CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 061667Orig1s026

Name: Vancomycin Hydrochloride for Oral Solution, USP, 250 mg (base)/5 mL

Sponsor: ANI Pharmaceuticals, Inc.

Approval Date: June 20, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

APPROVAL LETTER

ANDA 061667/S-026

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 September 27, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Vancocin (Vancomycin Hydrochloride for Oral Solution, USP), 250 mg (base)/5 mL.

Reference is also made to the complete response letter issued by this office on March 8, 2019, and to any amendments thereafter.

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

- Reformulation of the drug product.
- Qualification of new API source.
- Qualification of new manufacturing and testing facilities.
- New drug product container closure system.
- Revision of drug product storage condition.

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 506I 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 506I(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 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

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

Sincerely yours,

{See appended electronic signature page}

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

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

Sarah Kurtz

Digitally signed by Sarah Kurtz
Date: 6/20/2019 09:03:04AM
GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

OTHER ACTION LETTERS

ANDA 061667/S-026

COMPLETE RESPONSE

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 September 27, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Vancocin® (Vancomycin Hydrochloride for Oral Solution USP), 250 mg base/5 mL.

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

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

- Reformulation of the drug product.
- Qualification of new API source.
- Qualification of new manufacturing and testing facilities.
- New drug product container closure system.
- Revision of drug product storage condition.

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. (b) (4)

2.

3. (b) (4)

4.

BIOEQUIVALENCE

The Office of Bioequivalence assessed your newly proposed formulation, however, the proposed level of (b) (4) flavor, (b) (4) Mixed Berry (b) (4) could not be appropriately evaluated at this time as the compositional breakdown of (b) (4) flavor was not provided. Please provide the quantitative compositional breakdown for (b) (4) Mixed Berry (b) (4)

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.

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.

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 **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY/BIOEQUIVALENCE

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

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

simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

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

If you have any questions, call Sarah Nguyen, Regulatory Project Manager, Division of Project Management, at (240) 402 - 8731.

Sincerely yours,

{See appended electronic signature page}

For Aaron W. Sigler, PharmD, BCPS, PMP, CPH
CAPT, USPHS
Acting Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

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

Andrew Kim

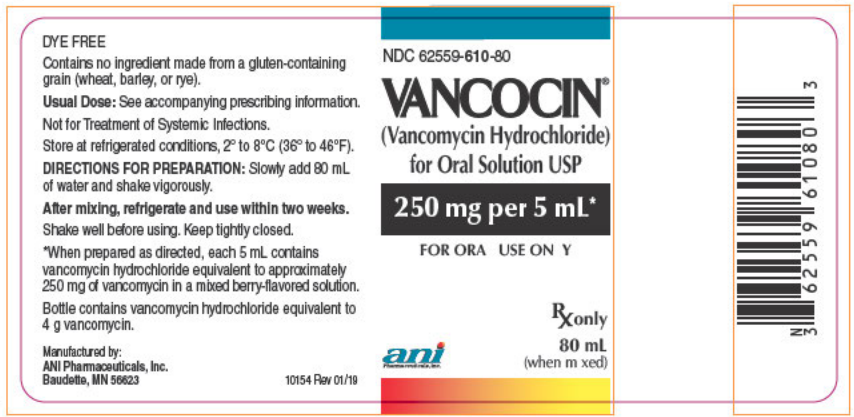
Digitally signed by Andrew Kim
Date: 3/08/2019 08:04:07PM
GUID: 508da70600028aaa57d6fc4456bcd799

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

LABELING



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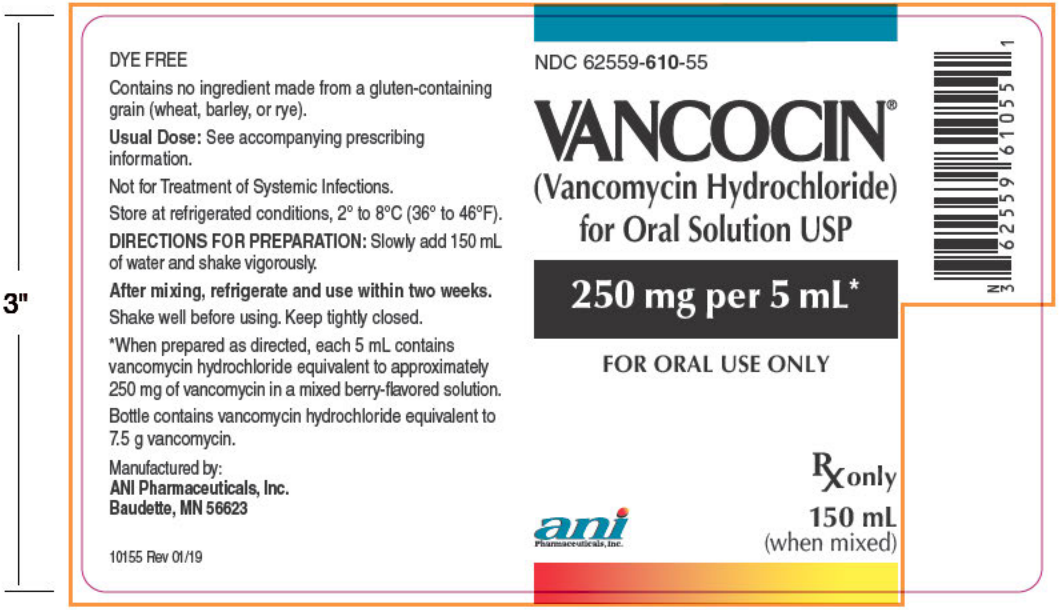
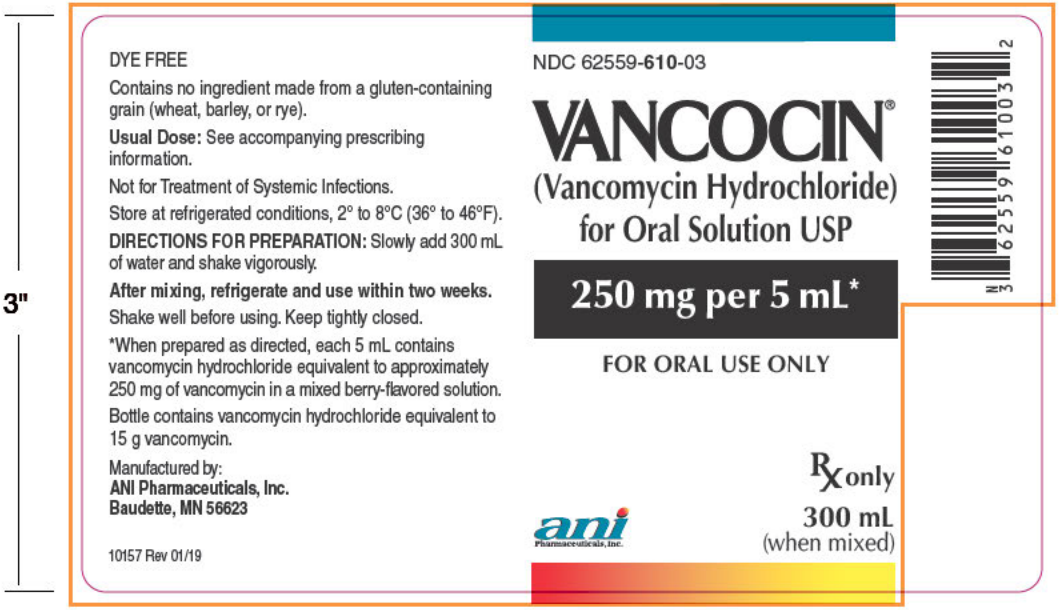


Label size: 3" x 5"

(b) (4)



Label size: 3" x 5"

(b) (4)

VANCOCIN®
Vancomycin Hydrochloride for Oral Solution USP

Rx only

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

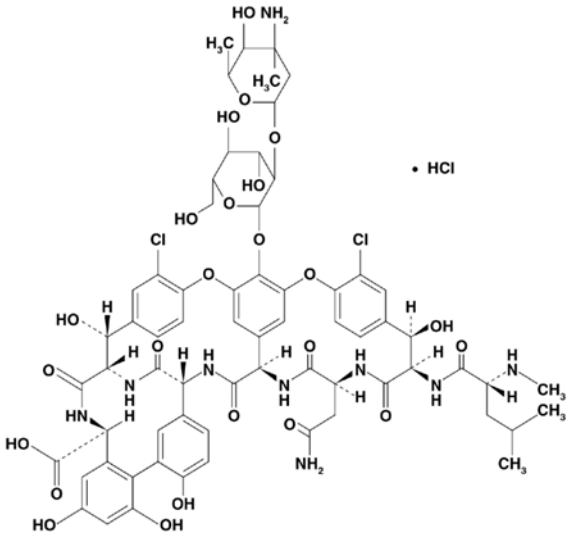
This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancocin must be given orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Orally administered Vancocin is not effective for other types of infection.

Parenteral administration of Vancocin is not effective for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *C. difficile.* If parenteral vancomycin therapy is desired, use an intravenous preparation of vancomycin and consult the package insert accompanying that preparation.

DESCRIPTION

Vancocin® (Vancomycin Hydrochloride) for Oral Solution USP contains chromatographically purified vancomycin hydrochloride USP, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24}$•HCl. The molecular weight of vancomycin hydrochloride is 1,485.73; 500 mg of the base is equivalent to 0.34 mmol.

Vancomycin hydrochloride has the following structural formula:



Vancocin (Vancomycin Hydrochloride) for Oral Solution USP is intended for reconstitution with water. Each 5 mL of reconstituted solution contains vancomycin hydrochloride equivalent to 250 mg (0.17 mmol) vancomycin.

Inactive ingredients: citric acid anhydrous, sodium benzoate, sucralose, and mixed berry flavor. Contains no ingredient made from a gluten-containing grain (wheat, barley or rye).

CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. In anephric patients with no inflammatory bowel disease, blood concentrations of vancomycin were barely measureable (0.66 μg/mL) in 2 of 5 subjects who received 2 g of Vancocin for Oral Solution daily for 16 days. No measurable blood concentrations were attained in the other 3 subjects. With doses of 2 g daily, very high concentrations of drug can be found in the feces (>3,100 mg/kg) and very low concentrations (<1 μg/mL) can be found in the serum of patients with normal renal function who have pseudomembranous colitis. Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. After multiple-dose oral administration of vancomycin, measurable serum concentrations may infrequently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.

Microbiology

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

NOTE: The oral form of vancomycin is effective only for the infections noted in the **INDICATIONS AND USAGE** section. The oral form is ***not*** effective for any other type of infection.

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

Aerobic gram-positive microorganisms
Staphylococcus aureus (including methicillin-resistant strains) associated with enterocolitis

Aerobic gram-positive microorganisms
Clostridium difficile antibiotic-associated pseudomembranous colitis

INDICATIONS AND USAGE

Vancocin for Oral Solution is administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Parenteral administration of Vancocin is not effective for the above indications; therefore, Vancocin must be given orally for these infections. **Orally administered Vancocin is not effective for other types of infection.**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancocin and other antibacterial drugs, Vancocin 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.

CONTRAINDICATIONS

Vancocin is contraindicated in patients with known hypersensitivity to vancomycin.

PRECAUTIONS

General

Significant systemic absorption has been reported in some patients (e.g., patients with renal insufficiency and/or colitis) who have taken multiple oral doses of vancomycin hydrochloride for *C. difficile*-associated diarrhea. In these patients, serum vancomycin concentrations reached therapeutic levels for the treatment of systemic infections. Some patients with inflammatory disorders of the intestinal mucosa also may have significant systemic absorption of vancomycin. These patients may be at risk for the development of adverse reactions associated with higher doses of vancomycin oral solution; therefore, monitoring of serum concentrations of vancomycin may be appropriate in some instances, e.g., in patients with renal insufficiency and/or colitis or in those receiving concomitant therapy with an aminoglycoside antibacterial drug.

Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) has occurred following oral vancomycin hydrochloride therapy in randomized controlled clinical trials, and can occur either during or after completion of therapy. The risk of nephrotoxicity is increased in patients over 65 years of age.

In patients over 65 years of age, including those with normal renal function prior to treatment, renal function should be monitored during and following treatment with vancomycin oral solution to detect potential vancomycin induced nephrotoxicity.

Ototoxicity has occurred in patients receiving Vancocin. It may be transient or permanent. It has been reported mostly in patients who have been given excessive intravenous doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

Use of vancomycin may result in the overgrowth of non-susceptible bacteria. If superinfection occurs during therapy, appropriate measures should be taken.

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

Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or intravitreal route have not been established by adequate and well-controlled studies. Vancomycin is not indicated for prophylaxis of endophthalmitis.

Information for Patients

Patients should be counseled that antibacterial drugs including Vancocin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Vancocin 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 Vancocin or other antibacterial drugs in the future.

Pregnancy

Animal reproduction studies have not been conducted with Vancocin. It is not known whether Vancocin can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin on infants were evaluated when the drug was administered intravenously to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancocin was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to Vancocin was noted. One infant whose mother received Vancocin in the third trimester experienced conductive hearing loss that was not attributed to the administration of Vancocin. Because the number of patients treated in this study was limited and Vancocin was administered only in the second and third trimesters, it is not known whether Vancocin causes fetal harm. Vancocin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Vancomycin is excreted in human milk based on information obtained with the intravenous administration of vancomycin. However, systemic absorption of vancomycin is very low following oral administration of Vancocin for Oral Solution (see **CLINICAL PHARMACOLOGY**). It is not known whether oral vancomycin is excreted in human milk, as no studies of vancomycin concentration in human milk after oral administration have been done. Caution should be exercised when Vancocin is administered to a nursing woman.

Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use

In clinical trials, 54% of vancomycin hydrochloride-treated subjects were > 65 years of age. Of these, 40% were between the ages of > 65 and 75, and 60% were > 75 years of age.

Clinical studies with vancomycin hydrochloride in *C. difficile*-associated diarrhea have demonstrated that geriatric subjects are at increased risk of developing nephrotoxicity following treatment with oral vancomycin hydrochloride, which may occur during or after completion of therapy. In patients over 65 years of age, including those with normal renal function prior to treatment, renal function should be monitored during and following treatment with vancomycin hydrochloride to detect potential vancomycin induced nephrotoxicity.

Patients over 65 years of age may take longer to respond to therapy compared to patients 65 years of age and younger. Clinicians should be aware of the importance of appropriate duration of vancomycin hydrochloride treatment in patients over 65 years of age and not discontinue or switch to alternative treatment prematurely.

ADVERSE REACTIONS

Nephrotoxicity

Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) occurred in 5% of subjects treated with vancomycin hydrochloride. Nephrotoxicity following vancomycin hydrochloride typically first occurred within one week after completion of treatment (median day of onset was Day 16). Nephrotoxicity following vancomycin hydrochloride occurred in 6% of subjects over 65 years of age and 3% of subjects 65 years of age and younger. Nephrotoxicity can also occur during oral vancomycin administration.

The incidences of hypokalemia, urinary tract infection, peripheral edema, insomnia, constipation, anemia, depression, vomiting, and hypotension were higher among subjects over 65 years of age than in subjects 65 years of age and younger.

Discontinuation of study drug due to adverse events occurred in 7% of subjects treated with vancomycin hydrochloride. The most common adverse events leading to discontinuation of vancomycin hydrochloride were *C. difficile* colitis (< 1%), nausea (< 1%), and vomiting (< 1%).

Ototoxicity

Cases of hearing loss associated with intravenously administered vancomycin have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Hematopoietic

Reversible neutropenia, usually starting 1 week or more after onset of intravenous therapy with vancomycin or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when Vancocin is discontinued. Thrombocytopenia has rarely been reported.

Miscellaneous

Anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis have been reported in association with the administration of Vancocin.

A condition has been reported that is similar to the IV-induced syndrome with symptoms consistent with anaphylactoid reactions, including hypotension, wheezing, dyspnea, urticaria, pruritus, flushing of the upper body ("Red Man Syndrome"), pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours.

OVERDOSAGE

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

For current information on the management of overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

DOSAGE AND ADMINISTRATION

Adults

Oral Vancocin is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and staphylococcal enterocolitis. Vancocin is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.

Pediatric Patients

The usual daily dosage is 40 mg/kg in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g.

PREPARATION AND STABILITY

Mix the contents of the bottle with water as directed below. When reconstituted, each 5 mL contains approximately 250 mg of vancomycin. These mixtures may be kept for two weeks in a refrigerator without significant loss of potency.

Directions for mixing Vancocin (Vancomycin Hydrochloride) for Oral Solution USP:

80 mL – Slowly add 80 mL water and shake vigorously.

150 mL – Slowly add 150 mL water and shake vigorously.

300 mL – Slowly add 300 mL water and shake vigorously.

The appropriate oral solution dose may be diluted in 1 oz of water and given to the patient to drink. The diluted material may be administered via nasogastric tube.

HOW SUPPLIED

Vancocin® (Vancomycin Hydrochloride) for Oral Solution USP equivalent to 250 mg per 5 mL vancomycin is available as:

80 mL bottle (4 g*)	NDC 62559-610-80
150 mL bottle (7.5 g*)	NDC 62559-610-55
300 mL bottle (15 g*)	NDC 62559-610-03

* Equivalent to vancomycin

Store at refrigerated conditions, 2° to 8°C (36° to 46°F).
After mixing, refrigerate and use within two weeks. Shake well before using. Keep tightly closed.

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

ani Pharmaceuticals, Inc.

10158 Rev 01/19

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

LABELING REVIEWS

***** This document contains proprietary information that cannot be released to the public***v.41**

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	2/5/2019
Review Cycle Number	2
ANDA(s) and Supplement Number(s)	061667/S-026
Applicant Name	ANI Pharmaceuticals, Inc.
Proprietary Name, Established Name, and Strength(s) [Add "(OTC)" after strength if applicable]	Vancomycin Hydrochloride for Oral Solution, USP 250 mg per 5 mL
Current Received Date	1/24/2019
Previous Received Date(s) of Proposed Supplement	9/27/2018
Primary Labeling Reviewer	Oluwakemi O. Odesina
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ ACCEPTABLE - No Comments.

☐ ACCEPTABLE - Include Post approval comments.

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

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

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

On Policy Alert List ☒ Yes ☐ No

Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

☐ **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
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

1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS	
Are there any pending issues in DLR's SharePoint Drug Facts? If Yes, please explain: Title: Vancomycin Hydrochloride for Oral Solution Template Date: 2/5/2019 Is this a Review? ☐ What Type of File? Template Attachments: DAIP Consult Response.pdf; Vancocin Oral Solution Final Template rev 011119.pdf Hyperlink to Review: No hyperlink inserted Active Ingredient: Vancomycin Dosage Forms: Oral Suspension Manufacturer: Brief Description: DLR developed a template in collaboration with OND/DAIP to update the labeling for Vancomycin Oral Solution to ensure that it provides for the safe and effective use of the drug product. This template is specific to ANI's ANDA 061667 which was originally approved in 1972 as an abbreviated antibiotic application (AADA) pursuant to Form-6 procedures and has historically made labeling updates independent of an RLD.	**YES**
Is the drug product listed in the Policy Alert Tracker on DLRS SharePoint? If Yes, please explain: S/E Determina **Determine whether original ANDA 061667 was withdrawn from the market for reasons of safety or** **effectiveness.** **No Approval Actions (AP/TA) can be taken prior** **to final S/E Determination** **All disciplines can continue communications** **(CRL, CC/IR/DRL)**	**YES**

<table>
<tr><td>This request has been expedited per pending applications.</td><td></td></tr>
<tr><td>Is the drug product listed on the Susceptibility Test Interpretive Criteria web page?
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm

We note per the web page:

<table><tr><td>Vancomycin*</td><td>Oral</td><td>No</td><td>No</td><td>12/13/17</td></tr></table>
*No STIC are recognized by FDA for this drug at this time.</td><td>Yes, and applicant has not updated labeling referencing website.</td></tr>
<tr><td colspan="2">Reason for Submission:

1/24/2019 Amendment:

The below comments are from the C1 labeling review based on the submission dated 9/27/2018

b. R
“
H

As
lab</td></tr>
</table>

c. **Revise the principal display panel (PDP) to ensure that the manufacturer name and logo does not compete in size and prominence with the presentation of the proprietary and established name**

In order to not compete with the proprietary and established name, the size of the ANI Pharmaceuticals Inc. logo was decreased on all three labels. Additionally, on the 80 mL label, the manufacturer name and address were relocated to the bottom of the left side panel.

d. **Remove the equivalency statement (i.e. "Equivalent to…Vancomycin") that presently appears on the (PDP). Instead, add an asterisk after the expression of the strength (e.g. 250 mg per 5 mL*)**

As requested, the equivalency statement on the principal display panel was removed and an asterisk was added to the product strength designation.

e. **Place an asterisk prior to the equivalency statement on the side panel**

To avoid duplication that would be caused by adding a separate equivalency statement, an asterisk was placed prior to the current equivalency statement "When prepared as directed, each 5 mL contains vancomycin hydrochloride equivalent to approximately 250 mg of vancomycin in a mixed berry-flavored solution."

Please refer to the Labeling Summary Table for links to the container labels incorporating these revisions.

2. **PRESCRIBING INFORMATION**

Revise your prescribing information in accordance with the attached template

The prescribing information (PI) was revised in accordance with the provided template. Any revisions in addition to those included in the template are annotated. Please refer to the Labeling Summary Table that follows for location of the revised PI within this amendment.

We note that the Applicant has made the requested revisions; we find it acceptable.

9/27/2018 Original Submission:

We note that the Applicant is proposing a re-formulation of the previously approved drug product:

The approved drug product, originally owned by Eli Lilly under this ANDA 061667, was essentially a sterile, lyophilized active ingredient (Vancomycin HCl) with EDTA in a glass vial. Eli Lilly utilized the same injectable product approved under ANDA 060180 and directly marketed it for different indications as a powder for oral solution under ANDA 061667 in order to fulfill an unmet patient need. The changes being proposed to the drug product are targeted to provide an orally administered vancomycin in solution that would not only improve the marketability of the drug, but it would also increase patient acceptability through taste masking and improved palatability. This included a desire to move to a non-sterile powder for solution in a plastic bottle, as well as a 'reformulation' by adding excipients that would improve the flavor. Although the reformulation consisted of considerations for improved patient palatability, excipients were carefully selected in specific quantities as to not affect the local availability of vancomycin in the GI tract, while ensuring a stable drug product throughout its proposed shelf life.

ANI is also proposing to add three new container sizes to this strength: 80 mL, 150 mL and 300 mL. The proposal of these three new sizes are more favorable to the dosing and administration of this product. The addition of these three new container sizes to this ANDA is in accordance with the *Guidance for Industry: Variations in Drug Products that May be Included in a Single ANDA (1998)* ("Single ANDA Guidance"). Various container sizes can be submitted within the same ANDA when intended to be used for the same route of administration and for the same indications. The qualification of various container sizes for the same drug product is also supported by the Changes Guidance, Section IX.D.3.

Cover Letter
(SN0010_ 2018-09-27_

Is this supplement combined with another discipline?	**YES**
Is this product an OTC product?	**NO**
Is this ANDA the RLD?	**YES (see table 3)**

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				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	Bottles of 80 mL, 150 mL and 300 mL (when mixed)	1/24/2019	Satisfactory
Blister	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
(Other – specify)	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 2 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	10158 Rev 01/19	1/24/2019	Satisfactory
Medication Guide	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

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, Patient Labeling, and Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)
☐ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☒ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** We note that the last approved labeling for the subject ANDA is S-023 approved on 9/9/1997. We note that the subject ANDA was originally approved in 1972 as an abbreviated antibiotic application (AADA) pursuant to Form -6 procedures and has historically made labeling updates independent of an RLD. OGD/DLR developed a template, in collaboration with OND/DAIP, to update the Applicant's proposed labeling to ensure that it provides for the safe and effective use of the drug product. The template is used as the model labeling for this review    Vancocin Oral Solution Final Templat    Consult Request Form ANDA 061667S( DAIP Consult Response.pdf
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the NDA listed in the discontinued section of the Orange Book? **N/A**
If yes, then comment below regarding the current model labeling.

Comment:

We note that the last approved labeling for the subject ANDA is S-023 approved on 9/9/1997. We note that the subject ANDA was originally approved in 1972 as an abbreviated antibiotic application (AADA) pursuant to Form -6 procedures and has historically made labeling updates independent of an RLD.

2.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/5/2019.

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 (061667) 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)

The USP was searched on 2/5/2019.

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
Currently Official	YES		Vancomycin Hydrochloride for Oral Solution	ADDITIONAL REQUIREMENTS •Packaging and Storage: Preserve in tight containers.
Not Yet Official	Click here to enter text.	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labels/labeling? **NO**

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 were requested and were the changes addressed?**
S-023	9/9/1997	NA We note that we were unable to obtain an electronic version of the last labeling review; due to the length of time since the last approved supplement, we will defer the evaluation of this section at this time. We will rely on the Applicant's provided annotated labeling for the evaluation of Sec 3.1.3
Are there any Pending Labeling Supplements for this ANDA that impact labeling? NO		
Pending 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:

- We note that the Applicant is proposing a re-formulation of the drug product and has submitted revised container labels to that effect; we find them acceptable.

- We note that a gluten-free statement appears on the side panel of the Applicant's proposed labeling; we find it acceptable:

- [Note to reviewer: As per the Gluten in Drug Products and Associated Labeling Recommendations Guidance for Industry, the Agency recommends that drug manufacturers that wish to make statements about gluten anywhere on oral drug product labels or in required labeling use the following statement, when it is truthful and substantiated: "Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)." Please refer to the Guidance at the link provided above for the recommended locations where the statement should be included.

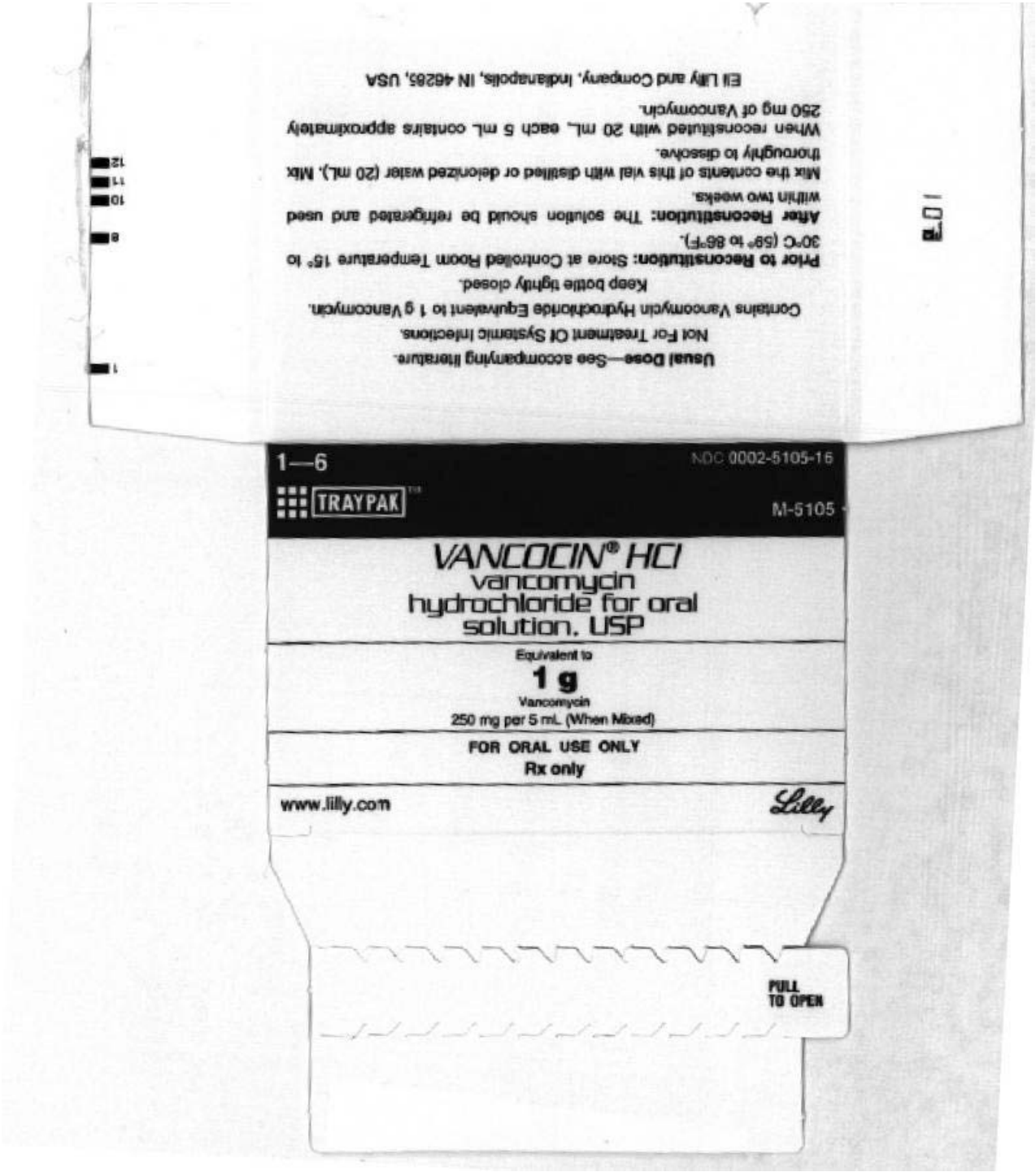
3.1.1 MODEL CONTAINER LABELS

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

Model container/carton/blister labels [Source: See below]

*Although we note that the subject ANDA was approved based pursuant to AADA Form 6 application; we will use both the last approved ANDA labeling (provided by Applicant in Annotated Draft Labeling) as well as the labeling for the only comparable NDA product (for reference purposes FIRVANQ, NDA 208910/S-000 approved 01/26/2018)

Note: Best available copy of previous approved labeling was used for annotation.


1—6
NDC 0002-5105-16
TRAYPAK
M-5105
VANCOCIN® HCl
vancomycin
hydrochloride for oral
solution, USP
Equivalent to
1 g
Vancomycin
250 mg per 5 mL (When Mixed)
FOR ORAL USE ONLY
Rx only
www.lilly.com
Lilly
PULL
TO OPEN
Usual Dose—See accompanying literature.
Not For Treatment Of Systemic Infections.
Contains Vancomycin Hydrochloride Equivalent to 1 g Vancomycin.
Keep bottle tightly closed.
Prior to Reconstitution: Store at Controlled Room Temperature 15° to 30°C (59° to 86°F).
After Reconstitution: The solution should be refrigerated and used within two weeks.
Mix the contents of this vial with distilled or deionized water (20 mL). Mix thoroughly to dissolve.
When reconstituted with 20 mL, each 5 mL contains approximately 250 mg of Vancomycin.
Eli Lilly and Company, Indianapolis, IN 46285, USA


FIRVANQ™
(vancomycin hydrochloride) for oral solution
Vancomycin 25 mg/mL
Each bottle contains Vancomycin Hydrochloride USP, powder for oral solution, equivalent to
3.75 g Vancomycin
When reconstituted, each mL contains:
Vancomycin Hydrochloride, USP equivalent to 25 mg Vancomycin
Must be reconstituted before dispensing
MUST BE REFRIGERATED
Pharmacist: Use this bottle for dispensing after reconstitution; contents must be used within 14 days, discard if hazy.
150 mL final volume after reconstitution
MANUFACTURED BY:
CUTISPHARMA®
WILMINGTON, MA 01887 USA
℞ ONLY
3 65628 20405 7
LOT: XXXXXX
EXP: XX/XX
R00


FIRVANQ™
(vancomycin hydrochloride) for oral solution
Vancomycin 25 mg/mL
Each bottle contains Vancomycin Hydrochloride USP, powder for oral solution, equivalent to
7.5 g Vancomycin
When reconstituted, each mL contains:
Vancomycin Hydrochloride, USP equivalent to 25 mg Vancomycin
Must be reconstituted before dispensing
MUST BE REFRIGERATED
Pharmacist: Use this bottle for dispensing after reconstitution; contents must be used within 14 days, discard if hazy.
300 mL final volume after reconstitution
MANUFACTURED BY:
CUTISPHARMA®
WILMINGTON, MA 01887 USA
℞ ONLY
3 65628 20510 8
LOT: XXXXXX
EXP: XX/XX
R00

3.1.2 RX PRESCRIBING INFORMATION, PATIENT LABELING, & DRUG FACTS LABELING (OTC)

Reviewer Assessment:

Was labeling submitted in this supplement? **YES**
Are the Prescribing Information or Drug Facts Labeling (OTC) 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).
Are the specific requirements for format met under 21 CFR 201.57 (new), or 201.80 (old), or 201.66 (OTC)? **YES**

Comment:

Acceptable.

3.1.3 DESCRIPTION, HOW SUPPLIED, MANUFACTURED, DISTRIBUTED, AND/OR PACKED BY STATEMENT

[For OTC products, please include the inactives in Table 8; package sizes being marketed in Table 9; and drug product manufacturer/distributor/packer statement in Table 10.]

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or OTC labeling? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED section or OTC package sizes? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 8, 9, and 10.

Table 8: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 9: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 9: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		

Table 10: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**

4. SPECIAL CONSIDERATIONS

Please include other information that may pertain to your drug product application.

Oluwakemi Odesina

Digitally signed by Oluwakemi Odesina
Date: 2/05/2019 02:10:15PM
GUID: 5423006c00721f6b43db6c5df1f43327

Theresa Liu

Digitally signed by Theresa Liu
Date: 2/06/2019 11:33:43AM
GUID: 508da70a00028d58911de18a598cda6f

***** This document contains proprietary information that cannot be released to the public***v.41**

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	12/31/2018
Review Cycle Number	1
ANDA(s) and Supplement Number(s)	061667/S-026
Applicant Name	ANI Pharmaceuticals, Inc.
Proprietary Name, Established Name, and Strength(s) [Add "(OTC)" after strength if applicable]	Vancomycin Hydrochloride for Oral Solution USP 250 mg per 5 mL
Current Received Date	9/27/2018
Previous Received Date(s) of Proposed Supplement	NA
Primary Labeling Reviewer	Oluwakemi O. Odesina
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE - No Comments.

☐ ACCEPTABLE - Include Post approval comments.

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

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

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

On Policy Alert List ☐ Yes ☒ No

Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

☐ **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
2. CONTAINER LABEL
3. CARTON LABELING
4. PRESCRIBING INFORMATION
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

☒ **For combined supplement(s):**

Labeling deficiencies determined on 1/14/2018, based on your submission received on 9/27/2018

1. CONTAINER LABEL

    a. Increase the prominence of the following statement "After mixing, refrigerate and use within two weeks," which appears on the side panel by using a bold font and/or different color in order to minimize the potential for medication errors.

    b. Revise the presentation of the established name such that only the terms "Vancomycin Hydrochloride" appears in parenthesis; e.g. "(Vancomycin Hydrochloride) for Oral Solution USP"

    c. Revise the principal display panel (PDP) to ensure that the manufacturer name and logo does not compete in size and prominence with the presentation of the proprietary and established name

d. Remove the equivalency statement (i.e. “Equivalent to…Vancomycin”) that presently appears on the (PDP). Instead, add an asterix after the expression of the strength (e.g. 250 mg per 5 mL*)

e. Place an asterix prior to the equivalency statement on the side panel

2. PRESCRIBING INFORMATION

Revise your prescribing information in accordance with the attached template

Contents

1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS	
Are there any pending issues in DLR's SharePoint Drug Facts? If Yes, please explain:	**NO**
Is the drug product listed in the Policy Alert Tracker on DLRS SharePoint? If Yes, please explain:	**NO**
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? **https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm** We note per the web page: Vancomycin* | Oral | No | No | 12/13/17 *No STIC are recognized by FDA for this drug at this time.	Yes, and applicant has not updated labeling referencing website.

Reason for Submission:

We note that the Applicant is proposing a re-formulation of the previously approved drug product:

The approved drug product, originally owned by Eli Lilly under this ANDA 061667, was essentially a sterile, lyophilized active ingredient (Vancomycin HCl) with EDTA in a glass vial. Eli Lilly utilized the same injectable product approved under ANDA 060180 and directly marketed it for different indications as a powder for oral solution under ANDA 061667 in order to fulfill an unmet patient need. The changes being proposed to the drug product are targeted to provide an orally administered vancomycin in solution that would not only improve the marketability of the drug, but it would also increase patient acceptability through taste masking and improved palatability. This included a desire to move to a non-sterile powder for solution in a plastic bottle, as well as a 'reformulation' by adding excipients that would improve the flavor. Although the reformulation consisted of considerations for improved patient palatability, excipients were carefully selected in specific quantities as to not affect the local availability of vancomycin in the GI tract, while ensuring a stable drug product throughout its proposed shelf life.

ANI is also proposing to add three new container sizes to this strength: 80 mL, 150 mL and 300 mL. The proposal of these three new sizes are more favorable to the dosing and administration of this product. The addition of these three new container sizes to this ANDA is in accordance with the *Guidance for Industry: Variations in Drug Products that May be Included in a Single ANDA (1998)* ("Single ANDA Guidance"). Various container sizes can be submitted within the same ANDA when intended to be used for the same route of administration and for the same indications. The qualification of various container sizes for the same drug product is also supported by the Changes Guidance, Section IX.D.3.

 Cover Letter (SN0010_ 2018-09-27_

Is this supplement combined with another discipline?	**YES**
Is this product an OTC product?	**NO**
Is this ANDA the RLD?	**YES (see table 3)**

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				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	Bottles of 80 mL, 150 mL and 300 mL (when mixed)	9/27/2018	Revise
Blister	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
(Other – specify)	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 2 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	10158 Rev 09/18	9/27/2018	Revise
Medication Guide	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

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, Patient Labeling, and Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)
☐ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☒ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** We note that the last approved labeling for the subject ANDA is S-023 approved on 9/9/1997. We note that the subject ANDA was originally approved in 1972 as an abbreviated antibiotic application (AADA) pursuant to Form -6 procedures and has historically made labeling updates independent of an RLD. OGD/DLR developed a template, in collaboration with OND/DAIP, to update the Applicant's proposed labeling to ensure that it provides for the safe and effective use of the drug product. The template is used as the model labeling for this review Vancocin Oral Solution Final Templat Consult Request Form ANDA 061667SC DAIP Consult Response.pdf
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the NDA listed in the discontinued section of the Orange Book? **N/A**
If yes, then comment below regarding the current model labeling.

Comment:

We note that the last approved labeling for the subject ANDA is S-023 approved on 9/9/1997. We note that the subject ANDA was originally approved in 1972 as an abbreviated antibiotic application (AADA) pursuant to Form -6 procedures and has historically made labeling updates independent of an RLD.

2.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/31/2018.

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 (061667) 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)

The USP was searched on 12/31/2018.

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
Currently Official	YES		Vancomycin Hydrochloride for Oral Solution	ADDITIONAL REQUIREMENTS •Packaging and Storage: Preserve in tight containers.
Not Yet Official	Click here to enter text.	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labels/labeling? **NO**

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 were requested and were the changes addressed?**
S-023	9/9/1997	NA We note that we were unable to obtain an electronic version of the last labeling review; due to the length of time since the last approved supplement, we will defer the evaluation of this section at this time. We will rely on the Applicant's provided annotated labeling for the evaluation of Sec 3.1.3
Are there any Pending Labeling Supplements for this ANDA that impact labeling? NO		
Pending 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:

- We note that the Applicant is proposing a re-formulation of the drug product and has submitted revised container labels to that effect.

- We note that a gluten-free statement appears on the side panel of the Applicant's proposed labeling; we find it acceptable:

- [Note to reviewer: As per the Gluten in Drug Products and Associated Labeling Recommendations Guidance for Industry, the Agency recommends that drug manufacturers that wish to make statements about gluten anywhere on oral drug product labels or in required labeling use the following statement, when it is truthful and substantiated: "Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)." Please refer to the Guidance at the link provided above for the recommended locations where the statement should be included.

- We will issue the following comment to the Applicant:

CONTAINER LABEL

a. Increase the prominence of the following statement "After mixing, refrigerate and use within two weeks," which appears on the side panel by using a bold font and/or different color in order to minimize the potential for medication errors.

b. Revise the presentation of the established name such that only the terms "Vancomycin Hydrochloride" appears in parenthesis; e.g. "(Vancomycin Hydrochloride) for Oral Solution USP"

c. Revise the principal display panel (PDP) to ensure that the manufacturer name and logo does not compete in size and prominence with the presentation of the proprietary and established name

d. Remove the equivalency statement (i.e. "Equivalent to…Vancomycin") that presently appears on the (PDP). Instead, add an asterix after the expression of the strength (e.g. 250 mg per 5 mL*)

e. Place an asterix prior to the equivalency statement on the side panel

3.1.1 MODEL CONTAINER LABELS

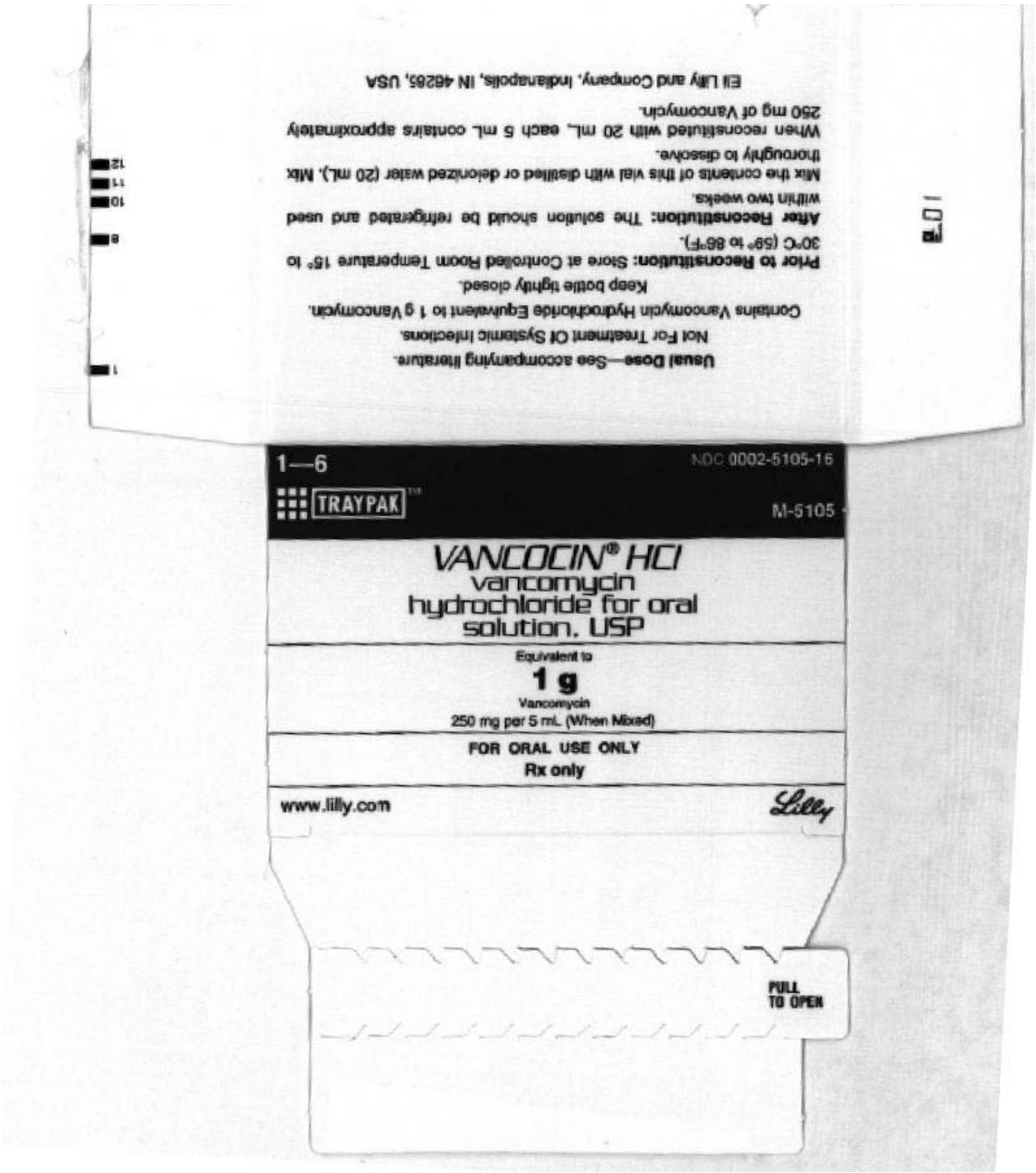
Please provide the reference listed drug labels if applicant submits container, blister, carton, etc.

Model container/carton/blister labels [Source: See below]

*Although we note that the subject ANDA was approved based pursuant to AADA Form 6 application; we will use both the last approved ANDA labeling (provided by Applicant in Annotated Draft Labeling) as well as the

labeling for the only comparable NDA product (for reference purposes FIRVANQ, NDA 208910/S-000 approved 01/26/2018)

Note: Best available copy of previous approved labeling was used for annotation.


1—6
NDC 0002-5105-16
TRAYPAK
M-5105
VANCOCIN® HCl
vancomycin
hydrochloride for oral
solution, USP
Equivalent to
1 g
Vancomycin
250 mg per 5 mL (When Mixed)
FOR ORAL USE ONLY
Rx only
www.lilly.com
Lilly
PULL
TO OPEN
Usual Dose—See accompanying literature.
Not For Treatment Of Systemic Infections.
Contains Vancomycin Hydrochloride Equivalent to 1 g Vancomycin.
Keep bottle tightly closed.
Prior to Reconstitution: Store at Controlled Room Temperature 15° to 30°C (59° to 86°F).
After Reconstitution: The solution should be refrigerated and used within two weeks.
Mix the contents of this vial with distilled or deionized water (20 mL). Mix thoroughly to dissolve.
When reconstituted with 20 mL, each 5 mL contains approximately 250 mg of Vancomycin.
Eli Lilly and Company, Indianapolis, IN 46285, USA


FIRVANQ™
(vancomycin hydrochloride) for oral solution
Vancomycin 25 mg/mL
Each bottle contains Vancomycin Hydrochloride USP, powder for oral solution, equivalent to
3.75 g Vancomycin
When reconstituted, each mL contains:
Vancomycin Hydrochloride, USP equivalent to 25 mg Vancomycin
Must be reconstituted before dispensing
MUST BE REFRIGERATED
Pharmacist: Use this bottle for dispensing after reconstitution; contents must be used within 14 days, discard if hazy.
150 mL final volume after reconstitution
MANUFACTURED BY:
CUTISPHARMA®
WILMINGTON, MA 01887 USA
℞ ONLY
3 65628 20405 7
LOT: XXXXXX
EXP: XX/XX
R00


FIRVANQ™
(vancomycin hydrochloride) for oral solution
Vancomycin 25 mg/mL
Each bottle contains Vancomycin Hydrochloride USP, powder for oral solution, equivalent to
7.5 g Vancomycin
When reconstituted, each mL contains:
Vancomycin Hydrochloride, USP equivalent to 25 mg Vancomycin
Must be reconstituted before dispensing
MUST BE REFRIGERATED
Pharmacist: Use this bottle for dispensing after reconstitution; contents must be used within 14 days, discard if hazy.
300 mL final volume after reconstitution
MANUFACTURED BY:
CUTISPHARMA®
WILMINGTON, MA 01887 USA
Rx ONLY
3 65628 20510 8
LOT: XXXXXX
EXP: XX/XX
R00

3.1.2 RX PRESCRIBING INFORMATION, PATIENT LABELING, & DRUG FACTS LABELING (OTC)

Reviewer Assessment:

Was labeling submitted in this supplement? **YES**
Are the Prescribing Information or Drug Facts Labeling (OTC) 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).
Are the specific requirements for format met under 21 CFR 201.57 (new), or 201.80 (old), or 201.66 (OTC)? **YES**

Comment:

We will issue the following comment to the Applicant:

PRESCRIBING INFORMATION

Revise your prescribing information in accordance with the attached template

3.1.3 DESCRIPTION, HOW SUPPLIED, MANUFACTURED, DISTRIBUTED, AND/OR PACKED BY STATEMENT

[For OTC products, please include the inactives in Table 8; package sizes being marketed in Table 9; and drug product manufacturer/distributor/packer statement in Table 10.]

Reviewer Assessment:

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

Table 8: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 8: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Vancocin HCl (Vancomycin Hydrochloride for Oral Solution USP) is intended for reconstitution with water. Each 5 mL of reconstituted solution contains vancomycin hydrochloride equivalent to 250 mg (0.17 mmol) (b) (4) (b) (4) vancomycin. (b) (4) (b) (4)	. Each 5 mL of reconstituted solution contains vancomycin hydrochloride equivalent to .250 mg (0.17 mmol)	Per the Applicant provided Annotated Comparision; (b) (4) We note that the Applicant has proposed the above revisions; we find it acceptable

Table 9: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
HOW SUPPLIED Vancocin® HCl for Oral Solution (or Vancomycin Hydrochloride for Oral Solution, USP) equivalent to 250 mg per 5 mL vancomycin is available asin: (b) (4) (b) (4) Equivalent to vancomycin (b) (4) Store at refrigerated conditions, 2° to 8°C (36° to 46°F). (b) (4) (b) (4) After mixing, refrigerate and use within two weeks. Shake well before using. Keep tightly closed. (b) (4)	HOW SUPPLIED Vancocin® (Vancomycin Hydrochloride for Oral Solution, USP) equivalent to 250 mg per 5 mL vancomycin is available asin: 80 mL bottle (4 g*) NDC)62559-610-80 150 mL bottle (7.5 g*) 62559-610-55 300 mL bottle (15 g*) NDC 62559-610-03 * Equivalent to vancomycin Store at refrigerated conditions, 2° to 8°C (36° to 46°F) After mixing, refrigerate and use within two weeks. Shake well before using. Keep tightly closed.	(b) (4) We note that the Applicant has proposed the above changes; we find it acceptable

Table 10: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
Literature Revised May 21, 2001 Eli Lilly and Company, Indianapolis, IN 46285, USA www.lilly.com PA 0794 AMP	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	We note that the manufacturing information has been updated to reflect to currect manufacturer, we find it acceptable

4. SPECIAL CONSIDERATIONS

Please include other information that may pertain to your drug product application.

Oluwakemi Odesina

Digitally signed by Oluwakemi Odesina
Date: 1/14/2019 11:26:32AM
GUID: 5423006c00721f6b43db6c5df1f43327

Theresa Liu

Digitally signed by Theresa Liu
Date: 1/15/2019 11:01:34AM
GUID: 508da70a00028d58911de18a598cda6f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

MEDICAL REVIEWS

Review and Evaluation of Clinical Data
Consult for Office of Generic Drugs

ANDA:	061667 PLS-26
Sponsor:	ANI Pharmaceuticals, Inc.
Drug:	Vancomycin Hydrochloride for Oral Solution USP
Correspondence Date:	21 November 2018
Date Received by Reviewer:	27 November 2018
Date Review Completed:	12 December 2018
Reviewer:	Sheral Patel, MD (DAIP/OAP/OND/CDER)
Team Leader:	Peter Kim, MD, MS (DAIP/OAP/OND/CDER)
Materials Reviewed:	Vancocin Oral Solution Proposed Template

1. Consult Request

The following consult was received from Oluwakemi O. Odesina, PharmD, BCPS, CPH CDER/OGD/ORO/DLR (*verbatim*).

> *ANI Pharmaceuticals Inc. submitted a PAS for ANDA 061667/S-026, Vancomycin Hydrochloride Oral Solution, on 09/27/2018 for a reformulation of the drug product. We note that the last approved labeling is S-020 approved on 07/29/1993. We note that the ANDA was originally approved in 1972 as an abbreviated antibiotic application (AADA) pursuant to Form -6 procedures and has historically made labeling updates independent of an RLD.*
>
> *We note that the only comparable drug product in the market place is Firvanq (vancomyin hydrochloride) for oral solution, NDA 208910/S-000 approved on January 26, 2018.*
>
> *Questions for OND to address*
> 1. *Kindly evaluate the proposed ANDA labeling in its entirety to determine if labeling changes are necessary to ensure the safe and effective use of the drug product.*
> 2. *For any recommended updates to the labeling, kindly confirm that the information is necessary for the safe and effective use of the drug product. (Kindly note that the regulatory pathway does not allow for the PLR conversion of this labeling at this time).*

2. Regulatory Background

Vancomycin hydrochloride was first approved in the oral solution form (ANDA 061667). However, the oral solution formulation was subsequently withdrawn from the market (**Table 2-1**). Per the consult request, a prior approval supplement for Vancomycin Hydrochloride Oral Solution (ANDA 061667/S-026) was submitted by the Sponsor on 27 September 2018 for a reformulation of the drug product.

Table 2-1: Orally administered vancomycin hydrochloride solution products

	Vancomycin hydrochloride Formulation	NDA/ ANDA	Notes
1	Oral capsules	NDA 050606	Approved in 1986 on the basis supportive safety and efficacy data from vancomycin hydrochloride oral solution (ANDA 061667), as well as in vitro dissolution data.
2	Oral solution	ANDA 061667	Approved in 1972, manufacture stopped 2002. Prior approval supplement 27 September 2018.
3	Oral solution	ANDA 063321	Approved in 1993, withdrawn in 2007.
4	Injection, powder lyophilized, for solution	ANDA 62911, and multiple others	Oral administration in INDICATIONS and DOSAGE AND ADMINISTRATION sections of the label.
5	Oral solution kit	NDA 208910	Approved 26 January 2018 based on findings of safety and effectiveness of oral capsules (NDA 050606) and Injection, powder lyophilized, for solution (ANDA 062911).

Firvanq (vancomyin hydrochloride) for oral solution, NDA 208910/S-000 was approved on January 26, 2018 by the Division of Anti-Infective Products. The Sponsor for Firvanq pursued the 505(b)(2) NDA regulatory pathway for approval of the Vancomycin Hydrochloride Powder for Oral Solution Kit. Based on prior Agency agreements, the Sponsor for Firvanq relied on FDA's findings of safety and effectiveness of the listed vancomycin products for oral administration [Vancocin® Capsules (NDA 050606) and Vancomycin Hydrochloride Injection, powder, lyophilized for solution, (Hospira, Inc. ANDA 062911)]. The Sponsor was requested to establish a scientific bridge between the proposed Vancomycin Hydrochloride Powder for Oral Solution Kit and each listed drug. *No new clinical safety or efficacy studies were submitted to support this application.*

It is important to note that the regulatory pathway for Firvanq required complex discussions within the Agency during the pre-IND phase (IND 123456). In addition to all review disciplines within the Division of Anti-Infective Products, numerous Offices and Divisions within the Agency contributed including Biopharmaceutics, Product Quality Microbiology, Office of Compliance, Office of Generic Drugs, Office of Regulatory Policy, Office of Chief Counsel and the Division of Pediatrics and Maternal Health.

The Firvanq label was last updated on 26 February 2018 (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5aca5508-b577-446c-9980-ab4c7582b4b9). The U.S. Prescribing Information (USPI) for Vancomycin Hydrochloride Powder for Oral Solution Kit was adapted from the USPI of the FDA-approved labeling for the referenced listed drugs [Vancocin® Capsules (NDA 050606, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a078d9c2-f89c-4f9f-8ded-60ffb2983c3f) and Vancomycin Hydrochloride for Injection, USP (Hospira, Inc.; ANDA 062911, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=37592c56-6679-48f4-169f-3a00c2ab114e)]. The Sponsor for Firvanq added text specifically applicable to the proposed drug product, such as the product name and manufacturer information, and provided updates to meet

the current Physician Labeling Rule (PLR)/Pregnancy and Lactation Labeling Rule (PLLR) requirements.

3. Response to OGD Questions

1. Kindly evaluate the proposed ANDA labeling in its entirety to determine if labeling changes are necessary to ensure the safe and effective use of the drug product.

Clinical Reviewer Response: Please see Vancocin Oral Solution Proposed Template in **Appendix 1**. DAIP Clinical Reviewer responses follow OGD Reviewer Questions in comment boxes. As a general rule, the Division recommends that the label for ANDA 061667 [Vancocin (Vancomycin Hydrochloride for Oral Solution USP)] is updated to reflect the content of the label for NDA 208910 [Firvanq (Vancomycin Hydrochloride Powder for Oral Solution Kit)].

Please note that the U.S. Prescribing Information (USPI) for Firvanq (Vancomycin Hydrochloride Powder for Oral Solution Kit) was adapted from the USPI of the FDA-approved labeling for the referenced listed drugs [Vancocin® Capsules (NDA 050606) and Vancomycin Hydrochloride for Injection, USP (Hospira, Inc.; ANDA 062911)]. The Sponsor for Firvanq added text specifically applicable to the proposed drug product, such as the product name and manufacturer information, and provided updates to meet the current Physician Labeling Rule (PLR)/Pregnancy and Lactation Labeling Rule (PLLR) requirements. *No new clinical safety or efficacy studies were submitted to support NDA 208910.*

2. For any recommended updates to the labeling, kindly confirm that the information is necessary for the safe and effective use of the drug product. (Kindly note that the regulatory pathway does not allow for the PLR conversion of this labeling at this time).

Clinical Reviewer Response: Please see Vancocin Oral Solution Proposed Template in **Appendix 1**. DAIP Clinical Reviewer responses follow OGD Reviewer Questions in comment boxes. All recommended updates to labeling are necessary for the safe and effective use of the drug product.

Following this page, 11 Pages of Draft Labeling have been Withheld in Full as (b)(4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARMEN L DEBELLAS
12/17/2018

SHERAL S PATEL
12/18/2018

PETER W KIM
12/18/2018

DMITRI IARIKOV
12/18/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

CHEMISTRY REVIEWS

Disciplines Involved	Outcome		Disciplines Involved	Outcome
Chemistry	AC		Biopharmaceutics	NA
Microbiology	NA		Bioequivalence	PN
Facilities	AC		DMF (Chemistry)	Adequate
Labeling	AC		DMF (Microbiology)	NA
Submissions Assessed				
Received Date:	September 27, 2018			
Amendment(s) Received Date:	July 27, 2018; October 9, 2018; March 22, 2019- Complete Response Amendment May 20, 2019 – Response to Drug product Information Request May 28, 2019- Response to Drug product Information Request			

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.

OFFICE OF PHARMACEUTICAL QUALITY
ASSESSMENT OF SUPPLEMENT TO ABBREVIATED NEW DRUG APPLICATION

Chemistry Assessment Number : Review#2

ANDA/Supplement Number : 61667/S26_AMD91

Drug Product Name, Strength : Vancocin® (Vancomycin Hydrochloride for Oral Solution USP, Eq. to 250 mg base/5 mL (b) (4)

Pharmacological Category/ Indication(s) : Treatment of staphylococcal entercolitis and antibiotic associated pseudomembranous colitis caused by C. difficile.

Applicant Name (or US Agent if Applicable) : ANI Pharmaceuticals, Inc.

Supplement Provides For : (1) Reformulation of drug product; (2) Qualification of new API source (DMF (b) (4); (3) Qualification of new manufacturing and testing facility; (4) New drug product container closure system; and (5) Revision of drug product storage condition.

Filing Category with basis for decision/comments (based on guidance for industry/CFR quotes) : PAS

Relevant Supporting DMF(s) Cited (If Applicable)

DMF No.	DMF	Result of Assessment	Date Assessment Completed
(b) (4)	(b) (4)	Adequate	2/11/2019
	Comment: Reviewed by H. Liao		

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(b) (4)

RECOMMENDATION

☒ Supplement is CMC Approvable

☐ Supplement is NOT CMC Approvable (with brief explanation:)

(Choose ☐ IR, ☐ CR-Minor, ☐ CR-Major); Deficiencies noted below:

Deficiencies to be communicated: N/A

Primary Assessor :Huiqi He **Date : May 30, 2019**

Huiqi He

Digitally signed by Huiqi He
Date: 5/30/2019 03:04:13PM
GUID: 5449382100047e04e3dafc7da83252e5

George Miesegaes

Digitally signed by George Miesegaes
Date: 5/30/2019 03:05:52PM
GUID: 508da6d7000262acdf86ba005b1737f3

Disciplines Involved	Outcome		Disciplines Involved	Outcome
Chemistry	CR-minor		Biopharmaceutics	N/A
Microbiology	N/A		Bioequivalence	PN
Facilities	AC^		DMF (Chemistry)	PN
Labeling	PN		DMF (Microbiology)	N/A

Submissions Assessed	
Received Date:	September 27, 2018
Amendment(s) Received Date:	July 27, 2018 – Pre-submission Facility Correspondence October 9, 2018 – Amendment (Response to Filing IR dated October 5, 2018)

^ (b) (4)
FEI # 2111358 – ANI Pharmaceuticals, Inc.
(b) (4)

Facilities are listed as "Approve" by OPF on December 19, 2018

OFFICE OF PHARMACEUTICAL QUALITY
ASSESSMENT OF SUPPLEMENT TO ABBREVIATED NEW DRUG APPLICATION

Chemistry Assessment Number : 1

ANDA/Supplement Number : 061667/026

Drug Product Name, Strength : Vancocin® (Vancomycin Hydrochloride for Oral Solution USP, Eq. to 250 mg base/5 mL)

Pharmacological Category/ Indication(s) : Treatment of staphylococcal entercolitis and antibiotic associated pseudomembranous colitis caused by C. difficile

Applicant Name (or US Agent if Applicable) : ANI Pharmaceuticals, Inc.

Supplement Provides For : (1) Reformulation of drug product, (2) Qualification of new API source (DMF # (b) (4)), (3) Qualification of new manufacturing and testing facility, (4) New drug product container closure system, (5) Revision of drug product storage condition.

Filing Category with basis for decision/comments (based on guidance for industry/CFR quotes) : PAS

Relevant Supporting DMF(s) Cited (If Applicable)

DMF No.	DMF	Result of Assessment	Date Assessment Completed

(b) (4)	(b) (4)	Pending	See comment below
	Comment	Last reviewed by H. Liao and found adequate on August 28, 2018. However, an unsolicited amendment dated December 20, 2018 was received and is currently under review.	

Following this page, 27 Pages Withheld in Full as (b)(4)

Additional Information provided:
An in vitro nasogastric tube study was performed using the proposed DP. The study report is provided in Section 5.3.1.2.

Assessment: **ACCEPTABLE**

Bioequivalence division notes that the provided in vitro NG tube study is not required for establishing BE for Vancomycin Oral Solution. (b) (4)

(b) (4)

(b) (4)

RECOMMENDATION

☐ Supplement is CMC Approvable

☒ Supplement is NOT CMC Approvable (with brief explanation:)

(b) (4)

(Choose ☐ IR, ☒ CR-Minor, ☐ CR-Major); Deficiencies noted below:

Deficiencies to be communicated:

1) The Drug Master File (DMF) (b) (4) for Vancomycin Hydrochloride, USP has been reviewed and we have no further comments at this time. Please be advised that recent unsolicited amendment(s) to the DMF are currently under review. We remind you that the DMF holder is required under 21 CFR 314.420(c) to notify you of any changes to their DMF.
2) (b) (4)
3)

(b) (4)

4)

5)

Primary Assessor : Pick-Wei Lau **Date : December 26, 2018**

Pick-Wei Lau

Digitally signed by Pick-Wei Lau
Date: 1/03/2019 12:28:58PM
GUID: 537f8499000279d8289f9c2cf1341d44

George Miesegaes

Digitally signed by George Miesegaes
Date: 1/04/2019 09:42:10AM
GUID: 508da6d7000262acdf86ba005b1737f3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	061667/S-026
Drug Product Name	Vancocin® (vancomycin hydrochloride) for Oral Solution, USP
Strength(s)	Eq. 250 mg base/5 mL*
Applicant Name	ANI Pharmaceuticals, Inc.
Applicant Address	210 Main Street West Baudette, MN 56623 ellen.camos@anipharmaceuticals.com
US Contact Name and US Mailing Address	Ellen Camos, Vice President, Regulatory Affairs 210 Main Street West Baudette, MN 56623 ellen.camos@anipharmaceuticals.com
US Contact Telephone Number	218.634.3500
US Contact Fax Number	888.519.0459
Original Submission Date(s) and Dates of Previously Submitted Supplements	10/09/2018 Supple-26 (Response to Information Request) 09/27/2018 Suppl-26 (New/Supplement) 07/27/2018 Suppl-26 (Quality)
Submission Date(s) of Supplement Under Review	03/22/2019 Supple-26 SD0016 (Formulation: composition of (b) (4) (b) (4) Mixed Berry Flavor)
Primary Reviewer	Zakia R. Greene (Williams), Ph.D.
Secondary Reviewer	Rong Wang, Pharm D., Ph.D.
Tertiary Reviewer	N/A
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) **Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent) [1]
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A
Formulation	☒ Adequate ☐ Inadequate
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A
Deficiency Classification	☐ Major (Deficiencies to be communicated by CR) ☐ Minor ☒ N/A (Review is Adequate)

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

Overall Review Result	☒ Adequate ☐ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
9, 10, 11, 16	Waiver/Deem Bioequivalent	Eq. 250 mg base/5 mL	☒ Adequate ☐ Inadequate

* Eq. 250 mg base/5 mL will be used interchangeably with 250 mg base/5 mL.

Review of a Prior Approval Supplement Amendment

1 EXECUTIVE SUMMARY

The current Complete Response (CR) Amendment of a Prior Approval Supplement (PAS)[2] was submitted in response to CR Letter (CRL) dated March 8, 2019[3]. The response to the bioequivalence (BE) deficiency in the CRL is assessed in the current review.

On September 27, 2018, the applicant, ANI Pharmaceuticals Inc. (ANI Pharma), requested a waiver of *in vivo* bioequivalence (BE) study requirements under Section 21 Code of Federal Regulations (CFR) 320.22 (b) (3) for its newly formulated "test" product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, 250 mg base/5 mL. It is important to note that the current ANDA *is* the innovator product, therefore, the assessor will refer to the applicant's product as the newly proposed "test" product, and previously approved "reference" product; see the original PAS BE review[4] for a greater detail on the drug product's history. The BE outcome of the original PAS was deemed inadequate due to a formulation deficiency, i.e. the compositional breakdown of the (b) (4) Mixed Berry Flavor (b) (4) used to formulate its newly revised product was not provided.

In the current Cover Letter of the CR Amendment response, the applicant referenced Drug Master File (DMF No. (b) (4) for the (b) (4) Mixed Berry Flavor and provided a summary breakdown of its components. Upon review of the individual components of the (b) (4) Mixed Berry Flavor, the assessor deems the formulation of the newly formulated "test" product acceptable. See full details of the flavor components and evaluation of their amounts in Section 3 Review of Current Amendment of the current review.

---

[2] GlobalSubmit Review. Search Term 061667. Sequence 0016 03/22/2019 Module1.2
\\cdsesub1\evsprod\anda061667\0016\m1\us\cover-letter-signed.pdf

[3] GDRP. Search Term: 061667. Application Life Cycle Tab. File name: A061667N026DPM-SupplementCompleteResponse01
http://panorama.fda.gov/project/view?ID=5c987d010010f58b9c80a21d01e8cfe4

[4] GDRP. Search Term: 061667. Application Life Cycle Tab. File name: A061667N000DB-SupplementReview01-09272018
http://panorama.fda.gov/project/view?ID=5c987d010010f58b9c80a21d01e8cfe4

As with the previously approved "reference" product, the newly formulated "test" product is a powder that is reconstituted and taken as an oral solution. However, the newly formulated "test" product contains four (04) inactive ingredients that are not in the previously approved "reference" product (See both formulations under the Review of Current Amendment Section). The quantities of the inactive ingredients in the reformulated "test" product, based on the maximum daily dose (MDD) of 2 g of Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL are within the respective limits in the FDA-approved drug products for the same route of administration. None of the inactive ingredients in the "test" product are expected to have an impact on bioavailability of the drug product or significantly affect GI absorption/motility of the active ingredient.

Based on the information provided, the Division of Bioequivalence I (DBI) ***grants*** the waiver request for the newly formulated "test" product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, 250 mg base/5 mL, per criteria set forth in *21 CFR § 320.22 (b) (3*).

Therefore, the application is **adequate.**

NOTE TO THE REGULATORY PROJECT MANAGER (RPM):

As of 05/31/2019, the current ANDA 061667 is listed as discontinued in the Orange Book. There is no listed Reference Listed Drug (RLD) or Reference Standard (RS) for this drug product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL. As of 05/31/2019, there is a Policy Alert for this drug product due to Safety and Effectiveness (S/E) Determination[5]. Based on the Approval Action, no approval actions (AP/TA) can be taken prior to final S/E Determination. All disciplines can continue communications (CRL, CC/IR/DRL).

[5] OGD Policy Alert List OGD Policy Alert List as of 05292019. http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/OGDPAL/SitePages/Home.aspx

2 TABLE OF CONTENTS

3 REVIEW OF CURRENT AMENDMENT

DB Deficiency Comment #1:

The DBI assessed the formulation for your revised proposed formulation, however, the proposed level of (b) (4) flavor, (b) (4) Mixed Berry (b) (4) could not be appropriately evaluated at this time as the compositional breakdown of (b) (4) flavor was not provided. Please provide the quantitative compositional breakdown for (b) (4) Mixed Berry (b) (4)

Applicant's Response to DB Deficiency Comment #1
In accordance with FDA's request, ANI is providing an Ingredient Breakdown Statement from (b) (4) in Module 3.2.P.1. This statement provides a (b) (4) Mixed Berry Flavor (b) (4) (b) (4) ANI previously provided a Letter of Authorization to the Drug Master File (DMF No. (b) (4)) for this flavor in the Pre-Submission Facility Correspondence dated July 27, 2018 and has also confirmed with (b) (4) that full quantitative compositional breakdowns may be found on page 3 of the filed DMF. Based on the Ingredient Breakdown Statement, ANI assessed the components of this flavor and has summarized our findings in the table below.

Finally, ANI is also providing the updated stability reports with current available stability data for the drug product in Module 3.2.P.8.3. The data continues to support the quality and integrity of the drug product.

Assessor's Comment

The applicant's response is satisfactory.

1. To evaluate the amount of each component in the modified "test" product formulation, the assessor has listed below the applicant's proposed formulation submitted in its July 27, 2018 submission:

Newly Proposed "Test" Formulation[6]

Table 1 – Final Dry Powder Formulation for Vancocin® (vancomycin hydrochloride for oral solution), Eq. to 250 mg base/5 mL

Component	Function	250 mg/5 mL	
		% w/w	mg/dose
Vancomycin HCl USP	Drug Substance	(b) (4)	*250.000
Citric Acid USP Anhydrous			(b) (4)
Flavor – (b) (4) Mixed Berry			
Sodium Benzoate NF			
Sucralose NF			
Total			

*The unit dose weight for each powder batch will be calculated based on the activity of the Vancomycin HCl USP lots that were used during manufacturing in order to ensure a label claim of 250 mg vancomycin activity.

Table 2 – Final Reconstituted Formulation for Vancocin® HCl (vancomycin hydrochloride for oral solution), Eq. to 250 mg base/5 mL

Component	Function	250 mg base/5 mL	
		% w/v	mg/dose
Vancomycin HCl USP	Drug Substance	(b) (4)	*250.000
Citric Acid USP Anhydrous			(b) (4)
Flavor – (b) (4) Mixed Berry			
Sodium Benzoate NF			
Sucralose NF			
Purified Water USP	Reconstituting Agent	Q.S.	Q.S.

*The unit dose weight for each powder batch will be calculated based on the activity of the Vancomycin HCl USP lots that were used during manufacturing in order to ensure a label claim of 250 mg vancomycin activity.

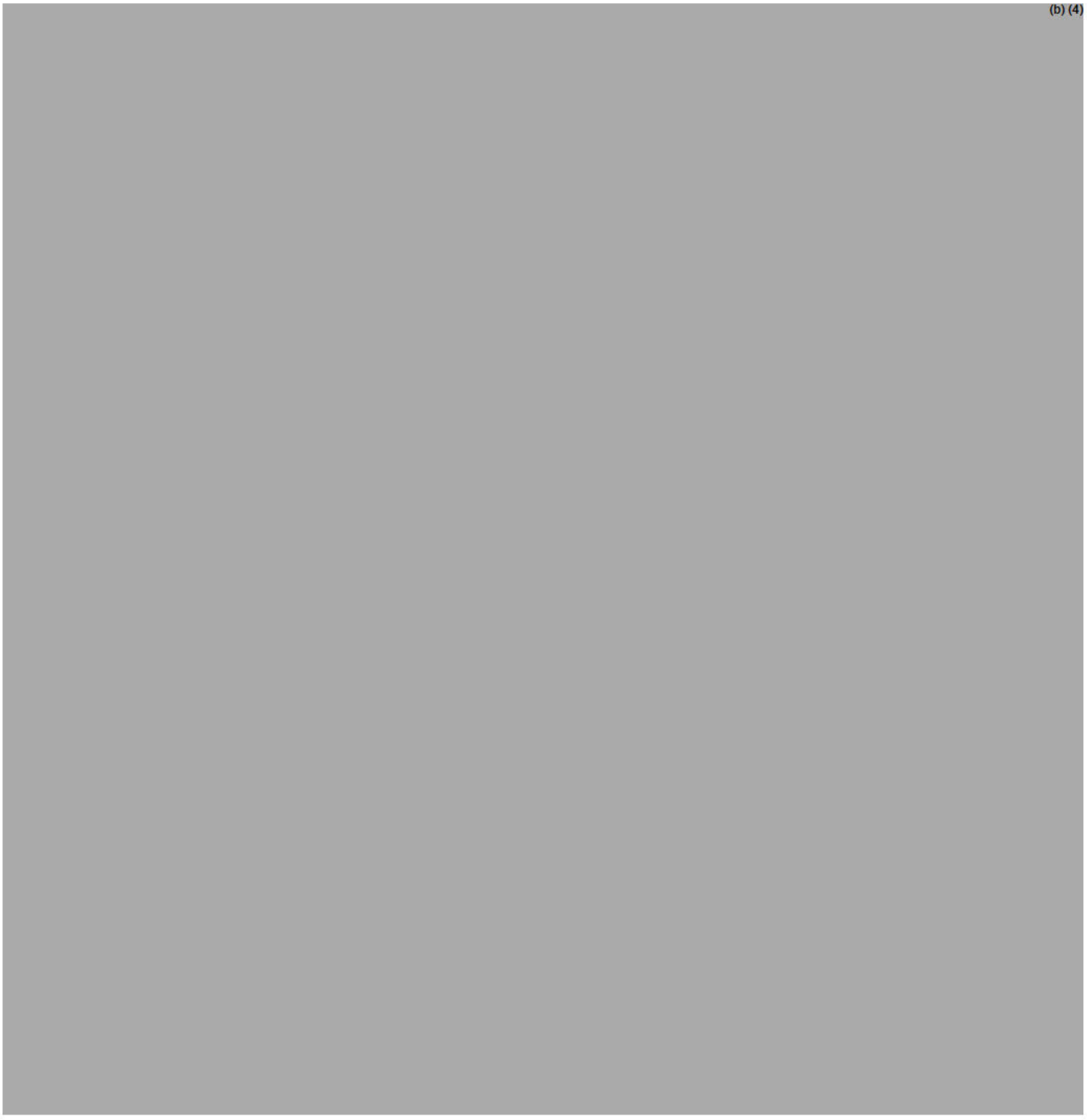
In the current Amendment Response, the applicant submitted the breakdown of (b) (4) (b) (4) Mixed Berry Flavor provided from (b) (4) in Module 3.2.P.1[7].

[6] GlobalSubmit Review ANDA 061667 Sequence 009 Module 3.2.P.1 Description and Composition of the Drug Product \\cdsesub1\evsprod\anda061667\0009\m3\32-body-data\32p-drug-prod\vancocin\32p1-desc-comp\description-and-composition.pdf

[7] GlobalSubmit Review. Search Term 061667. Sequence 0016 03/22/2019 Module 3.2.P.1 (b) (4) (b) (4) Mixed Berry Flavor Breakdown \\cdsesub1\evsprod\anda061667\0016\m3\32-body-data\32p-drug-prod\vancocin\32p1-desc-comp\description-and-composition.pdf

Ingredient Breakdown Statement

Product Name: (b) (4) MIXED BERRY FLAVOR, (b) (4)
Product Code: (b) (4)



The amount (mg) and percentage of each component were further calculated to determine if the levels are within inactive ingredients (IIG) per day limits based on

the maximum daily dose of the drug product, and/or if the levels are within the Agency's regulatory total unit weight (w/w) limit of 0.1%.

(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

Summary Comments on Test Product:

1. The proposed "test" product is the reformulated version of the previously approved "reference" product.

2. The newly proposed "test" and previously approved "reference" products contain the same active ingredient in the same concentration.

3. The previously approved "reference" product contained only one excipient, Edetate Calcium Disodium (EDTA,) in its formulation, whereas the newly proposed "test" product formulation contains four (04) excipients (Citric Acid USP Anhydrous, Sodium Benzoate NF, Sucralose NF, and (b) (4) Mixed Berry Flavor) that are not

[10]GlobalSubmit Review. Search Term 061667. Sequence 0014 01/24/2019 Module 1.14.1 \\cdsesub1\evsprod\anda061667\0014\m1\us\spl\label.jpg and \\cdsesub1\evsprod\anda061667\0014\m1\us\ani-outsert.docx

[11] GDRP. Search Term: 061667. Application Life Cycle Tab. File name: A061667N026DLR_Rvw_C2.pdf http://panorama.fda.gov/project/view?ID=5c987d010010f58b9c80a21d01e8cfe4

[12] GlobalSubmit Review: 210041, Sequence (9) 03/14/2018 Section 3.2.P.1 Description and Composition of the Drug Product \\cdsesub1\evsprod\anda210041\0008\m3\32-body-data\32p-drug-prod\potassium-chlor-oral-soln-usp-20-40meq\32p1-desc-comp\32p1-description-and-composition.pdf

[13] Drugs@FDA. Search Term 206814 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206814s008lbl.pdf Action date 05/07/2019 Last accessed 05/28/2019

[14] EDR: ANDA 210041, Module 1.14.3.3, Sequence 0000, Submission Date 12/27/2016

composed in the previously approved "reference" product formulation. None of the 4 excipients are expected to impact bioavailability of the drug product or significantly affect GI absorption/motility of the active ingredient. In addition, according to the test product labeling which was deemed acceptable by the labeling reviewer[11], vancomycin is poorly absorbed after oral administration. No blood concentrations were detected and urinary recovery did not exceed 0.76%.

4. All excipients in the newly proposed "test" product formulation, except for the (b) (4) Mixed Berry Flavor, were deemed acceptable in the original review[4].

5. All components of the (b) (4) Mixed Berry Flavor (b) (4) (b) (4), based on the maximum daily dose (MDD) of 2 g of Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL are within the respective limits in the FDA's inactive ingredients database or less than 0.1% w/w of the test formulation.

6. Based on the information provided, the DBI agrees that the test product is acceptable. The DBI **grants** the waiver request for in vivo BE study requirements for the applicant's newly formulated "test" product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, 250 mg base/5 mL per 21 CFR 320.22(b)(3).

NOTE TO THE REGULATORY PROJECT MANAGER (RPM):

As of 05/31/2019, the current ANDA 061667 is listed as discontinued in the Orange Book. There is no listed Reference Listed Drug (RLD) or Reference Standard (RS) for this drug product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL. As of 05/31/2019 there is a Policy Alert for this drug product due to Safety and Effectiveness (S/E) Determination. Based on the Approval Action, no approval actions (AP/TA) can be taken prior to final S/E Determination. All disciplines can continue communications (CRL, CC/IR/DRL).

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	061667/S-026
APPLICANT:	ANI Pharmaceuticals, Inc.
DRUG PRODUCT:	Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq. 250 mg base/5 mL

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3.1 Outcome Page

Completed Assignment for 061667 ID: 38854

Reviewer:	Greene, Zakia	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	Amendment: Vancocin® (vancomycin hydrochloride) for Oral Solution, USP Eq. 250 mg base/5 mL		

Items:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Score***	***Subtotal***
38854	3/22/2019	BIO	Supplement Amendments [1]	1	1
38854	3/22/2019	Parallel	Minor Amendment (original or supplement) [1]	1	1
				Total:	2

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	061667/S-026
Drug Product Name	Vancocin® (vancomycin hydrochloride) for Oral Solution, USP
Strength(s)	Eq. 250 mg base/5 mL*
Applicant Name	ANI Pharmaceuticals, Inc.
Applicant Address	210 Main Street West Baudette, MN 56623 ellen.camos@anipharmaceuticals.com
US Contact Name and US Mailing Address	Ellen Camos, Vice President, Regulatory Affairs 210 Main Street West Baudette, MN 56623 ellen.camos@anipharmaceuticals.com
US Contact Telephone Number	218.634.3500
US Contact Fax Number	888.519.0459
Original Submission Date(s)	October 8, 1971[1]
Submission Date(s) of Supplement Under Review	09/27/2018 Suppl-26 (New/Supplement) 07/27/2018 Suppl-26 (Quality) 10/9/2018 Suppl-26 (Response to Information Request)
Primary Reviewer	Zakia R. Williams, Ph.D.
Secondary Reviewer	Rong Wang, Pharm D., Ph.D.
Tertiary Reviewer	N/A
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) **Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent)[2]
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A

[1] The Approval Package contains historical accounts of this application: Drugs@FDA. Search Term 61667 https://www.accessdata.fda.gov/drugsatfda_docs/anda/pre96/061667Orig1s000.pdf . This product was originally held by Eli Lilly for its Vancocin® (vancomycin), sterile product for intravenous (IV) use. On Oct. 8, 1971 Lilly submitted a Form 6 Amendment for the higher strength, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, [redacted] (b) (4) under the application # 60-180. On July 24, 1972, the Agency approved the Form 6 Amendment for the Vancocin® (vancomycin hydrochloride) for Oral Solution (pg 46/91). Since application #60-180 was designated for Eli Lilly's Vancocin (vancomycin), sterile product for intravenous (IV), it was communicated to the applicant on August 15, 1972 that application #61-667 was assigned for Vancocin® (vancomycin hydrochloride) for Oral Solution (pg 47/91).

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

Formulation	☐ **Adequate** ☒ **Inadequate**		
Will Response to CR Result in a Reformulation?	☒ **Possibly** ☐ **No** ☐ **N/A**		
Deficiency Classification	☐ **Major (Deficiencies to be communicated by CR)** ☒ **Minor** ☐ **N/A (Review is Adequate)**		
Overall Review Result	☐ **Adequate** ☒ **Inadequate**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
9, 10, 11	**Waiver/Deem Bioequivalent**	**Eq. 250 mg base/5 mL**	☐ **Adequate** ☒ **Inadequate**

* Eq. 250 mg base/5 mL will be used interchangeably with 250 mg base/5 mL.

Prior Approval Supplement

1 EXECUTIVE SUMMARY

The applicant has submitted a Prior Approval Supplement (PAS) for this Abbreviated New Drug Application (ANDA) on July 27, 2018.

ANI Pharmaceuticals Inc. (ANI Pharma) has requested a waiver of *in vivo* bioequivalence (BE) study requirements under Section 21 Code of Federal Regulations (CFR) 320.22 (b) (3) for its newly formulated "test" product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, 250 mg base/5 mL. The assessor notes that the Orange Book lists two strengths for this ANDA, i.e. 250 mg base/5 mL and 500 mg base/6 mL[3]; and it is currently listed in the discontinued section of the Orange Book. Since the applicant submitted the PAS on the 250 mg base/5 mL strength, focus of waiver requirements is on this strength only.

In addition to this ANDA being listed in the discontinued section of the Orange Book, to date, there is no designated Reference Listed Drug (RLD) or Reference Standard (RS) for this product in the Orange Book.

In the Cover Letter included in the amendment dated October 9, 2018, ANI Pharma provided "Reviewer's Aid: ANDA 061667 Regulatory History" and indicated that *the applicant is referencing its own drug product and ANDA, as the Basis of Submission (BOS)*[4].

To assist with this application, a Consult Request was sent to the Office of Generic Drugs Policy (OGDP) to obtain guidance on how the Division of Bioequivalence I (DBI) should

[3] Orange Book. Search Term 061667 https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm. Last accessed 12/17/18

[4] GlobalSubmit Review. 10/09/18 Submission. Module 1.12.11 \\cdsesub1\evsprod\anda061667\0011\m1\us\basis-submission.pdf

evaluate the waiver request in this PAS per 21 CFR 320.22(b)(3), which requires a product be compared to the RLD product. The regulatory history of this application is convoluted and complex as it was originally filed in 1971 pursuant to the Form-6 procedures per section 507 of the Federal Food, Drug and Cosmetic Act ("FD&C Act") i.e. under the abbreviated antibiotic application (AADA) pathway. Under the FDA Modernization Act of November 1997 ("FDAMA"), section 507 was repealed, and certain antibiotic applications were considered approved under 505(j); therefore, although ANDA 061667 was the first application approved for Vancomycin HCl for Oral Solution and considered the innovator product, it was *not* designated as an NDA, rather an ANDA. With respect to the evaluation of the PAS, in the Consult Response[5], the OGDP assessor suggested "*OGDP recommends DBI conduct the review of the changes proposed in the PAS as it normally would for any supplemental application to an ANDA in determining the acceptability of the changes proposed in the PAS*". In addition, OGDP has initiated a determination with Office of New Drug (OND) of whether ANDA 061667 was originally withdrawn from the market for reasons of safety or effectiveness.

It is important to note that the current ANDA *is* the innovator product, which is also listed as the basis of submission for the current PAS; therefore, in the current review, the assessor will refer to the applicant's product as such: newly proposed "test" product, and previously approved "reference" product.

The proposed "test" product is supplied in 4g/bottle, 7.5 g/bottle and 15 g/bottle vial size, which is different from the approved vial size (i.e. 1g/bottle for 250 mg/5 mL strength) of the "reference" product. To address the differences in the vial size between the previously approved "reference" product and the currently proposed "test" product, an inquiry to the OGDP was included in the above mentioned Consult Request. Specifically, DBI wanted to know if a suitability petition is necessary from the Applicant since the proposed "test" product vial size is different from the previously approved "reference" product. In brief, the OGDP assessor stated in the Consult Response[5] *"[C]onsistent with OGD's current practice, it does not seem that a suitability petition would be necessary for the three new container sizes ANI is proposing to add to the 250 mg/5 mL strength…… no suitability petition would be necessary*".

The previously approved "reference" product contained only one excipient, Edetate Calcium Disodium (EDTA,) in its formulation. In the current submission, the applicant has proposed a newly formulated drug product which contains an active ingredient in the same concentration (Eq. to 250 mg base/5 mL) and same dosage form (oral solution) as the previously approved "reference" drug product, however, the modified formula does not contain EDTA, and contains 04 additional excipients (See Formulation Section 4.1). These four excipients (b) (4) are not expected to have an impact on the drug absorption. Except for the (b) (4) Mixed Berry Flavor (b) (4) the quantities of the other three inactive ingredients in the reformulated "test" product, based on the maximum daily dose (MDD) of 2 g of Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL are within the

[5] V:\DIVISION\BIO\BIO1\Email Reference. File Name: 2019_1_25 OGDP Consult Response re ANDA 061667docx.

limits recommended in the FDA's inactive ingredients database. The applicant did not submit the compositional breakdown for the (b) (4) Mixed Berry Flavor (b) (4) Consequently, the assessor was not able to verify if all excipients in the flavor are within acceptable limits when the drug product is consumed at the maximum daily dose. The applicant will be asked to provide such information for review. The formulation of the newly proposed "test" product is currently deemed **unacceptable**.

Therefore, the application is **inadequate.**

NOTE TO THE REGULATORY PROJECT MANAGER (RPM):

As of 02/1/2019, the current ANDA 061667 is listed as discontinued in the Orange Book. There is no listed Reference Listed Drug (RLD) or Reference Standard (RS) for this drug product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL. There is a Policy Alert for this drug product due to Safety and Effectiveness (S/E) Determination. Based on the Approval Action, no approval actions (AP/TA) can be taken prior to final S/E Determination. All disciplines can continue communications (CRL, CC/IR/DRL).

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[6]

"Test" Drug Product and Strength(s)*	Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL.
"Reference" Product and Strength(s)*	Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL.
RS Holder; NDA/ANDA Number; Approval Date[3]	There is no currently listed RS for this product in the Orange Book.
Reference Listed Drug (RLD) and Strength(s)	There is no currently listed RLD for this product in the Orange Book.
RLD Holder; NDA/ANDA Number; Approval Date	ANI Pharmaceuticals Inc; approved 07/13/1983

Reviewer's Note: This ANDA, 061667, is currently listed in the discontinued section in the Orange Book. Since there is no designated RS or RLD product, and the BOS for this application is itself, the assessor has indicated the newly proposed formulation as "Test" product and the previously approved formulation as "Reference" product.
According to the Orange Book, Vancomycin Hydrochloride for Oral Solution, 500 mg/6mL is also listed under the discontinued ANDA 061667.

3.2 PK/PD Information[7]

Most recent RLD label (provide embedded document).	ANDA 061667 Label PA 0794 AMP.pdf Likely due the discontinuation status of the current ANDA (or "RLD" product), the labeling of the current ANDA (or "RLD" product) is not available in Drugs@FDA or DailyMed. However, the reviewer obtained a label submitted in an archival copy of Jacket 6.1 (see pdf insert above). This Jacket contained Supplement -025 from the applicant which informs the Agency of an update to the label's PRECAUTIONS Section. In a Cover Letter stamp dated 12/19/2002, the Agency approved the label in this supplemental application[8]. This was the latest version found by the

[6] Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process Last accessed 12/17/2018
[7] Clinical Pharmacology http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=638&n=Vancocin&t=0&enh=1 Last accessed 12/18/18

ANDA 061667 Jacket 6.1 Supp-025.

[8] Archival Copy ANDA 061667 Volume 6.1

	assessor before the applicant submitted a withdrawal request on January 13, 2003 Re: Supplements 019, 022, and 025 stating that they were no longer marketing the product[9]. The assessor also obtained information from the Drug Monograph-Vancomycin in Clinical Pharmacology database; some of the information was the same as the provided in the label.
Indication	Vancocin HCI for Oral Solution is administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic- associated pseudomembranous colitis caused by C. *difficile*. Parenteral administration of Vancocin HCI is not effective for the above indications; therefore, Vancocin HCI must be given orally for these indications. Orally administered Vancocin HCI is not effective for other types of infection.
Boxed warning	No
Bioavailability	This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancomycin is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%.... Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present.
Food Effect	Not mentioned
Tmax	Not mentioned
Metabolism	Not mentioned
Excretion	Due to poor oral bioavailability, oral doses of vancomycin are excreted mainly in the feces (exceeding 100 mg/kg) with urinary recovery not exceeding 0.76% of the dose
Half-life	Not mentioned
Maximum Daily Dose	2000 gm

ANDA 061667
Jacket 7.1.pdf

[9] Archival Copy ANDA 061667 Volume 7.1

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	According to 21 CFR 320.22 (b) (3), a waiver of the requirement for the submission of evidence measuring *in vivo* bioavailability or demonstrating bioequivalence may be granted to a drug product if the drug product: 1) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; and 2) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and 3) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.	
Summary of OGD or DB History	Approved ANDAs:	(b) (4)
	Pending ANDAs:	There are no pending ANDAs for this drug product, i.e. citing RLD 061667
	Controls[10]:	Multiple There are no CC listed in GDRP or Office Generic Drugs - CONTROLS (Correspondence) Document Tracking from the current applicant. There is CC 13-0011 (b) (4) (b) (4) (b) (4)[11]
	Protocols[12]:	None

[10] Panaroma. http://panorama fda.gov/report/view?ID=53878d320004221ce814f564e0669978 OGD CC Database http://cdsogd1/controls/DOCGRID.ASP Both last accessed 12/18/18

[11] (b) (4) (b) (4)

[12] There were no Protocols listed in the OGD-DB Protocol Tracking database and none listed in the GDRP on this drug product. http://ogd fda.gov/seltrack/ProtocolGrid.ASP Last accessed 12/18/18

	Pending Citizen Petitions and other legal and regulatory issues:[13] If yes, please comment.	☒ Yes ☐ No Note; a Safety and Effectiveness (S/E) Determination has been initiated for the current application. As of 1/29/2019, there is a policy alert for this application to determine if there is a S/E related to the withdrawal status of this application.

4 APPENDIX

4.1 Formulation Data

4.1.1 Proposed "Test" Formulation[14]

Table 1 – Final Dry Powder Formulation for Vancocin® (vancomycin hydrochloride for oral solution), Eq. to 250 mg base/5 mL

Component	Function	250 mg/5 mL	
		% w/w	mg/dose
Vancomycin HCl USP	Drug Substance	(b) (4)	*250.000
Citric Acid USP Anhydrous			(b) (4)
Flavor – (b) (4) Mixed Berry			
Sodium Benzoate NF			
Sucralose NF			
Total			

*The unit dose weight for each powder batch will be calculated based on the activity of the Vancomycin HCl USP lots that were used during manufacturing in order to ensure a label claim of 250 mg vancomycin activity.

Table 2 – Final Reconstituted Formulation for Vancocin® HCl (vancomycin hydrochloride for oral solution), Eq. to 250 mg base/5 mL

Component	Function	250 mg base/5 mL	
		% w/v	mg/dose
Vancomycin HCl USP	Drug Substance	(b) (4)	*250.000
Citric Acid USP Anhydrous			(b) (4)
Flavor – (b) (4) Mixed Berry			
Sodium Benzoate NF			
Sucralose NF			

[13] OGD Policy Alert List as of 01292019 http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx. Last accessed 02/1/2019

[14] GlobalSubmit Review ANDA 061667 Sequence 010 Module 3.2.P.1 Description and Composition of the Drug Product \\cdsesub1\evsprod\anda061667\0009\m3\32-body-data\32p-drug-prod\vancocin\32p1-desc-comp\description-and-composition.pdf

Purified Water USP	Reconstituting Agent	(b) (4)

*The unit dose weight for each powder batch will be calculated based on the activity of the Vancomycin HCl USP lots that were used during manufacturing in order to ensure a label claim of 250 mg vancomycin activity.

4.1.2 Previously Approved "Reference" Product Formulation: Vancocin® HCl (vancomycin hydrochloride) for Oral Solution, Eq. to 250 mg base/5 mL[15]

The table below was taken from the Archival Copy Jacket 5.1 (Supplement-019)[16]. In the Cover Letter dated December 8, 1998, the applicant stated "The revisions incorporated the changes designated as "approvable" in the December 10, 1996 letter from …(OGD), FDA". The Unit Formula table submitted in this Supplement (shown below) had been previously approved[17].

[15] The assessor notes that the original formulation did not contain Ca-EDTA. In Supplement-014 (Archival Copy ANDA 061667 Volume 3.1), the applicant proposed a revision to the formulation to include EDTA stating the change in the formula includes EDTA (b) (4) (b) (4) with vancomycin". The Bioequivalence (BE) Review evaluating the formulation change was deemed "Recommend Approval"; the assessor notes that the EDTA amount (b) (4) listed in the BE review for Vancocin HCl for Oral Solution, equivalent to 1g Vancomycin (which refers to the 250 mg base/5 mL strength) may be a typographical error as the applicant's submission (shown above) lists (b) (4)

ANDA 061667 Jacket 3.1.pdf

ANDA 061667 Jacket 5.1.pdf

[16] Archival Copy ANDA 061667 Volume 5.1

[17] This was the latest version found by the assessor before the applicant submitted a withdrawal request on January 13, 2003 Re: Supplements 019, 022, and 025 stating that they were no longer marketing the product. See Footnote 8.

(b) (4) Vancocin HCl for Oral Solution, equivalent to 1 g Vancomycin

Ingredient	Quantity/Bottle	Reasonable Variation
Vancomycin base equivalent to vancomycin activity	1.0 g[2]	(b) (4)
Edetate calcium disodium (b) (4)		
(b) (4)		

(b) (4)

The assessor created the table below to exhibit the amount per dose in the previously approved "Reference" Product.

Component	Function	250 mg base/5 mL mg/dose
Vancomycin HCl USP	Drug Substance	250.000
Edetate Calcium Disodium (b) (4)		(b) (4)
		(b) (4)

The amount/dose was calculated using the Unit Formula and the label information submitted in the Archival Copy Jacket 5.1 (see image below). Thus, [(quantity/bottle)/(20 mL dilution)] * 5 ml per dose.

(b) (4)

4.2 Change in the Drug Product Formulation

The firm provided a comparison of formulation composition between the previously approved (currently discontinued) "reference" product (formally owned by Lilly) and the proposed "test" product submitted in the current Prior Approval Supplements (currently owned by ANI Pharma) in the tables:

Proposed "Test" Product Formulation Compared to the Previously Approved (Currently Discontinued) "RLD" Product Formulation

INACTIVE INGREDIENT COMPARISON		
PROPOSED DRUG PRODUCT	**APPROVED DRUG PRODUCT**	**INACTIVE INGREDIENT FUNCTION**
	Edetate Calcium Disodium	(b) (4)
Citric Acid USP Anhydrous		
(b) (4) **Mixed Berry**		
Sodium Benzoate NF		
Sucralose NF		

The assessor created the following table to exhibit the amount/dose of each drug product in the previously approved and currently proposed formulations:

Component	**Function**	**Proposed "Test" Product Formula**	**Previously approved "Reference" Product Formula**
		mg/dose	**mg/dose**
Vancomycin HCl USP	Active	250.00	250.00
Edetate Calcium Disodium			(b) (4)
Citric Acid USP Anhydrous			
Flavor – (b) (4) Mixed Berry			
Sodium Benzoate NF			
Sucralose NF			

(b) (4)

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes ☐ No ☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☐ Yes ☒ No
If no, are they all within IIG (per day) limits?	☐ Yes ☒ No ☐ N/A Applicant did not submit compositional breakdown of Flavor – (b) (4) Mixed Berry
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☒ Yes ☐ No ☐ N/A
Are all strengths of the test formulation acceptable?	☐ Yes ☒ No

Comments on Formulation:

1. The newly proposed "test" product formulation contains 4 excipients that were not composed in the previously approved "reference" product formulation.
2. (b) (4)

[18] IIG-MDD_Master Spreadsheet_: http://sharepoint fda.gov/orgs/CDER-OGD/BIO/IIGMDD%20Master%20Spreadsheet/Forms/AllItems.aspx , accessed 12/21/2018

3. The newly proposed "test" product contains sucralose, (b) (4)

(b) (4)

4. Except for the (b) (4) Mixed Berry Flavor (b) (4) (b) (4) all other quantities of the inactive ingredients in the reformulated "test" product, based on the maximum daily dose (MDD) of 2 g of Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL are within the limits recommended in the FDA's inactive ingredients database. The firm did not provide the individual components of its (b) (4) Mixed Berry Flavor (b) (4). The applicant provided a statement from the manufacturer, (b) (4) stating the following:

(b) (4)

While the assessor acknowledges the statement above, a compositional breakdown of the (b) (4) Mixed Berry Flavor should be provided to ensure all ingredients in the Flavor are within the Agency's allowable limit. Therefore, the applicant will be asked to provide this information for review.

(b) (4)

5. In the Description and Composition report, the applicant reports [redacted] This is consistent with what is exhibited in the table of the previously approved formulation as shown above.

6. The proposed "Test" product formulation is **not acceptable**.

4.3 Reviewer's Comments

1. Per the previously approved "reference" product labelling, the reference product was supplied as a 1 g bottle. Per the Preparation and Stability section, *"[T]he contents of the 1-g bottle may be mixed with distilled or deionized water (20 mL). When reconstituted with 20 mL, each 5 mL contains approximately 250 mg of vancomycin*."

   The proposed "test" product is supplied in 4g/bottle, 7.5 g/bottle and 15 g/bottle vial size. Per the Draft Labeling, the Directions For Preparations state "*when prepared as directed, each 5 mL contains vancomycin hydrochloride equivalent to approximately 250 mg of vancomycin in a mixed berry-flavored solution*". The corresponding volumes of water for the aforementioned vial sizes are 80 mL, 150 mL, and 300 mL, respectively. Please note that the proposed vial sizes are different from that of the "reference" product, i.e. 1 g/bottle for 250 mg/5 mL strength. Although the presentation of the currently proposed "test" product vial size is different, per consultation with OGD Policy, a Suitability Petition is not necessary since the concentration of the drug product remains the same, i.e. 250 mg/5 mL**Error! Bookmark not defined.**.

2. The test and RLD products contain the same active ingredient in the same concentration.

3. (b) (4) (b) (4)

4. The formulation of the proposed "test" product is not acceptable. The applicant will be asked to provide the compositional breakdown of the (b) (4) Mixed Berry Flavor (b) (4) (see Reviewer's comments on formulation for details).

5. The assessor notes that the applicant submitted an Oral Syringe and Nasogastric (NG) Tube *in vitro* Study in Module 5, which is typically where data and information are reviewed by the Division of Bioequivalence. Per the current BE review practice, oral solution/liquid dosage forms do not need NG tube testing for BE purposes, therefore, evaluation of the NG tube study data was deferred to the Office of Pharmaceutical Quality (OPQ). The Drug Product Review was completed by a CMC assessor who deemed the NG tube study acceptable[24].

6. The applicant's request for waiver of the *in vivo* bioequivalence study requirements per 21 CFR § 320.22 (b) (3) is **denied** at this time.

[24] GDRP. Search Term: 061667. Application Life Cycle Tab. File name: 061667x026_v1.docx. http://panorama.fda.gov/project/view?ID=5bb19ce00184c5ccea9e91963f98d04a

NOTE TO THE REGULATORY PROJECT MANAGER (RPM):

As of 02/1/2019, the current ANDA 061667 is listed as discontinued in the Orange Book. There is no listed Reference Listed Drug (RLD) or Reference Standard (RS) for this drug product, Vancocin® (vancomycin hydrochloride) for Oral Solution USP, Eq to 250 mg base/5 mL. There is a Policy Alert for this drug product due to Safety and Effectiveness (S/E) Determination. Based on the Approval Action, no approval actions (AP/TA) can be taken prior to final S/E Determination. All disciplines can continue communications (CRL, CC/IR/DRL).

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	061667/S-026
APPLICANT:	ANI Pharmaceuticals, Inc.
DRUG PRODUCT:	Vancocin® (vancomycin hydrochloride) for Oral Solution, USP Eq. 250 mg base/5 mL

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiency:

1. The DBI assessed the formulation for your newly proposed formulation, however, the proposed level of (b) (4) flavor, (b) (4) Mixed Berry (b) (4) could not be appropriately evaluated at this time as the compositional breakdown of (b) (4) flavor was not provided. Please provide the quantitative compositional breakdown for (b) (4) Mixed Berry (b) (4)

Sincerely yours,

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.4 Outcome Page

Completed Assignment for 061667 ID: 37837

Reviewer:	Greene, Zakia	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	Vancocin® (vancomycin hydrochloride) for Oral Solution, USP Eq. 250 mg base/5 mL		

Items:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Score***	***Subtotal***
37837	9/27/2018	BIO	Supplement [1]	1	1
37837	9/27/2018	BIO	Consult Review (For Consults to Other Office) [1]	1	1
37837	9/27/2018	Parallel	Waiver Oral Solution (Per application) [1]	1	1
				Total:	3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 061667Orig1s026

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CHECKLIST FOR THE CHEMISTRY REVIEW:

ANDA-061667-SUPPL-26-AMEND-91

Function	**Performed By (Initial and Date)**	**Check appropriate box**
Is this package for new strength PAS?	MK, RBPM, 6/3/19	☐ Yes ☒ No
DMF adequate?	MK, RBPM, 6/3/19	☒ Yes ☐ No *(see comments)
Any outstanding consults?	MK, RBPM, 6/3/19	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee PS 6/3/19	☐ Yes ☐ No ☒ N/A
Are all facility inspections acceptable?	MK, RBPM, 6/3/19	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	MK, RBPM, 6/3/19	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee PS 6/3/19	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee PS 6/3/19	☒ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee PS 6/3/19	☒ Yes ☐ No *(see comments) ☐ N/A
Is the final review uploaded into the current IT platform?	MK, RBPM, 6/3/19	☒ Yes ☐ No
Comments		
DMF (b) (4) adequate – reviewed by Hongbiao Liao on 2/11/19		
Division	Name	Date

Paul Schwartz

Digitally signed by Paul Schwartz
Date: 6/04/2019 05:12:58PM
GUID: 508da701000286c5e39356dd569b8a5b

ANDA 061667/S-026

INFORMATION REQUEST

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

Dear Madam:

This letter is in reference to your supplemental abbreviated new drug application (sANDA) received for review on March 22, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Vancocin® (vancomycin hydrochloride for oral solution USP), eq. to 250 mg base/5 mL.

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

1. Reformulation of drug product
2. Qualification of new API source (DMF# (b) (4))
3. Qualification of new manufacturing and testing facility
4. New drug product container closure system
5. Revision of drug product storage condition

We also refer to your March 22, 2019 submission, containing your information request response sent on 5/20/19.

We are reviewing the Quality section of your submission and have the following information requests. We request a prompt written response, no later than May 29, 2019, in order to continue our evaluation of your sANDA.

Information requests:

A. Drug Product

- (b) (4)

- (b) (4)

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
QUALITY

If you have any questions, please contact Maria Kim, DPT, OMPT, Regulatory Business Process Manager, at (301) 796 - 2824.

Sincerely,

{See appended electronic signature page}

Maria Kim, DPT, OMPT
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Maria Fatima Kim

Digitally signed by Maria Fatima Kim
Date: 5/24/2019 05:15:54PM
GUID: 5423006c00721ecf621f5562185ade9b

ANDA 061667/S-026

INFORMATION REQUEST

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

Dear Madam:

This letter is in reference to your supplemental abbreviated new drug application (sANDA) received for review on March 22, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Vancomycin Hydrochloride for Oral Solution USP, Eq. to 250 mg base/5 mL (b) (4)

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

1. Reformulation of drug product
2. Qualification of new API source (DMF# (b) (4))
3. Qualification of new manufacturing and testing facility
4. New drug product container closure system
5. Revision of drug product storage condition

We are reviewing the Quality section of your submission and have the following information requests. We request a prompt written response, no later than May 20, 2019, in order to continue our evaluation of your sANDA.

Information requests:

A. Drug Product

1. (b) (4)

2. (b) (4)

3.

4.

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
QUALITY

If you have any questions, please contact Maria Fatima Kim, Regulatory Business Process Manager, at (301) 796 - 2824.

Sincerely,

{See appended electronic signature page}

Maria Fatima Kim
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Maria Fatima Kim

Digitally signed by Maria Fatima Kim
Date: 4/22/2019 10:04:54PM
GUID: 5423006c00721ecf621f5562185ade9b

ANDA 061667/S-026

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

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 March 22, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Vancocin® (Vancomycin Hydrochloride for Oral Solution USP), 250 mg base/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 minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor supplement amendment is June 21, 2019.

If you have any questions, contact Sarah Nguyen, Regulatory Project Manager, at (240) 402 - 8731.

Sincerely,

{See appended electronic signature page}

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

Sarah Nguyen

Digitally signed by Sarah Nguyen
Date: 3/25/2019 09:07:47AM
GUID: 508da70900028cec38f523655fb8cb64

sANDA 061667 / S-026

DISCIPLINE REVIEW LETTER

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

Dear Ms. Camos:

This communication is in reference to your supplemental abbreviated new drug application (sANDA) dated September 27, 2018, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Vancomycin Hydrochloride for Oral Solution USP, 250 mg per 5 mL.

We have completed the Labeling review of this ANDA and have the following preliminary thoughts on possible deficiencies:

Labeling deficiencies determined on January 14, 2018, based on your submission received on September 27, 2018:

1. CONTAINER LABEL

    a. Increase the prominence of the following statement “After mixing, refrigerate and use within two weeks,” which appears on the side panel by using a bold font and/or different color in order to minimize the potential for medication errors.

    b. Revise the presentation of the established name such that only the terms “Vancomycin Hydrochloride” appears in parenthesis; e.g. “(Vancomycin Hydrochloride) for Oral Solution USP”

    c. Revise the principal display panel (PDP) to ensure that the manufacturer name and logo does not compete in size and prominence with the presentation of the proprietary and established name

    d. Remove the equivalency statement (i.e. “Equivalent to…Vancomycin”) that presently appears on the (PDP). Instead, add an asterisk after the expression of the strength (e.g. 250 mg per 5 mL*)

    e. Place an asterisk prior to the equivalency statement on the side panel

2. PRESCRIBING INFORMATION

Revise your prescribing information in accordance with the attached template

If you would like to respond to these possible deficiencies before the end of this review-cycle, we request a complete written response no later than January 31, 2019. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

If you do not submit a complete written response by January 31, 2019, these possible deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the GDUFA II Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

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

[1] The term "GDUFA II Commitment Letter" refers to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

If you have any questions, please contact Carol Lee, Labeling Project Manager, at Carol.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Following this page, 9 Pages of Draft Labeling have been Withheld in Full as (b)(4)

Carol Lee

Digitally signed by Carol Lee
Date: 1/17/2019 09:53:41AM
GUID: 5509900500075ef5af0b093081e71363

ANDA 061667/S-026

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

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

Dear Madam:

This is in reference to an amendment to the Drug Master File (DMF) # (b) (4) received on December 20, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Vancomycin Hydrochloride for Oral Solution USP, 250 mg per 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 minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor supplement amendment is March 19, 2019.

If you have any questions, contact Sarah Nguyen, Regulatory Project Manager, at (240) 402 - 8731.

Sincerely,

{See appended electronic signature page}

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

Sarah Nguyen

Digitally signed by Sarah Nguyen
Date: 1/02/2019 12:48:36PM
GUID: 508da70900028cec38f523655fb8cb64

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OND/OAP/DAIP
(If you know who the PM/Reviewer is please add them as a signer in DARRTS)

FROM:
Oluwakemi O. Odesina, PharmD, BCPS, CPH
CDER/OGD/ORO/DLR

DATE	ANDA NO.	TYPE OF DOCUMENT (Choose One)	DATE OF DOCUMENT:
11/21/2018	ANDA 061667/S-026	☐ ORIGINAL ANDA ● SUPPLEMENT TO ANDA	9/27/2018

NAME OF DRUG	PRIORITY CONSIDERATION (Choose One)	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Choose One)
Vancomycin Hydrochloride for Oral Solution, USP	■ GDUFA Due Date (HIGH) ☐ Low		GDUFA Due Date:1/26/19 Requested Due Date 12/28/2018

NAME OF FIRM: ANI Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION (carton/container label)
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
■ OTHER *(SPECIFY BELOW)*:
Review PI for accuracy to ensure that it provides for the safe and effective use of generic drug product

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

ANI Pharmaceuticals Inc. submitted a PAS for ANDA 061667/S-026, Vancomycin Hydrochloride Oral Solution, on 09/27/2018 for a reformulation of the drug product. We note that the last approved labeling is S-020 approved on 07/29/1993. We note that the ANDA was originally approved in 1972 as an abbreviated antibiotic application (AADA) pursuant to Form -6 procedures and has historically made labeling updates independent of an RLD.

We note that the only comparable drug product in the market place is Firvanq (vancomyin hydrochloride) for oral solution, NDA 208910/S-000 approved on January 26, 2018.

Questions for OND to address
1. Kindly evaluate the proposed ANDA labeling in its entirety to determine if labeling changes are necessary to ensure the safe and effective use of the drug product.
2. For any recommended updates to the labeling, kindly confirm that the information is *necessary* for the safe and effective use of the drug product. (Kindly note that the regulatory pathway does not allow for the PLR conversion of this labeling at this time).

Vancocin Oral Solution Proposed Te

SIGNATURE OF REQUESTER Oluwakemi O. Odesina (Electronic Signature)	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND ☐ DAARTS ■ PANORAMA
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

ANDA 061667/S-026

ACKNOWLEDGEMENT
sANDA RECEIPT

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

Dear Ellen Camos:

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

NAME OF DRUG: Vancomycin Hydrochloride for Oral Solution USP, 250 mg base/5 mL

DATE OF APPLICATION: September 27, 2018

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: September 27, 2018

Reference is made to the information request dated October 5, 2018 and to any amendments thereafter.

This supplement is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). Your request for a priority review of this submission meets the criteria listed in section 505(j)(11)(A) of the FD&C Act or the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority supplement, the GDUFA goal date for review of this priority supplement is January 26, 2019. If FDA determines that an inspection is required to validate the information contained in this priority supplement and a Pre-Submission Facility Correspondence was submitted and found eligible for further assessment, and at the time of your priority supplement submission the facility information was found to be complete and accurate, the GDUFA goal date for review of this priority supplement is May 26, 2019.

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

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

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Kevin Herkenham, Project Manager Team Leader, at Kevin.Herkenham@FDA.HHS.GOV[2] or 240-402-8964. We also recommend that you sign up for Generic Drug e-mail updates,[3] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Anh Hoang, Pharm.D.
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

[1]We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[2]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.
[3] http://go.fda.gov/subscriptionmanagement

Anh Hoang

Digitally signed by Anh Hoang
Date: 10/11/2018 07:23:42AM
GUID: 54204f580001917f2f9b18ab623760e7

ANDA FILING CHECKLIST

(Post June 20, 2014)

ANDA: **A061667-Suppl 26**
APPLICANT: **ANI Pharmaceuticals, Inc.**
RELATED APPLICATION(S): Related applications

DRUG PRODUCT NAME: **Vancomycin Hydrochloride for Oral Solution USP**
STRENGTH(S): **250 mg base/5 ml**

LETTER (356h) DATE: **September 27, 2018**
RECEIVED DATE: **September 27, 2018**
GDUFA GOAL DATE: January 26, 2019 *Goal date may have changed. Refer to the platform for most up-to-date goal date.*

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

BASIS OF SUBMISSION:

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

Reference listed drug (RLD):	**Vancocin**	Reference standard:	RS
New drug application (NDA) number:	**A061667**	NDA/ANDA number:	NDA/ANDA number
NDA holder:	**ANI Pharmaceuticals Inc**	NDA/ANDA holder:	NDA/ANDA holder
Drug product:	**Vancomycin Hydrochloride**	Drug product:	Drug product

Completion Signature	Recommendation:
10/10/2018 X Sun Hee Min Filing Reviewer Signed by: PIV	☒ **FILE** ☐ **REFUSE to RECEIVE**

1. ☒ Confirm that appropriate **Application Specific Inspection Criteria** have been checked
2. ☒ QC Application Information Task Completed (Update Product Information, Patent and Policy in Project and Program Level) *(any corrections should be sent to CDERInformatics)*
3. ☒ GDUFA Obligations Met (Filing Fee, Type II DMF Fee, and Facility Fee)- (internal notation-if not met contact: cder-gdufa-applications@fda.hhs.gov)
4. PFC: ☒ 60 days prior to ANDA submission ☐ Signed certification statement indicating information is unchanged
5. ☒ DMF Complete Assessment
6. ~~☐ Policy Alert List ANDA – check for updates prior to issuing IR/action letter~~
7. ☐ This is a combination product as defined under 21 CFR 3 (e.g., drug/device, drug/biologic)
8. ~~☐ Competitive Generic Therapy at the time of filing.~~ ~~Notify PET team through platform (tag: Rinku Patel and Iain Margand)~~
9. ☒ 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)

Copy and Paste the following Screen shots:

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

Fri 10/5/2018 1:23 PM

Gaines, Tangela

ANDA 061667/S-026 Filing Review Comments

To ellen.camos@amphenaceuticals.com

Cc ANDAFiling

Action Items + Get more add

Dear Ellen Camos:

This electronic mail is in reference to the Prior Approval Supplement for ANDA 061667 submitted on September 27, 2018 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

SPECIAL INSTRUCTIONS:

- We request that you acknowledge the receipt of this email correspondence.
- Provide a complete response to all of the items identified below **within 10 business days** from the date of this communication.
- If a complete response is not submitted to the ANDA and received within 10 business days, the application will be deemed incomplete and will be refused for receipt.
- Your response should contain a point-by-point reply to each of the identified comment(s) with corresponding hyperlink(s), where applicable, to the body of data within the ANDA.
- You should notify me via email or telephone when you have submitted your response.
- Your cover letter should clearly indicate **Filing – Response to Information Request**.
- Any questions or need for clarification with respect to any of the following deficiencies can be sent to me, the project manager assigned to this ANDA during filing review. A teleconference may be requested within 1 business day of this email. With your request, you must clearly identify your question(s). **(Note: The teleconference will be limited to a discussion of only the questions provided in your teleconference request. Also, your query does not place a hold on the timeframe in which the response must be submitted, as per bullet 2.)**

1. On Form FDA 356h, cite the basis of submission in Field 20. SEQ 0011
2. In module 1.12.11, provide the necessary information in regard to the Basis of Submission. SEQ 0011

Note: Provide a fillable PDF copy of the Form FDA 356h in all your submissions if you are submitting a scanned signed copy of the Form FDA 356h, otherwise the omission of the fillable PDF copy of the Form FDA 356h will be counted as a deficiency. The most current version of Form FDA 356h should be utilized.

MODULE 1: ADMINISTRATIVE

1.1 — 1.1.2

Rx **Signed and completed application form (356h)** (Prescription (Rx) /Over-the Counter (OTC) Status)
21 CFR 314.94(a)(1) (original signature)

YES **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

Needs to indicate BOS SEQ 0011

Select *Form FDA 3794 (PDF) GDUFA*

Comments

1.2 — *

YES **Cover letter**

N/A **Is the drug product subject to REMS requirements?**
http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Comments

1.2.1

Select **Form FDA 3674 (PDF)** 42 U.S.C. 282(j)(5)(B)

Select **Electronic, fillable copy** (if a signed, scanned copy is provided)

Comments

1.3.1

Contact/Applicant information

Select **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

Select *Field copy certification* *21CFR §314.94(d)(5)*

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)

Select 1. Debarment certification (original signature)

Select 2. List of convictions statement (original signature)

Comments

1.3.4

Financial Certifications 21 CFR §54 | 21 CFR §54.2(e) | 21 CFR §314.94(a)(13)

Select Bioavailability (BA)/Bioequivalence (BE) financial certification (Form FDA 3454)

Select Disclosure statement (Form FDA 3455)

Comments

1.3 — 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 *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book)

1.3.5.2 Patent certification or statement 21 CFR §314.94(a)(12)(i)(A)(1) through (4) or §314.94(a)(12)(iii)

1. Patent number(s)

Check all situations that apply:

	Certification	Patents
☐	No Relevant Patents	
☐	MOU	
☐	PI	
☐	PII	
☐	PIII	
☐	PIV	

Statement of notification (21 CFR §314.95 | 505(j)(2)(B)) ☐

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?

NO Pediatric exclusivity (new patent population (NPP), pediatric exclusivity (PED))

		N/A PEPFAR NCE-1 Wavier of Exclusivity ☒ Receipt date of ANDA submission after the approval date per Orange Book There are currently only two applications listed in the Orange Book for this specific drug product, ANI's ANDA 067667 and Lederle Parenterals Inc.'s ANDA 063321. Lederle Parenterals Inc.'s ANDA[3] was withdrawn per Federal Register (Docket No. 2004N-0159), leaving ANDA 061667 as the only legitimate ANDA remaining listed in the Orange Book for this specific drug product. The Orange Book does not currently list an RLD (or a Reference Standard) for Vancocin® (vancomycin hydrochloride for oral solution USP), eq. to 250 mg base/5 mL and 500 mg base/6 mL. Accordingly, there are no patent or exclusivities that remain for vancomycin hydrochloride for oral solution.

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

VANCOCIN HYDROCHLORIDE (VANCOMYCIN HYDROCHLORIDE)
EQ 250MG BASE/5ML — Marketing Status: Discontinued

Active Ingredient: VANCOMYCIN HYDROCHLORIDE
Proprietary Name: VANCOCIN HYDROCHLORIDE
Dosage Form; Route of Administration: FOR SOLUTION; ORAL
Strength: EQ 250MG BASE/5ML
Reference Listed Drug: No
Reference Standard: No
TE Code:
Application Number: A061667
Product Number: 002
Approval Date: Jul 13, 1983
Applicant Holder Full Name: ANI PHARMACEUTICALS INC
Marketing Status: Discontinued
Patent and Exclusivity Information

VANCOCIN HYDROCHLORIDE (VANCOMYCIN HYDROCHLORIDE)
EQ 500MG BASE/6ML — Marketing Status: Discontinued

Active Ingredient: VANCOMYCIN HYDROCHLORIDE
Proprietary Name: VANCOCIN HYDROCHLORIDE
Dosage Form; Route of Administration: FOR SOLUTION; ORAL
Strength: EQ 500MG BASE/6ML
Reference Listed Drug: No
Reference Standard: No
TE Code:
Application Number: A061667
Product Number: 001
Approval Date: Approved Prior to Jan 1, 1982
Applicant Holder Full Name: ANI PHARMACEUTICALS INC
Marketing Status: Discontinued
Patent and Exclusivity Information

Product 002
VANCOMYCIN HYDROCHLORIDE (VANCOCIN HYDROCHLORIDE) FOR SOLUTION EQ 250MG BASE/5ML

Product 001
VANCOMYCIN HYDROCHLORIDE (VANCOCIN HYDROCHLORIDE) FOR SOLUTION EQ 500MG BASE/6ML

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date

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.

Copy and Paste the RLD. If the RLD is an ANDA, then trace back to NDA on which the ANDA was based. A screenshot of section 1.12.11 Basis for Submission from the RLD ANDA should be provided.

1.4	**1.4.2**		**Statement of right of references** 21 CFR §314.50(g)(1) DMF Written Statement of authorization for reference (copy of letter of authorization (LoA) received from DMF holders)
		Select	1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient (API)
			2. Type II DMF# Enter Type II DMF #
		Select	3. Type III DMF authorization letter(s) for container closure
			Comments
1.12	**1.12.4**	Select	**Request for comments and advice** – Proprietary name requested

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

		highlighted and annotated a. Container closure system (if different from what is approved for the RLD) **N/A** i. Vial or ampule vs. prefilled syringe **N/A** ii. Vial vs. ampule **N/A** b. Drug product packaged in an IV bag **N/A** **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 Comments

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

MODULE 2: CTD SUMMARIES

2.3 QUALITY OVERALL SUMMARY (QOS)

21 CFR 314.50(c)

2.3	**Select** **E-Submission: PDF** **Select** **MS Word** **Additional information regarding QbR may be found at the following link:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm **Select** **Question based review (QbR)**
	Comments
	Select **2.3.S Drug substance (API)** 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
	Select **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 (API) 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 guidance for industry, *Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (March 2013) (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
2.7	**Clinical summary (BE)** module BE data summary tables 21 CFR 320.21(b) and § 320.24(b) See data-specific summary tables (below)
	Comments

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (API)

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

3.2.S.1

Select **General Information** (May not refer to DMF)

3.2.S.1.1 Nomenclature

3.2.S.1.2 Structure

3.2.S.1.3 General properties

Comments

3.2.S.2.1

Select **Manufacturer**

Drug substance (API)

Must correlate to the establishment information submitted in annex to Form FDA 356h

1. Name and full address(es) of the facility(ies)
2. Contact name, phone and fax numbers, email address
3. U.S. Agent's name (if applicable)
4. Specify function or responsibility
5. Type II DMF number(s) for API(s)
6. Central file number (CFN), facility establishment identifier (FEI), or data universal number system (DUNS) number (if available)
7. Additional sources of API and information (1 through 6, if applicable)

Comments

3.2.S.3

Select **Characterization**

All potential impurities should be listed in tabular format

IUPAC Chemical Name	Code #	Chemical Structure	Process/ Degradation Impurity	Source/ Mechanism

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

Comments

3.2.S.4 **Control of Drug Substance (API)**

3.2.S.4.1

Select **Specification**

Testing specifications and data

Comments

3.2.S.4.2

Select **Analytical Procedures**

Comments

3.2.S.4.3

Select **Validation of Analytical Procedures**

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

Select 1. Spectra and chromatograms for **reference standards** and **test samples** *(ref. std. can be located in 3.2.S.5)*

Select 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

Select 1. Certificate of analysis (COA) specifications and test results from drug substance manufacturer(s)

Select 2. Drug product manufacturer's certificate of analysis

API lot numbers API lot numbers

Comments

3.2.S.4.5

Justification of Specifications

All potential impurities should be listed in tabular format

Select **Specified identified impurities:**

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

										Regulatory QT Threshold (%)

Select

Specified unidentified impurities:

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

Select

Unspecified impurities:

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

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

Comments

3.2.S.5

Select **Reference standards or materials** (Do NOT refer to DMF)

Comments

3.2.S.6

Select **Container closure systems**

Comments

3.2.S.7

Stability

Select 1. Retest date or expiration date of API(s)

Comments

3.2.P DRUG PRODUCT

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

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

Copy and Paste Drug Product Composition (also found in Table 6 or 2.3.P.1)

Table 1 – Final Dry Powder Formulation for Vancocin® (vancomycin hydrochloride for oral solution), Eq. to 250 mg base/5 mL

Component	Function	250 mg/5 mL	
		% w/w	mg/dose
Vancomycin HCl USP	Drug Substance	(b) (4)	*250.000
Citric Acid USP Anhydrous			(b) (4)
Flavor – (b) (4) Mixed Berry			
Sodium Benzoate NF			
Sucralose NF			
Total			

*The unit dose weight for each powder batch will be calculated based on the activity of the Vancomycin HCl USP lots that were used during manufacturing in order to ensure a label claim of 250 mg vancomycin activity.

Table 2 – Final Reconstituted Formulation for Vancocin® HCl (vancomycin hydrochloride for oral solution), Eq. to 250 mg base/5 mL

Component	Function	250 mg base/5 mL	
		% w/v	mg/dose
Vancomycin HCl USP	Drug Substance		(b) (4)
Citric Acid USP Anhydrous			(b) (4)
Flavor – (b) (4) Mixed Berry			
Sodium Benzoate NF			
Sucralose NF			
Purified Water USP	Reconstituting Agent		(b) (4)

*The unit dose weight for each powder batch will be calculated based on the activity of the Vancomycin HCl USP lots that were used during manufacturing in order to ensure a label claim of 250 mg vancomycin activity.

Following this page, 1 Page Withheld in Full as (b)(4)