is to obtain an approval of a new manufacturing, packaging, and testing facility.

The proposed manufacturing site change is categorized as a Level III change defined by the SUPAC-IR guidance. As per the guidance, the Applicant is to demonstrate similarity of dissolution in the application/compendial medium between the old and new drug products at different site. The current drug product specification does not include dissolution testing. Hence, there is no dissolution data of the drug product manufactured at the old manufacturing site available for comparison. In accordance with the Agency and current expectations for this dosage form, the Applicant is proposing an in vitro dissolution test method and specification.

From a biopharmaceutics perspective, in vitro dissolution data is not sufficient to support the approval of the proposed changes of manufacturing, packaging, and testing facility based on the following considerations:

- Suspected BCS Class 4 (low solubility; low permeability) drug substance
- ANDA was acquired and the Applicant has no prior experience with the product
- Product discontinued since 2003 and there is no available “pre-change” product
- New in vitro dissolution testing method with no historical data available for comparison
- There are no approved ANDAs currently on the market

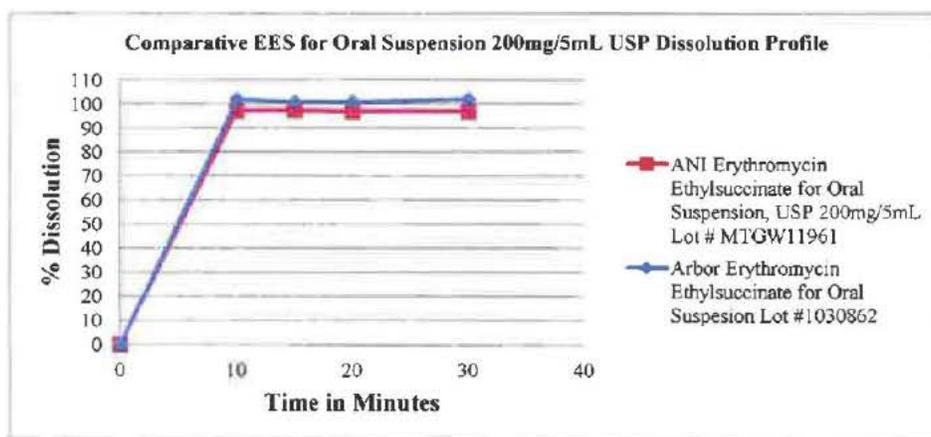
(b) (4)

The Division of Biopharmaceutics recommends that an OGD bioequivalence reviewer is included in the review team to assess the necessity of a bioequivalence study to support the proposed change. Therefore, from a biopharmaceutics perspective this post-approval supplement is NOT recommended for APPROVAL.

In the FDA’s Dissolution Methods Database the recommended dissolution method for this drug product (Erythromycin Ethylsuccinate for Oral Suspension – Oral Granule) is “develop a dissolution method”. The database also recommends a dissolution method for a similar dosage form of the same drug product (Erythromycin Ethylsuccinate Oral Suspension – Suspension), where specific dissolution parameters are provided for evaluation. Since the oral granule product is constituted to create an oral suspension, these parameters were studied for adequacy in monitoring the rate of release for this drug product by the Applicant. The Applicant’s proposed dissolution method is listed in the table below:

Drug Name	Dosage	USP	Speed (RPMs)	Medium	Volume (mL)
------------------	---------------	------------	---------------------	---------------	--------------------

Arbor Erythromycin Ethylsuccinate for Oral Suspension Lot #1030862						
Tablet ↓	% Dissolution					
	Min →	0	10	15	20	30
V1						(b) (4)
V2						
V3						
V4						
V5						
V6						
V7						
V8						
V9						
V10						
V11						
V12						
Min						
Max						
Ave		0	102	101	101	102
RSD%		N/A	3.9	3.8	3.9	4.1



The Applicant proposed a dissolution acceptance criterion of “NLT ^{(b) (4)}0% (Q) in 20 minutes”. Based on available dissolution data, the proposed dissolution acceptance criterion is too permissive. Acceptability of the dissolution acceptance criteria will not be completed at this time. The dissolution acceptance criterion will be recommended based on dissolution data generated with the bio-batch, if applicable.

The Applicant uses a HPLC analytical method to test dissolved drug substance. The Applicant conducted dissolution analytical method validation and provided a detailed method validation report (approved on April 25, 2016). The method was validated against specificity, linearity, precision, accuracy and ruggedness. Solution stability for the Standard has been demonstrated for 7 days when stored at 2-8°C. The sample solution will be analyzed immediately. The use of ^{(b) (4)} filters to clarify the solutions was verified.

The OGD Office of Bioequivalence will be asked to determine if an in vivo bioequivalence study is necessary in support of the proposed new drug product manufacturing, packaging and testing facility.

Primary Biopharmaceutics Reviewer Name and Date: Ge Bai, Ph.D. March 10, 2017

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

I concur with the Primary Reviewer assessment.

Kimberly Raines, Ph.D.

03/21/2017



Kimberly
Raines

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Date: 4/05/2017 10:55:33AM
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Ge
Bai

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Date: 4/25/2017 10:38:17AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-034

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



ANDA 062055/S-034

**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.

We also refer to your correspondence received on October 9, 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-034 on November 2, 2018. Consequently, I am denying your reconsideration request.

If you have any questions, call Lisa Oh, Regulatory Project Manager at (240) 402 - 3690.

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 03:47:04PM

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ANDA 062055/S-034

**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 9, 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 7, 2018.

If you have any questions, contact Lisa Oh, Regulatory Project Manager at (240) 402 - 3690.

Sincerely,

{See appended electronic signature page}

Lisa Oh
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research



Lisa
Oh

Digitally signed by Lisa Oh
Date: 10/24/2018 09:04:24AM
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ANDA 062055/S-034

**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 December 22, 2016, 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 (b) (4) 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.

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 09:42:14AM

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ANDA 062055/S-034

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 August 7, 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 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 December 6, 2018. 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 submitted and accepted, the GDUFA goal date for review of this priority major supplement amendment is April 6, 2019.

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

If you have any questions, contact Lisa Oh, Regulatory Project Manager, at (240) 402-3690.

Sincerely,

{See appended electronic signature page}

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



Lisa
Oh

Digitally signed by Lisa Oh
Date: 8/20/2018 08:07:17AM
GUID: 559c11bd0034d2c5b66e684b616011c9



ANDA 62055/S-034

DENIAL—
COMPETITIVE GENERIC THERAPY DESIGNATION

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

Dear Madam:

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 December 22, 2016. We acknowledge that you have requested, in an amendment to this supplement dated June 8, 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 (FD&C 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

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

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: 2018.08.07 16:40:12 -04'00'

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.



ANDA 062055/S-034

**PRE-SUBMISSION FACILITY CORRESPONDENCE
ELIGIBLE FOR FURTHER ASSESSMENT
FOR PRIOR APPROVAL SUPPLEMENT AMENDMENT**

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 Pre-Submission Facility Correspondence (PFC) received on June 8, 2018, for your supplemental abbreviated new drug application (sANDA) to be 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.

This PFC is subject to the provisions of the Food and Drug Administration Reauthorization Act of 2017 (FDARA) and the Generic Drug User Fee Amendments Reauthorization Performance Goals and Procedures Fiscal Years 2018-2022 (GDUFA II Commitment Letter).

We acknowledge your request for a priority review of your sANDA amendment. Based on your PFC, your sANDA amendment preliminarily appears to meet 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* (Prioritization MAPP). Therefore, your PFC is eligible for further assessment.

You should determine your sANDA amendment submission date with reference to Section 801 of FDARA and the GDUFA II Commitment Letter. If the sANDA amendment is submitted earlier than 60 days after submission of the PFC, the sANDA amendment generally will not be eligible for the shorter goal date.

After submission of your sANDA amendment, FDA will determine whether the sANDA amendment meets the criteria described in the Prioritization MAPP. Additionally, you should submit a signed certification statement in your submission stating that no changes have been made to the pre-submitted facility information. In order to remain eligible for an eight-month priority review GDUFA goal date, the sANDA amendment must meet the criteria in the Prioritization MAPP and the information submitted in the PFC must remain unchanged in the sANDA amendment, apart from the limited exceptions specified in Section 801 of FDARA.

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.

ANDA 062055

If you have any questions, please contact Lisa Oh, Regulatory Project Manager, at (240) 402 - 3690.

Sincerely,

{See appended electronic signature page}

Lisa Oh
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Lisa
Oh

Digitally signed by Lisa Oh

Date: 7/17/2018 09:04:46AM

GUID: 559c11bd0034d2c5b66e684b616011c9



ANDA 62055/S-034

**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 December 22, 2016. We acknowledge that you have requested, in an amendment dated February 14, 2018, to supplement 034, 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

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

Digitally signed by Rinku Patel -S4
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rinku Patel -S4,
0.9.2342.1.9200300.100.1.1=2000401187
Date: 2018.04.16 10:19:39 -04'00'

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.



ANDA 062055/S-034

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

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 amendment received on February 14, 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 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 June 13, 2018. 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 submitted and accepted, the GDUFA goal date for review of this priority major supplement amendment is October 13, 2018. If FDA determines that an inspection is required to validate the information contained in this priority major supplement amendment

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

If you have any questions, contact Lisa Oh, Regulatory Project Manager, at (240) 402-3690.

Sincerely,

{See appended electronic signature page}

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



Lisa
Oh

Digitally signed by Lisa Oh
Date: 3/06/2018 12:44:42PM
GUID: 559c11bd0034d2c5b66e684b616011c9



ANDA 062055/S-034

**PRE-SUBMISSION FACILITY CORRESPONDENCE
ELIGIBLE FOR FURTHER ASSESSMENT
FOR PRIOR APPROVAL SUPPLEMENT AMENDMENT**

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

Dear Ms. Camos:

This is in reference to your Pre-Submission Facility Correspondence (PFC) received on December 11, 2017, for your supplemental abbreviated new drug application (sANDA) amendment to be 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.

This PFC is subject to the provisions of the Food and Drug Administration Reauthorization Act of 2017 (FDARA) and the Generic Drug User Fee Amendments Reauthorization Performance Goals and Procedures Fiscal Years 2018-2022 (GDUFA II Commitment Letter).

We acknowledge your request for a priority review of your sANDA amendment. Based on your PFC, your sANDA amendment preliminarily appears to meet 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* (Prioritization MAPP). Therefore, your PFC is eligible for further assessment.

You should determine your sANDA amendment submission date with reference to Section 801 of FDARA and the GDUFA II Commitment Letter. If the sANDA amendment is submitted earlier than 60 days after submission of the PFC, the sANDA amendment generally will not be eligible for the shorter goal date.

After submission of your sANDA amendment, FDA will determine whether the sANDA amendment meets the criteria described in the Prioritization MAPP. Additionally, you should submit a signed certification statement in your submission stating that no changes have been made to the pre-submitted facility information. In order to remain eligible for an eight-month priority review GDUFA goal date, the sANDA amendment must meet the criteria in the Prioritization MAPP and the information submitted in the PFC must remain unchanged in the sANDA amendment, apart from the limited exceptions specified in Section 801 of FDARA.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and

beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, contact Lisa Oh, Regulatory Project Manager, at (240) 402-3690.

Sincerely,

Lisa E. Oh -A

Digitally signed by Lisa E. Oh -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Lisa E. Oh -A,
0.9.2342.1.9200300.100.1.1=2001696619
Date: 2018.01.25 13:56:27 -05'00'

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

ANDA FILING CHECKLIST

(Post June 20, 2014)

ANDA: **062055-SUPPL-34 (Reactivation Supplement)**

APPLICANT: **ANI Pharmaceuticals, Inc.**

RELATED APPLICATION(S): **Related Applications**

DRUG PRODUCT NAME: **Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL**

LETTER (356h) DATE: **December 22, 2016**

RECEIVED DATE: **December 22, 2016**

GDUFA GOAL DATE: **June 21, 2017**

Type II DMF #: **(b) (4)**

BASIS OF SUBMISSION:

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

NDA/ANDA: **NDA # 050207**

NDA: **NDA**

RLD/Ref.Std.: **E.E.S/Eryped**

RLD: **RLD**

FIRM: **Arbor Pharms LLC**

Firm: **FIRM**

Completion Signature

3/30/2017

X Edward Nguyen

Filing Reviewer

Signed by: Edward Nguyen -S

Recommendation:

FILE REFUSE to RECEIVE

ACK LETTER IS NOT REQUIRED AS THIS PAS IS A REACTIVATION OF A PREVIOUSLY APPROVED ANDA 062055

- Confirm that appropriate Application Specific Inspection Criteria have been checked
- Profile Codes Task Completed (not applicable for ANDAs received on or after 12/24/16)
- 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)
- DMF Complete Assessment – refer to screenshots below regarding Type II DMF **(b) (4)**
- Confirm OSIS Consult (Issue) was created (for clinical endpoints)
- Review Recommendation in Platform
- 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)
- 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:

ADDITIONAL COMMENTS:

Applicant contact information (U.S. Agent information)

APPLICANT INFORMATION		2. Name of Applicant ANI Pharmaceuticals, Inc.	
3. Telephone Number (Include country code if applicable and area code) 218.634.3500		4. Facsimile Number (Include country code if applicable and area code)	
5. Applicant Address			
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 53326	
32. Typed Name and Title of Applicant's Responsible Official Ellen Camos, Vice President of Regulatory Affairs			33. Date (mm/dd/yyyy) 12/21/2016
34. Telephone Number (Include country code if applicable and area code) (b) (6)		35. FAX Number (Include country code if applicable and area code) 888.519.0459	36. Email Address ellen.camos@anipharmaceuticals.com
37. 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	

MODULE 1: ADMINISTRATIVE

1.1	1.1.2	<input type="checkbox"/> Rx signed and Completed Application Form (356h) (Rx / OTC Status) (original signature) <input type="checkbox"/> YES <input type="checkbox"/> Electronic, Fillable Copy (if a signed, scanned copy is provided) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf																				
		Comments																				
		<input type="checkbox"/> YES Form FDA 3794 (PDF) GDUFA																				
1.2	*	<input type="checkbox"/> YES Cover Letter <input type="checkbox"/> NO the drug product subject to REMS requirements? http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm																				
		Comments																				
		<input type="checkbox"/> Form FDA 3674 (PDF) 42 U.S.C. 282(j)(5)(B) – not applicable as this is a Reactivation Supplement <input type="checkbox"/> N/A Electronic, Fillable Copy (if a signed, scanned copy is provided)																				
*	*	<input type="checkbox"/> N/A Table of Contents (paper submission only)																				
1.3	1.3.1	Contact/Sponsor/Applicant Information <input type="checkbox"/> N/A 1.3.1.2 U.S. Agent Appointment Letter 21 CFR §314.50(a)(5) If the applicant identifies a U.S. Agent on the 356h, a U.S. Agent Appointment letter should be provided.																				
		Comments																				
	1.3.2	<input type="checkbox"/> N/A Field Copy Certification 21CFR §314.94(d)(5) (For paper applications only, Original Signature)																				
		Comments																				
	1.3.3	Debarment Certification from Applicant Generic Drug Enforcement Act (GDEA)/ Other: FD&C Act §306(k), §306(a) and (b) (21 U.S.C. 335a(k), 335(a) and (b)) (no qualifying statement)																				
		<input type="checkbox"/> YES 1. Debarment Certification (original signature) <input type="checkbox"/> YES 2. List of Convictions statement (original signature)																				
1.3.4	Financial Certifications 21 CFR §54 21 CFR §54.2(e) 21 CFR §314.94(a)(13) <input type="checkbox"/> N/A Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) <input type="checkbox"/> N/A Disclosure Statement (Form FDA 3455)																					
	Comments																					
1.3.5	Patent and exclusivity 1.3.5.1 Patent Information 21 CFR §314.94(a)(12) FD&C Act 505(j)(2)(A)(vii) Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations 1.3.5.2 Patent Certification 21 CFR §314.94(a)(12)(i)(A)(1) through (4) or §314.94(a)(12)(iii)																					
	1. Patent number(s) Paragraph: (Check all certifications that apply)																					
	<table border="1"> <thead> <tr> <th></th> <th>Certification</th> <th>Patents</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td>No Relevant Patents</td> <td></td> </tr> <tr> <td><input type="checkbox"/></td> <td>MOU</td> <td></td> </tr> <tr> <td><input type="checkbox"/></td> <td>PI</td> <td></td> </tr> <tr> <td><input type="checkbox"/></td> <td>PII</td> <td></td> </tr> <tr> <td><input type="checkbox"/></td> <td>PIII</td> <td></td> </tr> <tr> <td><input type="checkbox"/></td> <td>PIV</td> <td></td> </tr> </tbody> </table>			Certification	Patents	<input type="checkbox"/>	No Relevant Patents		<input type="checkbox"/>	MOU		<input type="checkbox"/>	PI		<input type="checkbox"/>	PII		<input type="checkbox"/>	PIII		<input type="checkbox"/>	PIV
	Certification	Patents																				
<input type="checkbox"/>	No Relevant Patents																					
<input type="checkbox"/>	MOU																					
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<input type="checkbox"/>	PII																					
<input type="checkbox"/>	PIII																					
<input type="checkbox"/>	PIV																					
Statement of Notification (21 CFR §314.95 505(j)(2)(B)) <input type="checkbox"/>																						
<input type="checkbox"/> N/A 2. Pediatric Extension a. Expiration of Pediatric Extension? Pediatric Extension Date																						

1.3.5.3 Exclusivity Claim

N/A	Exclusivity Statement: State marketing intentions?
N/A	Pediatric Exclusivity (NPP, PED)
N/A	PEPFAR NCE-1 Waiver of Exclusivity

No new or existing patents/exclusivities associated with the RLD listed in OB for this Reactivation Supplement

Orange Book

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

E.E.S. (ERYTHROMYCIN ETHYLSUCCINATE)
EQ 200MG BASE/5ML

Marketing Status: Prescription

Active Ingredient: ERYTHROMYCIN ETHYLSUCCINATE
Proprietary Name: E.E.S.
Dosage Form; Route of Administration: GRANULE; ORAL
Strength: EQ 200MG BASE/5ML
Reference Listed Drug: Yes
TE Code: AB
Application Number: N050207
Product Number: 001
Reference Standard: No
Approval Date: Approved Prior to Jan 1, 1982
Applicant Holder Full Name: ARBOR PHARMACEUTICALS LLC
Marketing Status: Prescription
[Patent and Exclusivity Information](#)

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

Marketing Status: Prescription

Active Ingredient: ERYTHROMYCIN ETHYLSUCCINATE
Proprietary Name: ERYPED
Dosage Form; Route of Administration: GRANULE; ORAL
Strength: EQ 200MG BASE/5ML
Reference Listed Drug: Yes
TE Code: AB
Application Number: N050207
Product Number: 003
Reference Standard: No
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

Marketing Status: Prescription

Active Ingredient: ERYTHROMYCIN ETHYLSUCCINATE
Proprietary Name: ERYPED
Dosage Form; Route of Administration: GRANULE; ORAL
Strength: EQ 400MG BASE/5ML
Reference Listed Drug: Yes
TE Code:
Application Number: N050207
Product Number: 002
Reference Standard: Yes
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 001
ERYTHROMYCIN ETHYLSUCCINATE (E.E.S.) GRANULE EQ 200MG BASE/5ML

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
------------	-----------	-------------------	----------------------	--------------------	-----------------	------------------

There are no unexpired patents for this product in the Orange Book database.

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
------------	------------------	------------------------

There is no unexpired exclusivity for this product in the Orange Book database.

Patent and Exclusivity for: N050207

Product 002
ERYTHROMYCIN ETHYLSUCCINATE (ERYPED) GRANULE EQ 400MG BASE/5ML

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
------------	-----------	-------------------	----------------------	--------------------	-----------------	------------------

There are no unexpired patents for this product in the Orange Book database.

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
------------	------------------	------------------------

There is no unexpired exclusivity for this product in the Orange Book database.

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 Claim	Drug Product Claim	Patent Use Code	Delist Requested
------------	-----------	-------------------	----------------------	--------------------	-----------------	------------------

There are no unexpired patents for this product in the Orange Book database.

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
------------	------------------	------------------------

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 LoA received from DMF holders)</p> <p><input type="checkbox"/> YES 1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient</p> <p><input type="checkbox"/> YES 2. Type II DMF# (b) (4)</p> <p><input type="checkbox"/> YES 3. Type III DMF authorization letter(s) for container closure</p>
	Comments	
1.12	1.12.4	<p><input type="checkbox"/> N/A Request for Comments and Advice – Proprietary name requested If Yes, did the firm provide the request as a separate electronic amendment labeled “Proprietary Name Request” at initial time of filing</p> <p><input type="checkbox"/> N/A 1. Yes</p> <p>2. No – contact the firm to submit the request as a separate electronic amendment</p>
	Comments	
1.12	1.12.11	<p>Basis for Submission 21 CFR §314.94(a)(3) Applicant identifies the following:</p> <p><input type="checkbox"/> YES 1. NDA/ANDA: NDA # 050207</p> <p><input type="checkbox"/> YES 2. Ref Listed Drug: E.E.S/Eryped</p> <p><input type="checkbox"/> YES 3. Firm: Arbor Pharmaceuticals LLC</p> <p><input type="checkbox"/> N/A ANDA suitability petition required? 21 CFR §10.20 21 CFR §10.30 21 CFR §314.93 If Yes, Petition number Petition Number</p> <p><input type="checkbox"/> N/A Copy of FDA’s correspondence approving the petition (21 CFR §314.94(a)(3)(iii))</p> <p><input type="checkbox"/> N/A ANDA Citizen’s Petition required? 21 CFR §10.25(a) 21 CFR §10.30 21 CFR §314.122 If Yes, Petition number Petition Number</p> <p><input type="checkbox"/> N/A Copy of petition</p>
	Comments	
1.12	1.12.12	<p>Comparison between Generic Drug and RLD 505(j)(2)(A) 21 CFR §314.94(a)(4) to (6)</p> <p><input type="checkbox"/> N/A Conditions of Use</p> <p><input type="checkbox"/> N/A Active Ingredients</p> <p><input type="checkbox"/> N/A Inactive Ingredients (21 CFR §314.94(a)(9)(ii))</p> <p><input type="checkbox"/> N/A Route of Administration</p> <p><input type="checkbox"/> N/A Dosage Form</p> <p><input type="checkbox"/> N/A Strength</p>
	Comments	
1.12	1.12.14	<p>Environmental Analysis from Applicant 21 CFR §25.31 and §25.15(d), if applicable</p> <p><input type="checkbox"/> N/A Environmental Assessment (EA) (21 CFR §25.20)</p> <p><input type="checkbox"/> N/A If applicable, Environmental Impact Statement (EIS) (21 CFR 25.22)</p> <p><input type="checkbox"/> N/A Claim of Categorical Exclusion (21 CFR §25.30 or 21 CFR §25.31)</p> <p><input type="checkbox"/> N/A Statement: “to the applicant’s best of knowledge no extraordinary circumstances exist”</p>
	Comments	
1.12	1.12.15	<p>Request for Waiver 21 CFR 320.22 320.24(b)(6)</p>

	<input type="checkbox"/> N/A	Request for Waiver of In-Vivo BA/BE Study(ies)
	Comments	
1.14	1.14.1	<p>Draft Labeling (Multi Copies N/A for E-Submissions) 21 CFR 314.94(a)(8)(ii) (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</p> <p><input type="checkbox"/> YES Electronic copy (each strength and container) -OR- <input type="checkbox"/> N/A 4 copies of draft for paper submission only (each strength and container)</p> <p>1.14.1.2 Annotated draft labeling text 21 CFR §314.94(a)(8)(iv)</p> <p><input type="checkbox"/> N/A 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)</p> <p><input type="checkbox"/> 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</p> <p><input type="checkbox"/> N/A Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalsApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf</p>
		Comments
1.14	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)</p> <p><input type="checkbox"/> 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's approved for the RLD)</p> <p><input type="checkbox"/> N/A i. Vial or ampule vs. prefilled syringe <input type="checkbox"/> N/A ii. Vial vs. ampule <input type="checkbox"/> N/A iii. Delivery device that's different from the RLD, e.g. inhalers <input type="checkbox"/> N/A iv. Bottles vs blisters ("calendarized" packaging) <input type="checkbox"/> N/A v. Unit of use (dispensable bottle) vs. multiple use bottles (pharmacy bottle)</p> <p><input type="checkbox"/> N/A b. Drug product packaged in an IV bag</p> <p><input type="checkbox"/> YES 1.14.3.3 Labeling text for reference listed drug 21 CFR §314.94(a)(8)(iv) RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label</p>
		Comments

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



MODULE 2: CTD SUMMARIES

2.3 QUALITY OVERALL SUMMARY (QOS) – N/A as this is a Reactivation Supplement

2.3	N/A	E-Submission: PDF
	N/A	MS Word
		Additional information regarding QbR may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm
	N/A	Question based Review (QbR)
	Comments	
	N/A	2.3.S Drug Substance (Active Pharmaceutical Ingredient) 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards 2.3.S.6 Container Closure System 2.3.S.7 Stability
	Comments	
	N/A	2.3.P Drug Product 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product Oral Solids: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft <i>Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation</i> (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.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
	Comments	

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (Active Pharmaceutical Ingredient) – N/A as Reactivation Supplement

3.2.S.1	<p>N/A <u>General Information</u> (May not refer to DMF)</p> <p>3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties</p>
Comments	
3.2.S.2.1	<p>YES <u>Manufacturer</u> Drug Substance (Active Pharmaceutical Ingredient) 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. CFN, FEI, or DUNS number (if available) 7. Additional sources of API and information (1 through 6, if applicable) <p>Same DS manufacturer as previously approved but changed name.</p>

3.2.S.2.1 MANUFACTURER(S) (b) (4)

DRUG SUBSTANCE						
Name	DMF No.	Address	Contact	U.S. Agent	Facility ID No.	Function/ Responsibility
(b) (4)						
ANI Pharmaceuticals, Inc.	N/A	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	Not Applicable	FEI: 2111358 DUNs: 148515737	Analytical Testing

(b) (4)

3.2.S.3	N/A	Characterization All potential impurities should be listed in tabular format as given below:									
		<table border="1"> <thead> <tr> <th>IUPAC Chemical Name</th> <th>Code #</th> <th>Chemical Structure</th> <th>Process/Degradation Impurity</th> <th>Source/Mechanism</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> <p>http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf</p>	IUPAC Chemical Name	Code #	Chemical Structure	Process/Degradation Impurity	Source/Mechanism				
IUPAC Chemical Name	Code #	Chemical Structure	Process/Degradation Impurity	Source/Mechanism							
Comments											

Control of Drug Substance (Active Pharmaceutical Ingredient)			
3.2.S.4	3.2.S.4.1	N/A	Specification Testing specifications and data from drug substance manufacturer(s)
	Comments		
	3.2.S.4.2	N/A	Analytical Procedures
	Comments		
3.2.S.4.3	N/A	Validation of Analytical Procedures (API that is USP or reference made to DMF, MUST provide verification of USP or DMF procedures)	
	N/A	1. Spectra and chromatograms for reference standards and test samples (<i>ref. std. can be located in 3.2.S.5</i>)	
	N/A	2. Samples-Statement of Availability and Identification (21 CFR §314.50(e)(1)) a. Name of Drug Substance	
Comments			

3.2.S.4.4	Batch Analysis	
	N/A	1. COAs specifications and test results from DS manufacturer(s)
	N/A	2. Drug Product manufacturer's Certificates of analysis API lot numbers API lot numbers
Comments		

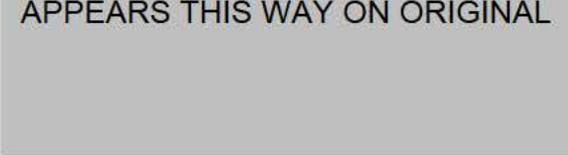
3.2.S.4.5	Justification of Specifications (Provide data in tabular format):								
	N/A	Specified Identified Impurities:							
		Chemical Name	Code #	MDD	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)
	N/A	Specified Unidentified Impurities:							
		Relative Retention Time	Code #	MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)
	N/A	Unspecified Impurities:							
		MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)		
<p>http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf</p>									
Comments									

3.2.S.5	N/A	Reference Standards or Materials (Do NOT refer to DMF)
Comments		

3.2.S.6	N/A	Container Closure Systems
Comments		

3.2.S.7	Stability	
	N/A	1. Retest date or expiration date of API(s)
Comments		

APPEARS THIS WAY ON ORIGINAL



3.2.P DRUG PRODUCT

<u>Description and Composition of the Drug Product</u>																			
3.2.P.1	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 5%; text-align: center; border: 1px solid black;">YES</td> <td>1. Unit composition with indication of the function of the inactive ingredient(s)</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">N/A</td> <td>2. Inactive ingredients and amounts are appropriate per IIG (per/dose, unit, or MDD justification) (provide justification in a tabular format) N/A since no changes in formulation</td> </tr> <tr> <td colspan="2">3. Formulation</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">N/A</td> <td style="padding-left: 20px;">Oral Tablet and Oral Capsules: % to mg/dosage unit</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">YES</td> <td style="padding-left: 20px;">Oral suspensions and oral solutions: % to mg/dose</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">N/A</td> <td style="padding-left: 20px;">Parenterals: same unit of measure as RLD</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">N/A</td> <td>4. Elemental iron: provide daily elemental iron calculation pursuant to 21 CFR 73.1200 (calculation of elemental iron intake based on maximum daily dose (MDD) of the drug product is preferred if this section is applicable)</td> </tr> <tr> <td style="text-align: center; border: 1px solid black;">N/A</td> <td>5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be Q1/Q2 and must be provided in the package configuration</td> </tr> <tr> <td colspan="2" style="border-top: 1px solid black;">Comments</td> </tr> </table>	YES	1. Unit composition with indication of the function of the inactive ingredient(s)	N/A	2. Inactive ingredients and amounts are appropriate per IIG (per/dose, unit, or MDD justification) (provide justification in a tabular format) N/A since no changes in formulation	3. Formulation		N/A	Oral Tablet and Oral Capsules: % to mg/dosage unit	YES	Oral suspensions and oral solutions: % to mg/dose	N/A	Parenterals: same unit of measure as RLD	N/A	4. Elemental iron: provide daily elemental iron calculation pursuant to 21 CFR 73.1200 (calculation of elemental iron intake based on maximum daily dose (MDD) of the drug product is preferred if this section is applicable)	N/A	5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be Q1/Q2 and must be provided in the package configuration	Comments	
	YES	1. Unit composition with indication of the function of the inactive ingredient(s)																	
	N/A	2. Inactive ingredients and amounts are appropriate per IIG (per/dose, unit, or MDD justification) (provide justification in a tabular format) N/A since no changes in formulation																	
	3. Formulation																		
	N/A	Oral Tablet and Oral Capsules: % to mg/dosage unit																	
YES	Oral suspensions and oral solutions: % to mg/dose																		
N/A	Parenterals: same unit of measure as RLD																		
N/A	4. Elemental iron: provide daily elemental iron calculation pursuant to 21 CFR 73.1200 (calculation of elemental iron intake based on maximum daily dose (MDD) of the drug product is preferred if this section is applicable)																		
N/A	5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be Q1/Q2 and must be provided in the package configuration																		
Comments																			

(b) (4)



3.2.P.2	<input type="checkbox"/> N/A Pharmaceutical Development Report Comments												
3.2.P.3	<p style="text-align: center;">Manufacture</p> <p><input checked="" type="checkbox"/> YES Drug Product Manufacturer(s) Must correlate to the establishment information submitted in annex to Form 356h for the finished dosage manufacturer and all outside contract testing laboratories.</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. cGMP Certification from Applicant 6. CFN, FEI, or DUNS numbers (if available) 												
	<p>3.2.P.3.1 DRUG PRODUCT</p> <table border="1"> <thead> <tr> <th>Name</th> <th>Address</th> <th>Contact</th> <th>Facility ID No.</th> <th>Function/ Responsibility</th> </tr> </thead> <tbody> <tr> <td rowspan="2">ANI Pharmaceuticals, Inc.</td> <td rowspan="2">210 Main Street West Baudette, MN 56623</td> <td>David J. Sullivan, Ph.D. VP, Quality Operations</td> <td>FEI: 2111358</td> <td rowspan="2"> Drug Substance: Analytical Testing Drug Product: Manufacturing, In-Process Analytical Testing, Final Dosage Form Release Analytical Testing, Stability Analytical Testing Excipients: Analytical Testing, Microbiological Testing </td> </tr> <tr> <td> Phone: 218.634.3507 Fax: 218.634.3540 Email: david.sullivan@anipharmaceuticals.com </td> <td>DUNS: 148515737</td> </tr> </tbody> </table>	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	FEI: 2111358	Drug Substance: Analytical Testing Drug Product: Manufacturing, In-Process Analytical Testing, Final Dosage Form Release Analytical Testing, Stability Analytical Testing Excipients: Analytical Testing, Microbiological Testing	Phone: 218.634.3507 Fax: 218.634.3540 Email: david.sullivan@anipharmaceuticals.com	DUNS: 148515737
	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	FEI: 2111358	Drug Substance: Analytical Testing Drug Product: Manufacturing, In-Process Analytical Testing, Final Dosage Form Release Analytical Testing, Stability Analytical Testing Excipients: Analytical Testing, Microbiological Testing									
		Phone: 218.634.3507 Fax: 218.634.3540 Email: david.sullivan@anipharmaceuticals.com	DUNS: 148515737										
<p>3.2.P.3.2 <input type="checkbox"/> N/A Batch Formula Largest Intended Commercial Batch Size Comments</p>													
3.2.P.3.3	<p>Description of Manufacturing Process and Process Controls</p> <p><input type="checkbox"/> N/A 1. Description of the Manufacturing Process and (for aseptic fill products) Facility</p>												

		N/A	2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified
		N/A	3. Master Packaging Records for intended marketing container(s)
			4. If sterile product []
		N/A	5. Reprocessing Statement (cite 21 CFR 211.115) from Applicant
		Comments	
3.2.P.3.4		N/A	Controls of Critical Steps and Intermediates
		Comments	
3.2.P.3.5		Process Validation and/or Evaluation	
			1. Terminally Sterilized Product
		N/A	• Is this pharmacy bulk? (Go to 1.14.1.4)
			2. Aseptically Filled Product
		N/A	• Validation (bacterial retention studies) of sterilizing grade filter(s)
		N/A	• Is this pharmacy bulk? (Go to 1.14.1.4)
		Comments	

Copy and Paste Bacterial Retention Filter Validation table – not applicable

Controls of Excipients (Inactive Ingredients) – N/A as Reactivation Supplement			
*		N/A	Source of Inactive Ingredients Identified
		Comments	
3.2.P.4	3.2.P.4.1		Specifications
		N/A	1. Testing specifications (including identification and characterization)
		N/A	2. Supplier's COA (specifications and test results)
		Comments	
	3.2.P.4.2	N/A	Analytical Procedures
		Comments	
	3.2.P.4.3	N/A	Validation of Analytical Procedures
		Comments	
	3.2.P.4.4		Justification of Specifications (as applicable)
		N/A	1. Applicant COA
		Comments	

Controls of Drug Product - N/A as Reactivation Supplement													
3.2.P.5	3.2.P.5.1	N/A	Specification(s)										
		Comments											
	3.2.P.5.2	N/A	Analytical Procedures										
		Comments											
	3.2.P.5.3	N/A	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))										
		N/A	Finished Dosage Form										
		Comments											
	3.2.P.5.4	N/A	Batch Analysis Certificates of Analysis for Finished Dosage Form Lot numbers and strength of Drug Products List of lot numbers and strength of drug products										
		Comments											
	3.2.P.5.5	N/A	Characterization of Impurities All potential degradation products should be listed in a tabular format as given below:										
			<table border="1"> <thead> <tr> <th>IUPAC Chemical Name</th> <th>Code #</th> <th>Chemical Structure</th> <th>Degradation Product</th> <th>Source/ Mechanism</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	IUPAC Chemical Name	Code #	Chemical Structure	Degradation Product	Source/ Mechanism					
IUPAC Chemical Name	Code #	Chemical Structure	Degradation Product	Source/ Mechanism									
		http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf											
		Comments											

3.2.P.5.6	Justification of Specifications (Provide data in tabular format):							
	N/A 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 (%)	
N/A 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/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf								
Comments								

3.2.P.7	Container Closure System - N/A as Reactivation Supplement							
	N/A	1. Summary of Container/Closure System (data should be provided for each resin)						
	N/A	2. Components Specification and Test Data						
	N/A	3. Packaging Configurations and Sizes						
	N/A	4. Container/Closure Testing (recommended additional testing for all plastic)						
	N/A	a. Solid Orals: water permeation, light transmission						
	N/A	b. Liquids: leachables, extractables, light transmission						
N/A	i. Injectables with rubber stoppers: extractables							
N/A	5. Source of supply and suppliers address							
Comments								

Stability - N/A as Reactivation Supplement							
3.2.P.8.1	Stability Summary and Conclusion (Finished Dosage Form)						
	N/A	1. Stability Protocol Submitted					
3.2.P.8.2	2. Expiration Dating Period for Marketed Packaging Expiration date						
	3. Expiration Dating Period for Bulk packaging (if applicable) Expiration date						
Comments							
3.2.P.8	Post-Approval Stability Protocol and Stability Commitment						
	N/A	1. Post-Approval Protocol and Commitment from Applicant					
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120979.pdf							
Comments							
3.2.P.8.3	Stability Data (Refer to the Final Guidance for Industry ANDAs: Stability Testing Drug Substances and Products, dated June 2013)						
	N/A	1. 3 batches?					
	N/A	a. Two API lots used? (provide the page number in the EBR that identifies the API lot in the comment box below)					
	N/A	b. All presentations of container closure systems amongst the 3 batches?					
	N/A	2. Additional stability data to support additional API sources (if applicable)					
	N/A	3. Data- At minimum, 6 months and 3 time points					
	N/A	a. Accelerated					
N/A	1. Significant change occurred						

	N/A	2. If yes, 6 months intermediate stability data
	N/A	b. Long term storage (Room Temperature)
	N/A	4. Batch numbers on stability records the same as the test batch
		5. Stability study initiated
	N/A	a. Accelerated
	N/A	b. Intermediate (if applicable)
	N/A	c. Long Term
		6. Date stability sample removed from stability chamber for each testing time point
	N/A	a. Accelerated
	N/A	b. Intermediate (if applicable)
	N/A	c. Long Term
	N/A	7. For liquid and semi-solid products, upright and inverted/horizontal storage orientation
Comments		

Copy and paste screenshot to show 2 APIs were used. (If the applicant provides a table to show that they have used at least 2 APIs for the 3 batches, this can be provided. If not, the API batch map tool should be used and a copy should be provided.)

Copy and paste the 180 Day Calculation indicating the date after 180 days from the stability start date.
<http://cdsogd1/test/180days.asp> (The 180 Days button must be used. The 6 month button should NOT be used.) If different batches have different start dates, a screenshot of each calculation should be provided.

3.2.R REGIONAL INFORMATION - N/A as Reactivation Supplement

21 CFR §314.50(d)(1)(ii)(b)

REGIONAL INFORMATION (DRUG PRODUCT)

3.2.R.P Drug Product	3.2.R.1.P	<p>1. Executed Batch Records</p> <p>N/A Copies of Executed Batch Records with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures)</p> <p>(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 Final Guidance for Industry ANDAs: <i>Stability Testing Drug Substances and Products, Questions and Answers</i>. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM366082.pdf)</p> <p>a. Two (2) Pilot Scales and one (1) small scale OR</p> <p>b. Three (3) Pilot scales</p>
		Comments
		<p>N/A Batch Reconciliation and Label Reconciliation</p> <p>a. Theoretical Yield Theoretical Yield</p> <p>b. Actual Yield Actual Yield</p> <p>c. Packaged Yield Packaged Yield</p>
		Comments
		<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>N/A a. Bulk Package Label (1.14.1)</p> <p>N/A b. Bulk Package Stability (3.2.P.8)</p> <p>N/A 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months</p> <p>N/A 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months</p> <p>N/A c. Bulk Package Container and Closure information (3.2.P.7)</p>
		Comments
		<p>N/A Information on Components</p> <p><i>Name(s) and Address(es) of the Active Pharmaceutical Ingredient (API), inactive ingredient(s), and containers and closures in tabular format. Hyperlinks are sufficient.</i></p>
		Comments
		<p>N/A Methods Validation Package</p> <p>Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)</p>
		Comments
3.2.R.3.P		

MODULE 5: CLINICAL STUDY REPORTS - N/A as Reactivation Supplement

5.2	<p>N/A Tabular Listing of Clinical Studies http://www.fda.gov/ucm/groups/fdagov-public/%40fdagov-drugs-gen/documents/document/ucm073290.pdf</p> <p>Comments</p>
5.3	<p>Bioavailability/Bioequivalence</p> <p>1. Formulation data same?</p> <p>N/A a. Comparison of all Strengths (proportionality of multiple strengths)</p> <p>N/A b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v))</p> <p>2. Lot Numbers and strength of Products used in BE Study(ies) Lot numbers and strengt</p> <p>3. In-Vivo PK study(ies)</p> <p>4. In-Vivo BE study(ies) with Clinical Endpoint(s)</p> <p>5. In-Vivo BE study(ies) with PD endpoints (pilot and pivotal vasoconstrictor)</p> <p>6. In-Vitro Binding study(ies)</p> <p>7. Nasal Products</p> <p>8. BCS</p> <p>(Continue with the appropriate study type box below)</p> <p>Comments</p>
Study Type	<p>MISCELLANEOUS</p> <p>N/A 1. Quantitative capsule rupture testing (liquid-filled capsule products)</p> <p>N/A a. Study Report</p> <p>N/A 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>N/A c. Apparatuses and the respective parameters as recommended per the drug product specific guidance</p> <p>N/A 2. In-vitro release tests (specifically for Acyclovir ointment and some Ophthalmic Susp)</p> <p>N/A a. 90% CI within 75-133% for 8th and 29th (first stage)</p> <p>N/A b. 90% CI within 75-133% for 100th and 215th (second stage, if first stage failed)</p> <p>N/A c. Study Report</p> <p>N/A d. Chromatograms/Histograms</p> <p>N/A e. Raw Data</p> <p>N/A 3. In-vitro comparative physicochemical data</p> <p>N/A 4. In-vitro microbial kill test</p>

Effective as of January 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>

EASILY CORRECTABLE DEFICIENCY

sANDA 062055 / S-034

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: ANI Pharmaceuticals, Inc.

TEL: [REDACTED] (b) (6)

ATTN: Ellen Camos

EMAIL: ellen.camos@anipharmaceuticals.com

FROM: Hyon J. Kim

FDA CONTACT EMAIL: Hyon.Kim@fda.hhs.gov

Dear Ms. Camos:

This communication is in reference to your supplemental abbreviated new drug application (sANDA) dated December 22, 2016, 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.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 13349738**

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

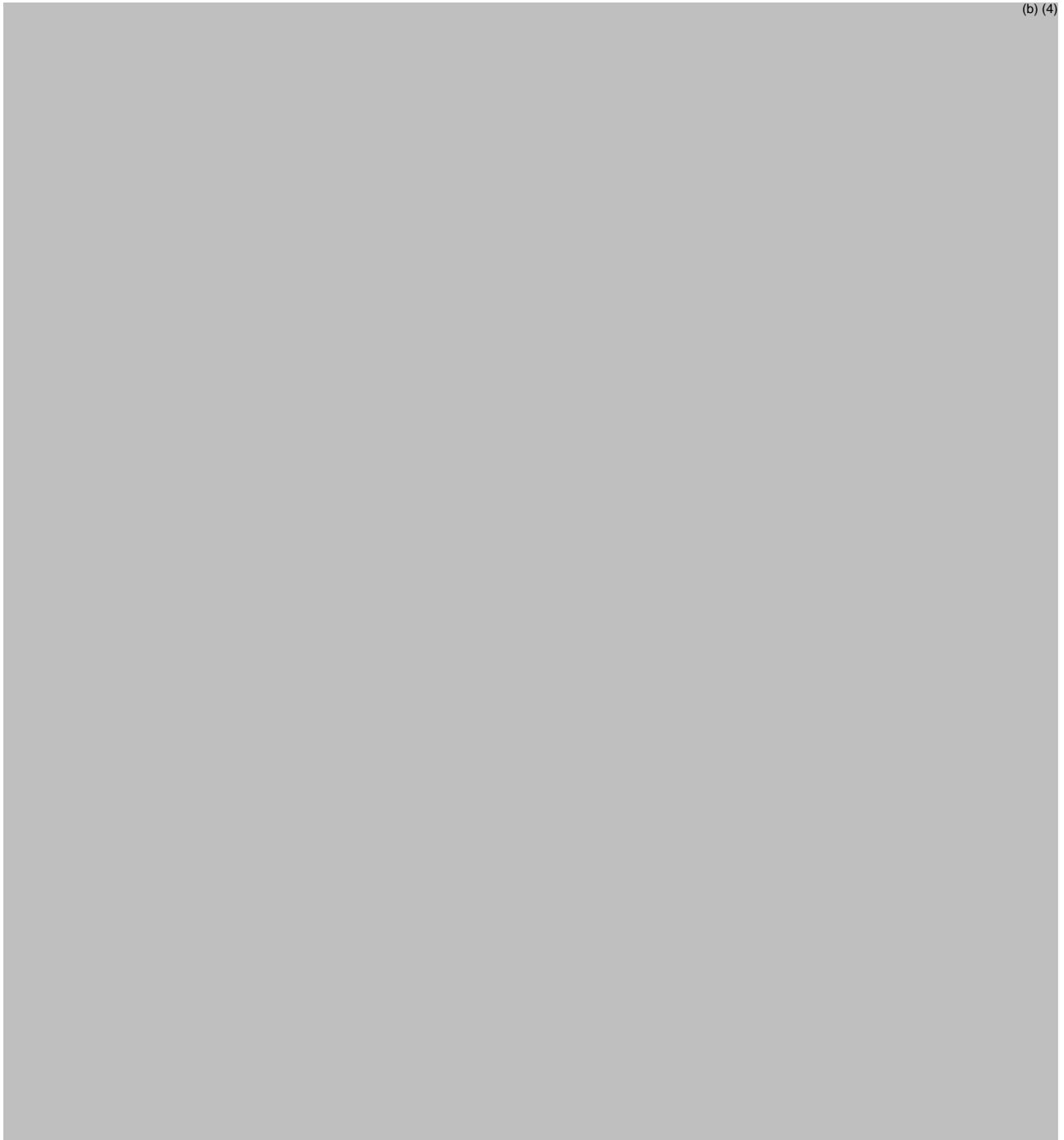
If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING:

1. Please update CLINICAL PHARMACOLOGY, Microbiology subsection and REFERENCES section as follows:



(b) (4)

2. Revise “µg” to read “mcg” throughout the text, including the tables.
3. INDICATIONS AND USAGE
Please revise “erythromycin ethylsuccinate” to read “erythromycin ethylsuccinate for oral suspension, USP” when the text makes reference to the established name of your drug product.
4. PRECAUTIONS – Geriatric Use

(b) (4)

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

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

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

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

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

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Hyon J. Kim, at Hyon.Kim@fda.hhs.gov.

Sincerely,

Hyon J. Kim -S

Digitally signed by Hyon J. Kim -S
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ou=FDA, ou=People, cn=Hyon J. Kim -S,
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Date: 2017.02.24 12:52:24 -05'00'

Hyon J. Kim, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



ANDA 062055/S-034

**ACKNOWLEDGMENT
PRIOR APPROVAL SUPPLEMENT**

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 53326
Attention: Ellen Camos
Vice President of Regulatory Affairs

Dear Madam:

We acknowledge receipt of your supplemental abbreviated new drug application (sANDA) dated December 22, 2016 submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5mL.

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA). The GDUFA goal date for review of this supplement is June 21, 2017. If this supplement does require an inspection, the goal date is October 21, 2017.

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

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

If you have any questions, contact Lisa Oh, Regulatory Project Manager, at (240) 402-3690.

Sincerely,

Lisa E. Oh -S

Digitally signed by Lisa E. Oh -S
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ou=People, cn=Lisa E. Oh -S,
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Lisa Oh
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration