CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 214585Orig1s000

Name: Mesalamine Extended-Release Capsules USP, 500 mg

Sponsor: Sun Pharmaceutical Industries Limited

Approval Date: May 11, 2022

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANDA 214585Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ANDA 214585Orig1s000

APPROVAL LETTER

ANDA 214585

ANDA APPROVAL

Sun Pharmaceuticals Industries, Inc.
U.S. Agent for Sun Pharma Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Praveen Devakadaksham:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Extended Release Capsules USP, 500 mg.

Reference is also made to the complete response letter issued by this office on January 26, 2022, and to any amendments thereafter.

Reference is also made to FDA's Competitive Generic Therapy Designation – Grant letter dated March 5, 2021.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Mesalamine Extended Release Capsules USP, 500 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Pentasa Extended-Release Capsules, 500 mg, of Takeda Pharmaceuticals USA Inc. (Takeda).

We note that Sun Pharma Industries Ltd (Sun) was granted a Competitive Generic Therapy (CGT) designation for Mesalamine Extended Release Capsules USP, 500 mg. Sun is the "first approved applicant" for Mesalamine Extended Release Capsules USP, 500 mg, as defined in section 505(j)(5)(B)(v)(III) of the FD&C Act. Therefore, with this approval, Sun is eligible for 180 days of CGT exclusivity for Mesalamine Extended Release Capsules USP, 500 mg, under section 505(j)(5)(B)(v) of the FD&C Act. This exclusivity will begin to run from the date of the first commercial marketing of the CGT (including the commercial marketing of the listed drug) by Sun, as specified in section 505(j)(5)(B)(v) of the FD&C Act. Furthermore, in accordance with section 505(j)(5)(B)(v)(I) of the FD&C Act, this 180-day CGT exclusivity will not block approval of other applications until Sun has commenced commercial marketing. Please submit a correspondence to this ANDA informing the Agency of the date you begin commercial

marketing. Please also submit notice of first commercial marketing via e-mail to the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov. This e-mail should be sent the same day you commence commercial marketing. Reference is also made to the Special Forfeiture Rule for Competitive Generic Therapy in section 505(j)(5)(D)(iv) of the FD&C Act. Please be aware that, pursuant to this forfeiture rule, you will forfeit your eligibility for the 180-day CGT exclusivity period for Mesalamine Extended Release Capsules USP, 500 mg, if you fail to market this CGT within 75 days after the date on which the approval of this application is made effective.

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

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

REPORTING REQUIREMENTS

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

PROMOTIONAL MATERIALS

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: https://www.fda.gov/media/128163/download).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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

Catherine Poole

Digitally signed by Catherine Poole
Date: 5/11/2022 10:53:28AM
GUID: 5407887a000a1c0c26055eafb8e3258a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214585Orig1s000

OTHER ACTION LETTERS

ANDA 214585

COMPLETE RESPONSE

Sun Pharmaceuticals Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Praveen Devakadaksham:

This is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Mesalamine Extended Release Capsules USP, 500 mg.

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

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

PHARMACEUTICAL QUALITY

Drug Substance

1. (b) (4)

2.

Drug Product

1.

2.

3.

4.

5.

(b) (4)

[redacted]

Manufacturing

1. (b) (4)

2.

3.

BIOPHARMACEUTICS/BIOEQUIVALENCE/LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if

any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (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.

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

It is also your responsibility to ensure that your ANDA addresses all listed patents and 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. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/MANUFACTURING

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 as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore 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 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.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or

marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

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

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

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 1/26/2022 09:33:03PM
GUID: 5277df670008860f7e1231f730a8684c

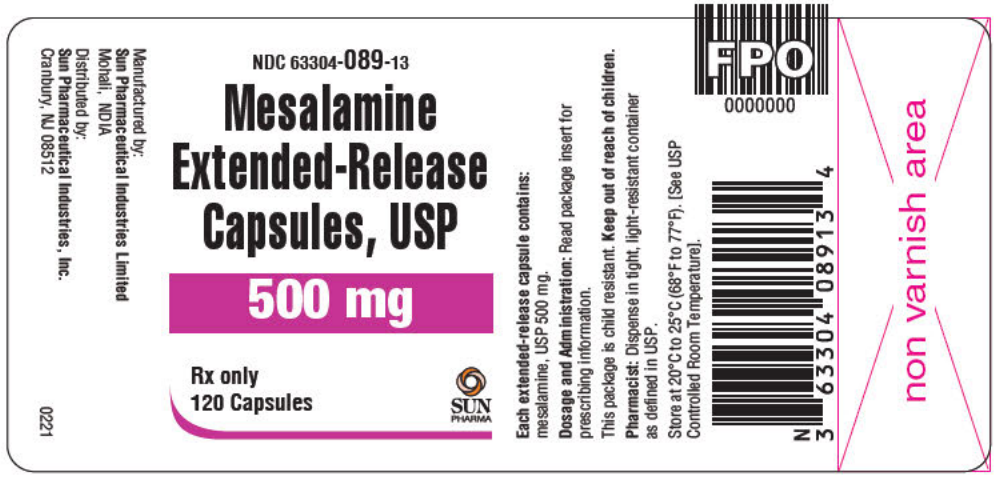
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214585Orig1s000

LABELING

Unwinding Direction



(b) (4)

MESALAMINE EXTENDED-RELEASE CAPSULES, USP

500 mg

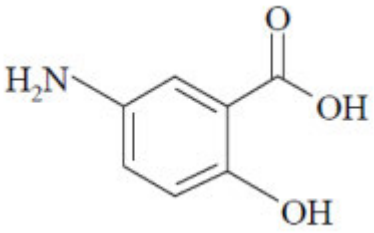
Rx only

DESCRIPTION

Mesalamine extended-release capsules, USP for oral administration are extended-release formulation of mesalamine, USP, an aminosalicylate anti-inflammatory agent for gastrointestinal use.

Chemically, mesalamine, USP is benzoic acid, 5-amino-2-hydroxy. It has a molecular weight of 153.14.

The structural formula is:



Each 500 mg mesalamine extended-release capsule contains 500 mg of mesalamine, USP. It also contains the following inactive ingredients: castor oil, colloidal silicon dioxide, diacetylated monoglyceride, ethylcellulose, hypromellose, stearic acid, sugar spheres (corn starch and sucrose), talc, and white wax. The capsule shell contains FD&C Blue 1, gelatin, sodium lauryl sulfate, and titanium dioxide. The imprinting ink contains ferrosoferric oxide, potassium hydroxide, and shellac.

FDA approved dissolution test specifications differ from USP.

CLINICAL PHARMACOLOGY

Sulfasalazine is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). The usual oral dose of sulfasalazine for active ulcerative colitis in adults is 2 to 4 g per day in divided doses. Four grams of sulfasalazine provide 1.6 g of free mesalamine to the colon.

The mechanism of action of mesalamine (and sulfasalazine) is not fully understood, but it appears to be a topical anti-inflammatory effect on colonic epithelial cells. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways (i.e., prostanoids) and through the lipoxygenase pathways (i.e., leukotrienes (LTs)) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with ulcerative colitis, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

Human Pharmacokinetics and Metabolism

Absorption: Mesalamine extended-release capsules are ethylcellulose-coated, extended-release formulation of mesalamine designed to release therapeutic quantities of mesalamine throughout the gastrointestinal tract. Based on urinary excretion data, 20% to 30% of the mesalamine in mesalamine extended-release capsules is absorbed. In contrast, when mesalamine is administered orally as an unformulated 1-g aqueous suspension, mesalamine is approximately 80% absorbed.

Plasma mesalamine concentration peaked at approximately 1 mcg/mL 3 hours following a 1-g mesalamine dose and declined in a biphasic manner. The literature describes a mean terminal half-life of 42 minutes for mesalamine following intravenous administration. Because of the continuous release and absorption of mesalamine from mesalamine extended-release capsule throughout the gastrointestinal tract, the true elimination half-life cannot be determined after oral administration. N-acetyl-5-aminosalicylic acid, the major metabolite of mesalamine (5-aminosalicylic acid), peaked at approximately 3 hours at 1.8 mcg/mL, and its concentration followed a biphasic decline. Pharmacological activities of N-acetyl-5-aminosalicylic acid are unknown, and other metabolites have not been identified.

Oral mesalamine pharmacokinetics were nonlinear when mesalamine extended-release capsules were dosed from 250 mg to 1 g four times daily, with steady-state mesalamine plasma concentrations increasing about nine times, from 0.14 mcg/mL to 1.21 mcg/mL, suggesting saturable first-pass metabolism. N-acetyl-5-aminosalicylic acid pharmacokinetics were linear.

Elimination: About 130 mg free mesalamine was recovered in the feces following a single 1-g mesalamine dose, which was comparable to the 140 mg of mesalamine recovered from the molar equivalent sulfasalazine tablet dose of 2.5 g. Elimination of free mesalamine and salicylates in feces increased proportionately with mesalamine dose. N-acetyl-5-aminosalicylic acid was the primary compound excreted in the urine (19% to 30%) following mesalamine dosing.

CLINICAL TRIALS

In two randomized, double-blind, placebo-controlled, dose-response trials (UC-1 and UC-2) of 625 patients with active mild to moderate ulcerative colitis, mesalamine, at an oral dose of 4 g/day given 1 g four times daily, produced consistent improvement in prospectively identified primary efficacy parameters, PGA, Tx F, and SI as shown in the table below.

The 4-g dose of mesalamine also gave consistent improvement in secondary efficacy parameters, namely the frequency of trips to the toilet, stool consistency, rectal bleeding, abdominal/rectal pain, and urgency. The 4-g dose of mesalamine induced remission as assessed by endoscopic and symptomatic endpoints.

In some patients, the 2-g dose of mesalamine was observed to improve efficacy parameters measured. However, the 2-g dose gave inconsistent results in primary efficacy parameters across the two adequate and well controlled trials.

Parameter Evaluated	Clinical Trial UC-1			Clinical Trial UC-2		
		Mesalamine			Mesalamine	
	PL (n = 90)	4 g/day (n = 95)	2 g/day (n = 97)	PL (n = 83)	4 g/day (n = 85)	2 g/day (n = 83)
PGA	36%	59%*	57%*	31%	55%*	41%
Tx F	22%	9%*	18%	31%	9%*	17%*
SI	-2.5	-5.0*	-4.3*	-1.6	-3.8*	-2.6
Remission†	12%	26%*	24%*	12%	27%*	12%

*p<0.05 vs placebo.

PGA: Physician Global Assessment: proportion of patients with complete or marked improvement.

Tx F: Treatment Failure: proportion of patients developing severe or fulminant UC requiring steroid therapy or hospitalization or worsening of the disease at 7 days of therapy, or lack of significant improvement by 14 days of therapy.

SI: Sigmoidoscopic Index: an objective measure of disease activity rated by a standard (15-point) scale that includes mucosal vascular pattern, erythema, friability, granularity/ulcerations, and mucopus: improvement over baseline.

† Defined as complete resolution of symptoms plus improvement of endoscopic endpoints. To be considered in remission, patients had a "1" score for one of the endoscopic components (mucosal vascular pattern, erythema, granularity, or friability) and "0" for the others.

INDICATIONS AND USAGE

Mesalamine extended-release capsules are indicated for the induction of remission and for the treatment of adult patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS

Mesalamine extended-release capsules are contraindicated in patients with known or suspected hypersensitivity to salicylates, aminosalicylates, or any components of this medication.

PRECAUTIONS

Renal Impairment

Renal impairment, including minimal change disease, acute and chronic interstitial nephritis, and renal failure have been reported in patients given mesalamine extended-release capsules or other products that contain mesalamine or are converted to mesalamine.

Mesalamine is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Evaluate renal function in all patients prior to initiation and periodically while on therapy with mesalamine extended-release capsules. Evaluate the risks and benefits of using mesalamine extended-release capsules in patients with known renal impairment or a history of renal disease or taking concomitant nephrotoxic drugs.

Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Symptoms include cramping, acute abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash. Monitor patients for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine extended-release capsules.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some patients may have a similar reaction to mesalamine or to other compounds that contain or are converted to mesalamine.

As with sulfasalazine, mesalamine-induced hypersensitivity reactions may present as internal organ involvement, including myocarditis, pericarditis, nephritis, hepatitis, pneumonitis, and hematologic abnormalities. Evaluate patients immediately if signs or symptoms of a hypersensitivity reaction are present. Discontinue mesalamine if an alternative etiology for the signs and symptoms cannot be established.

Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered other products containing mesalamine. Evaluate the risks and benefits of using mesalamine in patients with known liver impairment.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in with the use of mesalamine (see **ADVERSE REACTIONS**). Discontinue mesalamine at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Photosensitivity

Patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions. Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalamine, including stones with 100% mesalamine content. Mesalamine-containing stones are radiotransparent and undetectable by standard radiography or computed tomography (CT). Ensure adequate hydration during treatment.

Interference with Laboratory Tests

Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection because of the similarity in the chromatograms of normetanephrine and mesalamine's main metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). Consider an alternative, selective assay for normetanephrine.

Drug Interactions

No investigations of interactions between mesalamine and other drugs have been performed; however, the following drug-drug interactions have been reported for products containing mesalamine:

Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs), may increase the risk of nephrotoxicity. Monitor patients taking nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions.

Azathioprine or 6-Mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine and/or any other

drugs known to cause myelotoxicity may increase the risk for blood disorders, bone marrow failure, and associated complications. If concomitant use of mesalamine and azathioprine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50-kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.

No evidence of mutagenicity was observed in an *in vitro* Ames test and in an *in vivo* mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with mesalamine during controlled clinical trials.

Pregnancy

Teratogenic Effects

Published data from meta-analyses, cohort studies, and case series on the use of mesalamine during pregnancy have not reliably informed an association with mesalamine and major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is no clear evidence that mesalamine exposure in early pregnancy is associated with an increased risk of major congenital malformations, including cardiac malformations. Published epidemiologic studies have important methodological limitations which hinder interpretation of the data, including inability to control for confounders, such as underlying maternal disease, maternal use of concomitant medications, and missing information on the dose and duration of use for mesalamine products. Mesalamine should only be used during pregnancy if the benefits outweigh the risks.

In animal reproduction studies, oral administration of mesalamine during organogenesis to pregnant rats at doses up to 1000 mg/kg/day (5900 mg/m^2) and rabbits at doses of 800 mg/kg/day (6856 mg/m^2) revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Nonteratogenic Effects

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Nursing Mothers

Data from published literature report the presence of mesalamine and its metabolite, N-

acetyl-5-aminosalicylic acid in human milk in small amounts with relative infant doses (RID) of 0.1% or less for mesalamine. The clinical significance of this has not been determined and there is limited experience of nursing women using mesalamine.

There are reports of diarrhea observed in breastfed infants exposed to mesalamine. The effect of mesalamine on milk production is unknown. Exercise caution if mesalamine extended-release capsules are administered to a nursing woman and monitor breastfed infants for diarrhea.

In published lactation studies, maternal mesalamine doses from various oral and rectal formulations and products ranged from 500 mg to 4.8 g daily. The average concentration of mesalamine in milk ranged from non-detectable to 0.5 mg/L. The average concentration of N-acetyl-5-aminosalicylic acid in milk ranged from 0.2 to 9.3 mg/L. Based on these concentrations, estimated infant daily dosages for an exclusively breastfed infant are 0 to 0.075 mg/kg/day of mesalamine (RID 0% to 0.1%) and 0.03 to 1.4 mg/kg/day of N-acetyl-5-aminosalicylic acid.

Pediatric Use

Safety and efficacy of mesalamine in pediatric patients have not been established.

Geriatric Use

Clinical trials of mesalamine did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias (i.e., agranulocytosis, neutropenia, and pancytopenia) in patients receiving mesalamine-containing products such as mesalamine extended-release capsules who were 65 years or older compared to younger patients. Monitor complete blood cell counts and platelet counts in elderly patients during treatment with mesalamine extended-release capsules.

In general, consider the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy in elderly patients when prescribing mesalamine.

ADVERSE REACTIONS

In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received mesalamine therapy. Generally, mesalamine therapy was well tolerated. The most common events (i.e., greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).

In two domestic placebo-controlled trials involving over 600 patients with ulcerative colitis, adverse events were fewer in mesalamine-treated patients than in the placebo group (mesalamine 14% vs placebo 18%) and were not dose-related. Events occurring in more than 1% are shown in the table below. Of these, only nausea and vomiting were more frequent in the mesalamine group. Withdrawal from therapy due to adverse events was more common on placebo than mesalamine (7% vs 4%).

Table 1. Adverse Events Occurring in More than 1% of Either Placebo or Mesalamine Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (Mesalamine Comparison to Placebo)

Event	Mesalamine n = 451	Placebo n = 173
Diarrhea	16 (3.5%)	13 (7.5%)
Headache	10 (2.2%)	6 (3.5%)
Nausea	14 (3.1%)	-----
Abdominal Pain	5 (1.1%)	7 (4.0%)
Melena (Bloody Diarrhea)	4 (0.9%)	6 (3.5%)
Rash	6 (1.3%)	2 (1.2%)
Anorexia	5 (1.1%)	2 (1.2%)
Fever	4 (0.9%)	2 (1.2%)
Rectal Urgency	1 (0.2%)	4 (2.3%)
Nausea and Vomiting	5 (1.1%)	-----
Worsening of Ulcerative Colitis	2 (0.4%)	2 (1.2%)
Acne	1 (0.2%)	2 (1.2%)

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematological, liver, and kidney function.

The following adverse events, presented by body system, were reported infrequently (i.e., less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to mesalamine has not been established.

Gastrointestinal: abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliasis, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst

Dermatological: acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria

Nervous System: depression, dizziness, insomnia, somnolence, paresthesia

Cardiovascular: palpitations, pericarditis, vasodilation

Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocythemia, thrombocytopenia, urinary frequency

One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.

Published case reports and/or spontaneous postmarketing surveillance have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial

nephritis, hepatitis, aplastic anemia, pancytopenia, leukopenia, agranulocytosis, or anemia while receiving mesalamine therapy. Anemia can be a part of the clinical presentation of inflammatory bowel disease. Allergic reactions, which could involve eosinophilia, can be seen in connection with mesalamine therapy.

Postmarketing Reports

The following events have been identified during post-approval use of the mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Gastrointestinal: Reports of hepatotoxicity, including elevated liver enzymes (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), hepatitis, jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported.

Other: anaphylactic reaction, SJS/TEN, DRESS, AGEP, pleurisy/pleuritis, pneumonitis, granulocytopenia, systemic lupus erythematosus, lupus-like syndrome, acute renal failure, interstitial lung disease, hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), chronic renal failure, nephrogenic diabetes insipidus, nephrolithiasis, intracranial hypertension, angioedema, and oligospermia (reversible).

OVERDOSAGE

Mesalamine is an aminosalicylate, and symptoms of salicylate toxicity may be possible, such as: nausea, vomiting, abdominal pain, tachypnea, hyperpnea, tinnitus, and neurologic symptoms (headache, dizziness, confusion, seizures). Severe intoxication with salicylates may lead to electrolyte and blood-pH imbalance and potentially to other organ (e.g., renal and liver) damage.

Treatment of Overdosage: There is no specific antidote for mesalamine overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage and may include gastrointestinal tract decontamination to prevent further absorption. Correct fluid and electrolyte imbalance by the administration of appropriate intravenous therapy and maintain adequate renal function.

DOSAGE AND ADMINISTRATION

The recommended dosage for the induction of remission and the symptomatic treatment of mildly to moderately active ulcerative colitis in adults is 1 g (2 mesalamine extended-release 500-mg capsules) 4 times a day for a total daily dosage of 4 g. Treatment duration in controlled trials was up to 8 weeks.

Mesalamine extended-release capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. The capsules and capsule contents must not be crushed or chewed.

Drink an adequate amount of fluids.

Safety and efficacy of mesalamine in pediatric patients have not been established.

HOW SUPPLIED

Mesalamine extended-release capsules, USP 500 mg are supplied in bottles of 120 capsules with child-resistant closure (NDC 63304-089-13). Each dark blue capsule contains 500 mg of mesalamine, USP in extended-release pellets.

Mesalamine extended-release capsules, USP 500 mg are hard gelatin having dark blue cap and body with "**RL36**" printed on both cap and body in black ink containing off-white to light yellowish brown to dark yellowish brown colored pellets.

Store at 20 C to 25 C (68 F to 77 F). [See USP Controlled Room Temperature]. Preserve in tight, light-resistant containers.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured by:
Sun Pharmaceutical Industries Limited,
Mohali, INDIA

Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

November 2021 FDA-06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214585Orig1s000

LABELING REVIEWS

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	12/09/2021
ANDA Number(s)	214585
Review Number	2
Applicant Name	Sun Pharmaceutical Industries Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Mesalamine Extended Release Capsules USP, 500 mg
Proposed Proprietary Name	NA
Submission Received Date	August 04, 2021, October 20, 2021, November 03, 2021
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Ellen Koo

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

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C2)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C2)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C2)

The Division of Labeling has no further questions/comments at this time based on your labeling submissions received August 4, 2021, October 20, 2021, and November 03, 2021.

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

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

1.3 POST-APPROVAL REVISIONS (C2)

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

2 INSTRUCTIONS FOR ASSESSMENT (C2)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C2)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	500 mg: 120s	3/31/2021	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

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	Draft	November 2021 FDA-06	11/3/2021	Satisfactory
Medication Guide	N/A	NA		
Patient Information	N/A	NA		
Instructions for Use	N/A	NA		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C2)

4.1 REGULATORY INFORMATION (C2)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? Controlled Correspondence: **Controlled Correspondence Summary – 26097** Controlled Correspondence was filed on August 12, 2014 by Sun Pharmaceuticals. Number 26097 was assigned by Office of Generic Drugs. The title of inquiry was the following: Generic Pentasa (mesalamine) Controlled-Release Capsules. The firm would like to know the correct established name to use for their drug product, "Mesalamine Controlled-Release Capsules" or "Mesalamine Extended-Release Capsules"? Pentasa (mesalamine) Controlled-Release Capsules (NDA 020049) was approved May 10, 1993. Pentasa is listed as the reference listed drug (RLD) in the Orange Book. The Orange Book list the product as Mesalamine Extended-Release Capsule. There is currently a USP-NF monograph for Mesalamine Extended-Release Capsules. Whenever there is a USP-NF monograph for a drug product, USP-NF name is used as the generic name for the drug product. Refer to 21 CFR 299.4 and 21 CFR 299.5 was referenced). It was also noted that under USP General Chapters <1151> PHARMACEUTICAL DOSAGE FORMS, Capsules, there are 2 categories of Modified release capsule formulations recognized by the Pharmacopeia: Delayed-Release Capsules and Extended-Release Capsules. Extended –Release Capsules are formulated so that the API available over an extended period of following ingestion. Expression such as "prolonged-action", "repeat-action", "controlled-release" and "sustained-release "have also been used to describe such dosage forms. However, the term, extended-release, is used for Pharmacopeial purposes. Letter was sent by Office of Generic Drugs to Mr. Patel closing out the Controlled Correspondence, recommended to used generic name "Mesalamine Extended-Release Capsules" .

Yes	No	
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C2)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, 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): NDA 020049 / S-036

Supplement Approval Date: 11/01/2021

Proprietary Name: Pentasa

Established Name: Mesalamine Extended-Release Capsules

Description of Supplement:

We also refer to our letter dated August 3, 2021 notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for aminosalicylic acid and similar agents. This information pertains to the risk of severe cutaneous adverse reactions (SCARs), which includes Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), reported in FAERS.

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4801350_4392348_090140af805f3acf_NDA020049_3202164

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out)**:

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C2)

The Orange Book was searched on 12/09/2021

Table 4 provides Orange Book patents for the Model Labeling (NDA020049) and ANDA patent certifications. (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

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C2)

The USP was searched on 07/13/2021

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Mesalamine Extended-Release Capsules	Packaging and Storage: Preserve in tight, light-resistant containers. Add the following: ▲ •Labeling: When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.▲ (RB 1-Jun-2020)
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.

Deficiency	No Deficiency	
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

From the A214585 lt1 6 4 2021 Biopharm Assessment:

Proposed Dissolution Testing	
FDA Dissolution Database	
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Pending
Reviewer Evaluation	
Description of Links for Dissolution Methods	URL Link
USP NF Monograph	https://online.uspnf.com/uspnf/document/1_GUID-F44B5678-F9F2-4E44-BCA1-5C3D5B0468D_3_en-US?source=Quick%20Search&highlight=mesalamine
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	No
Reviewer Evaluation	
Number of units tested meets the requirements (e.g. 12 units)	Yes
Reviewer Evaluation	
Source of Dissolution Method	USP Monograph
Does the proposed drug product meet the USP Monograph standards?	Yes
The method in USP	Method 1
Reviewer Evaluation	

Deficiencies

Proposed Dissolution Methods and Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	(b) (4)
			[Deficiency/IR]
			Based on the submitted in vitro dissolution data, the proposed dissolution acceptance criteria are permissive for your mesalamine extended-release capsules and NOT acceptable. The following data-driven dissolution acceptance criteria are recommended for all strengths: (b) (4) (b) (4) for your proposed drug product at release and on stability. Implement these dissolution acceptance criteria for all strengths of your drug product at release and on stability and update the specifications of the drug product with the revised criteria for the dissolution test, accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet the revised dissolution acceptance criteria in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

The applicant provides revised labeling with the 7/1/2021 submission to include (b) (4) (b) (4) However, we note the Biopharmaceutics review states that USP dissolution method 1 is used with a (b) (4) acceptance criteria. Therefore, a dissolution statement is not needed in the labeling.

Assessment:

The applicant revises the (b) (4)" to read "FDA approved dissolution test specifications differ from USP." An email to the Biopharmaceutics reviewer was sent on 12/9/2021 to verify the accuracy of the statement. (b) (4)

(b) (4)

To make sure, we will send an IR tomorrow ensuring that they maintain this statement on their label and petition the USP. Thank you for bringing this to my attention.

As the applicant's statement is accurate, no further comment is needed.

Deficiency Comments:

Deficiency # 1 DESCRIPTION: Remove [redacted] (b) (4)

Created in C1

Prescribing Information Response / Assessment: The applicant revises [redacted] (b) (4). Acceptable. Please see above.

4.5 MODEL CONTAINER LABELS (C2)

Model container/carton/blister labels (Source: NDA 020049/S-034 approval letter from Panorama **)**

AR-28 dated 7/8/2021 revises distributor:

5 ASSESSMENT OF ANDA LABELING AND LABELS (C2)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C2)

5.1.1 DRUG PRODUCT REVIEW (C2)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

A214585 lt1 9 17 2021 Drug Product Assessment

Labeling	
Description Section	
Is the information accurate?	Yes
Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
		(b) (4)
Mesalamine, USP 500mg	25	"RL36" printed on both cap and body in black ink
Is the imprint code consistent with the labeling?	Yes	
Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**	

5.1.2 DESCRIPTION (C2)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each 250-mg capsule contains 250 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains D&C Yellow #10, FD&C Blue #1, FD&C Green #3, gelatin, titanium dioxide, and other ingredients. Each 500-mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C Blue #1, gelatin, titanium dioxide, and other ingredients.
Previous ANDA Labeling	(b) (4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	(b) (4) [redacted]
Current ANDA Labeling	Each 500 mg mesalamine extended-release capsule contains 500 mg of mesalamine, USP. It also contains the following inactive ingredients: castor oil, colloidal silicon dioxide, diacetylated monoglyceride, ethylcellulose, hypromellose, stearic acid, sugar spheres (corn starch and sucrose), talc, and white wax. The capsule shell contains FD&C Blue 1, gelatin, sodium lauryl sulfate, and titanium dioxide. The imprinting ink contains ferrosoferric oxide, potassium hydroxide, and shellac. Assessment: (b) (4) [redacted] No changes noted in the inactive ingredients for the 500 mg.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C2)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	PENTASA extended-release 250-mg capsules are supplied in bottles of 240 capsules (NDC 54092-189-81). Each green and blue capsule contains 250 mg of mesalamine in extended-release beads. PENTASA extended-release capsules are identified with a pentagonal starburst logo and the number 2010 on the green portion and S429 250 mg on the blue portion of the capsules. PENTASA extended-release 500-mg capsules are supplied in bottles of 120 capsules (NDC 54092-191-12). Each blue capsule contains 500 mg of mesalamine in extended-release beads. PENTASA extended-release capsules are identified with a pentagonal starburst logo and S429 500 mg on the capsules. Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Previous ANDA Labeling	(b) (4) [redacted]
Current ANDA Labeling	Mesalamine extended-release capsules, USP 500 mg are supplied in bottles of 120 capsules with child-resistant closure (NDC 63304-089-13). Each dark blue capsule contains 500 mg of mesalamine, USP in extended-release pellets. Mesalamine extended-release capsules, USP 500 mg are hard gelatin having dark blue cap and body with "RL36" printed on both cap and body in black ink

Table 8: Comparison of Model Labeling to ANDA Labeling	
	containing off-white to light yellowish brown to dark yellowish brown colored pellets. Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Preserve in tight, light-resistant containers. Assessment: (b) (4)

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C2)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Sun Pharmaceutical Industries Limited, Mohali, INDIA Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Sun Pharmaceutical Industries Limited, Mohali, INDIA Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512 Assessment: No change noted

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.

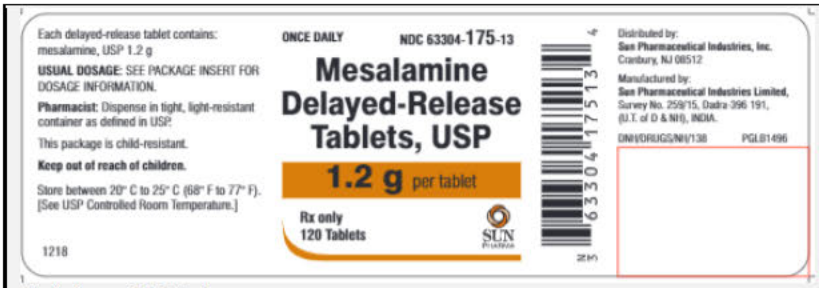
Deficiency	No Deficiency	
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

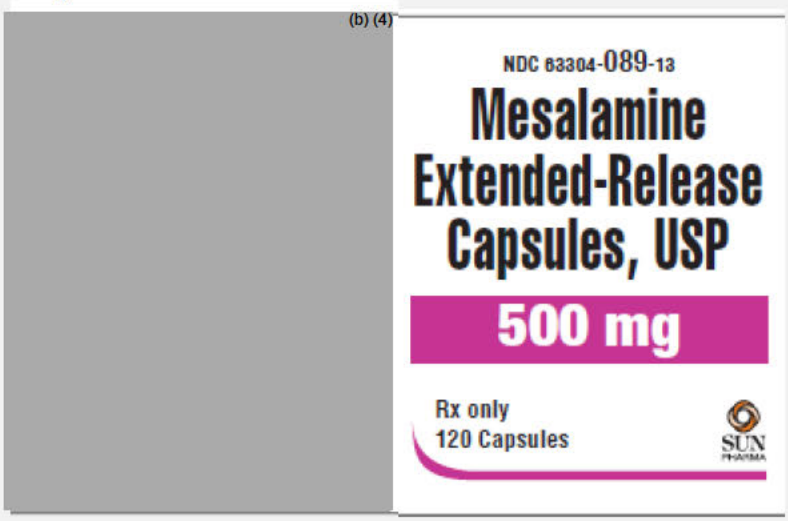
Related applications are adequately differentiated.

(b) (4)

Approved A211858:



Subject ANDA:



Bottles of (b) (4) and 120s (500 mg) are CRC.

Table 1: Details of the Container/Closure System

Strength	Count	Bottle	Cap
			(b) (4)
500 mg	120's count		(b) (4)

Deficiency Comments:

5.3 PRESCRIBING INFORMATION (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].

Deficiency	No Deficiency	
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The Prescribing Information from the 7/1/2021 submission supersedes the PI from the 03/31/2021 and 06/07/2021 submissions.

We will recommend revision to HOW SUPPLIED to add the strength to the second and fourth paragraphs and send a comment regarding drug substance vs drug product in the PI.

"Dispense in tight, light-resistant container as defined in USP" is stated on the container in line with the RLD. This statement is also in subject ANDA's PI. The RLD does not include the statement in their PI but we will not comment as it is in line with the container label.

Assessment:
The 8/4/2021 submission is the Labeling DRL response.
(b) (4).
The 11/3/2021 is in response to an RLD update. The labeling from this submission supersedes the labeling from the 8/4/2021 and 10/27/2021 submissions and satisfactorily updates the PI to be in accordance with the RLD.

Deficiency Comments:

Deficiency # 1 Created in C1 Prescribing Information	GENERAL: Ensure references to the drug substance and drug product are consistent throughout the Prescribing Information. Ensure to use the established name, Mesalamine Extended-Release Capsules, (i.e., dosage form included) when referring to the drug product.

Response / Assessment:	Addressed
Deficiency # 2 Created in C1 Prescribing Information Response / Assessment:	HOW SUPPLIED, second and fourth paragraphs: Add the strength to follow "Mesalamine extended-release capsules USP". (b) (4)

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C2)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:

Esther Kim

Digitally signed by Esther Kim
Date: 12/10/2021 08:25:01AM
GUID: 5423006c00721ec9406da22c031498a2

Ellen Koo

Digitally signed by Ellen Koo
Date: 12/14/2021 09:30:29AM
GUID: 508da73d0002b687dfbf9b3859d80789

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	07/13/2021
ANDA Number(s)	214585
Review Number	1
Applicant Name	Sun Pharmaceutical Industries Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Mesalamine Extended Release Capsules USP, (b) (4) (b) (4) 500 mg
Proposed Proprietary Name	NA
Submission Received Date	07/01/2021, 06/07/2021, 03/31/2021
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Ellen Koo

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

*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

TABLE OF CONTENTS

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submissions received March 31, 2021, June 7, 2021, and July 1, 2021:

PRESCRIBING INFORMATION

a. GENERAL: Ensure references to the drug substance and drug product are consistent throughout the Prescribing Information. Ensure to use the established name, Mesalamine Extended-Release Capsules, (i.e., dosage form included) when referring to the drug product.
b. DESCRIPTION: Remove [redacted] (b) (4)
c. HOW SUPPLIED, second and fourth paragraphs: Add the strength to follow "Mesalamine extended-release capsules USP".

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

1.3 POST-APPROVAL REVISIONS

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

2 INSTRUCTIONS FOR ASSESSMENT

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

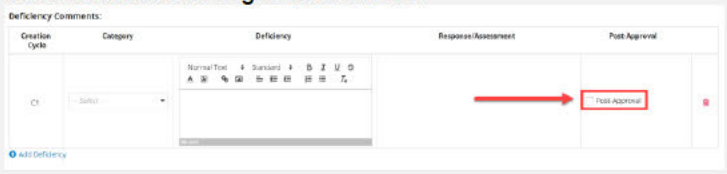
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	(b) (4) 500 mg: 120s	3/31/2021	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

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	Draft	June 2021	7/1/2021	Revise
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? Controlled Correspondence:

Yes	No	
		Controlled Correspondence Summary – 26097 Controlled Correspondence was filed on August 12, 2014 by Sun Pharmaceuticals. Number 26097 was assigned by Office of Generic Drugs. The title of inquiry was the following: Generic Pentasa (mesalamine) Controlled-Release Capsules. The firm would like to know the correct established name to use for their drug product, "Mesalamine Controlled-Release Capsules" or "Mesalamine Extended-Release Capsules"? Pentasa (mesalamine) Controlled-Release Capsules (NDA 020049) was approved May 10, 1993. Pentasa is listed as the reference listed drug (RLD) in the Orange Book. The Orange Book list the product as Mesalamine Extended-Release Capsule. There is currently a USP-NF monograph for Mesalamine Extended-Release Capsules. Whenever there is a USP-NF monograph for a drug product, USP-NF name is used as the generic name for the drug product. Refer to 21 CFR 299.4 and 21 CFR 299.5 was referenced). It was also noted that under USP General Chapters <1151> PHARMACEUTICAL DOSAGE FORMS, Capsules, there are 2 categories of Modified release capsule formulations recognized by the Pharmacopeia: Delayed-Release Capsules and Extended-Release Capsules. Extended –Release Capsules are formulated so that the API available over an extended period of following ingestion. Expression such as "prolonged-action", "repeat-action", "controlled-release" and "sustained-release "have also been used to describe such dosage forms. However, the term, extended-release, is used for Pharmacopeial purposes. Letter was sent by Office of Generic Drugs to Mr. Patel closing out the Controlled Correspondence, recommended to used generic name "Mesalamine Extended-Release Capsules" .
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, 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): NDA 020049 / S-035

Supplement Approval Date: 05/25/2021

Proprietary Name: Pentasa

Established Name: Mesalamine Extended-Release Capsules

Description of Supplement:

This Prior Approval sNDA provides for the addition of the terms toxic epidermal necrolysis (TEN) and pleurisy/pleuritis to the Prescribing Information (PI).

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4801350_4392348_090140af805f3acf_NDA020049_3202164

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out)**:

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments**:		

4.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 07/13/2021

Table 4 provides Orange Book patents for the Model Labeling (NDA020049) and ANDA patent certifications. (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							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 07/13/2021

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Mesalamine Extended-Release Capsules	Packaging and Storage: Preserve in tight, light-resistant containers. Add the following: ▲ •Labeling: When more than one

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
				Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.▲ (RB 1-Jun-2020)
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☒	☐	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

From the A214585_lt1_6_4_2021_Biopharm Assessment:

Proposed Dissolution Testing	
FDA Dissolution Database	
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Pending
Reviewer Evaluation	
Description of Links for Dissolution Methods	URL Link
USP NF Monograph	https://online.uspnf.com/uspnf/document/1_GUID-F44B5678-F9F2-4E44-BCA1-5C3D5B0468D_3_en-US?source=Quick%20Search&highlight=mesalamine
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	No
Reviewer Evaluation	
Number of units tested meets the requirements (e.g. 12 units)	Yes
Reviewer Evaluation	
Source of Dissolution Method	USP Monograph
Does the proposed drug product meet the USP Monograph standards?	Yes
The method in USP	Method 1
Reviewer Evaluation	

Deficiencies

Proposed Dissolution Methods and Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	(b) (4)
			[Deficiency/IR]
			Based on the submitted in vitro dissolution data, the proposed dissolution acceptance criteria are permissive for your mesalamine extended-release capsules and NOT acceptable. The following data-driven dissolution acceptance criteria are recommended for all strengths: (b) (4) (b) (4) for your proposed drug product at release and on stability. Implement these dissolution acceptance criteria for all strengths of your drug product at release and on stability and update the specifications of the drug product with the revised criteria for the dissolution test, accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet the revised dissolution acceptance criteria in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

The applicant provides revised labeling with the 7/1/2021 submission to include (b) (4) (b) (4) However, we note the Biopharmaceutics review states that USP dissolution method 1 is used with a tighter acceptance criteria. Therefore, a dissolution statement is not needed in the labeling.

Deficiency Comments:

Deficiency # 1 DESCRIPTION: Remove (b) (4)

Created in C1

Prescribing Information

Response / Assessment:

4.5 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA 020049/S-034 approval letter from Panorama)

AR-28 dated 7/8/2021 revises distributor:

5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

5.1.2 DESCRIPTION

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each 250-mg capsule contains 250 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	acid, sugar, talc, and white wax. The capsule shell contains D&C Yellow #10, FD&C Blue #1, FD&C Green #3, gelatin, titanium dioxide, and other ingredients. Each 500-mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C Blue #1, gelatin, titanium dioxide, and other ingredients.
ANDA Labeling	(b) (4)

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	PENTASA extended-release 250-mg capsules are supplied in bottles of 240 capsules (NDC 54092-189-81). Each green and blue capsule contains 250 mg of mesalamine in extended-release beads. PENTASA extended-release capsules are identified with a pentagonal starburst logo and the number 2010 on the green portion and S429 250 mg on the blue portion of the capsules. PENTASA extended-release 500-mg capsules are supplied in bottles of 120 capsules (NDC 54092-191-12). Each blue capsule contains 500 mg of mesalamine in extended-release beads. PENTASA extended-release capsules are identified with a pentagonal starburst logo and S429 500 mg on the capsules. Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
ANDA Labeling	(b) (4)

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

<table>
<tr><th colspan="2">Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements</th></tr>
<tr><td>Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)</td><td>From 3.2.P.3.1 dated 3/31/2021:
<table>
<tr><th>Site Name</th><th>Site Address</th><th>FDA Establishment Identifier (FEI)</th></tr>
<tr><td>Sun Pharmaceutical Industries Limited, Mohali</td><td>SEZ Unit-1, Plot No. A-41 Industrial Area, Phase-VIII A, S.A.S. Nagar, Mohali, Punjab 160071, India (IND)</td><td>FEI: 3002807979

DUNS: 650456002</td></tr>
</table></td></tr>
<tr><td>Name and Address on ANDA Container/Carton</td><td>Container:
Manufactured by:
Sun Pharmaceutical Industries Limited
Mohali, INDIA
Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512</td></tr>
<tr><td>Name and Address on ANDA Prescribing Information</td><td>Manufactured by:
Sun Pharmaceutical Industries Limited,
Mohali, INDIA

Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512</td></tr>
</table>

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).

Deficiency	No Deficiency	
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

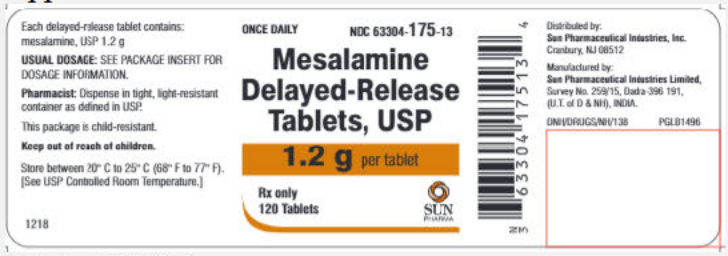
Reviewer Comments:

Related applications are adequately differentiated.

(b) (4)

[redacted]

Approved A211858:



Subject ANDA:

Bottles of (b) (4) 120s (500 mg) are CRC.

Table 1: Details of the Container/Closure System

Strength	Count	Bottle	Cap
			(b) (4)
500 mg	120's count		(b) (4)

Deficiency Comments:

5.3 PRESCRIBING INFORMATION

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.

Deficiency	No Deficiency	
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(j)].
		HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The Prescribing Information from the 7/1/2021 submission supersedes the PI from the 03/31/2021 and 06/07/2021 submissions.

We will recommend revision to HOW SUPPLIED to add the strength to the second and fourth paragraphs and send a comment regarding drug substance vs drug product in the PI.

"Dispense in tight, light-resistant container as defined in USP" is stated on the container in line with the RLD. This statement is also in subject ANDA's PI. The RLD does not include the statement in their PI but we will not comment as it is in line with the container label.

Deficiency Comments:

Deficiency # 1 Created in C1 Prescribing Information Response / Assessment:	GENERAL: Ensure references to the drug substance and drug product are consistent throughout the Prescribing Information. Ensure to use the established name, Mesalamine Extended-Release Capsules, (i.e., dosage form included) when referring to the drug product.
Deficiency # 2 Created in C1 Prescribing Information Response / Assessment:	HOW SUPPLIED, second and fourth paragraphs: Add the strength to follow "Mesalamine extended-release capsules USP".

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex

☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:

Esther Kim

Digitally signed by Esther Kim
Date: 7/22/2021 02:41:31PM
GUID: 5423006c00721ec9406da22c031498a2

Ellen Koo

Digitally signed by Ellen Koo
Date: 7/22/2021 02:54:09PM
GUID: 508da73d0002b687dfbf9b3859d80789

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214585Orig1s000

CHEMISTRY REVIEWS

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ **Approval**
☐ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☐ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 *Choose this option when both of the following apply:* • *Quality is Adequate except for inspection deferred due to travel restriction AND* • *OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)*

(b) (4)

U.S. FOOD & DRUG ADMINISTRATION

ANDA 214585
Assessment #02

Drug Product Name	Mesalamine Extended-Release Capsules
Dosage Form	Extended-Release Capsules
Strength	**500mg ***
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	SUN PHARMA INDUSTRIES LTD
US agent, if applicable	Praveen Devakadaksham Sun Pharmaceutical Industries, Inc.

(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Quality/Response to Information Request	05/04/2022	Quality/Drug Product
Quality/Response to Information Request	04/28/2022	Quality/Drug Product
Quality/Response to Information Request	02/25/2022	Quality/Drug Product, Manufacturing
Quality/Response to CRL Re-submission/After Action	02/15/2022	Quality/Drug Product, Manufacturing, Biopharm
Quality/Response to Information Request	12/14/2021	Quality/Biopharm
Quality/Response to Discipline Review Letter	10/27/2021	Quality
Response to Information Request	07/01/2021	Quality
Original Submission	03/31/2021	Quality/ALL

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance/Drug Product	Akhtar Siddiqui	Sanna Sander
Manufacturing	Chaoying Ma	Shujun Chen
Microbiology	N/A	N/A
Biopharmaceutics	Nadia Ahmed	Kimberly Raines
Regulatory Business Process Manager	Maya Johnson-Nimo	
Application Technical Lead	Sanna Sander	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
029575	II	SUN PHARMACEUTICAL INDUSTRIES LTD	Mesalamine USP	Adequate	05/20/21	Ying Lin No new amendments (last checked 04.21.22) https://panorama.fda.gov/program/view?ID=582a616f0023d2c6348891aa3324c691
Multiple	Other	Refer to Drug Product Quality assessment (P7), module 32P7 and 356h form				

B. Other Documents:

Document	Application Number	Description
RLD/RS	NDA 020049	PENTASA by Takeda (formerly Shire). RS 500 mg approved Jul 08, 2004; 250 mg approved May 10, 1993).

2. CONSULTS - None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY (APPROVALS ONLY)

For more details about the items in this template, please see the Executive Summary (Approvals Only) chapter of the ANDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The previous cycle R01 IQA assessment was inadequate minor due to remaining deficiencies for Drug product and manufacturing process modules. [redacted] (b) (4)

In the current R02 cycle, this application is now recommended for approval based on outcome of IQA team review assessment cycle R01 as summarized in Section II.

Drug product, Manufacturing facility, Manufacturing process, and Biopharmaceutics review assessments are adequate as of this R02.

OPQ recommends issuing an **APPROVAL Letter**

I. QUALITY ASSESSMENT OVERVIEW

Is the Firm's proposed recommended dissolution method/specification found acceptable by Biopharmaceutics?	☒ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications comply with the current USP?	☒ Yes ☒ DS ☒ DP ☐ No ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D recommendations (regarding elemental impurities)?	☒ Yes ☐ No ☐ N/A

Drug Product Background	Applicant's (Sun) **MESALAMINE ER CAPSULES 500mg** consist of ER pellets (b) (4) (b) (4) Capsules are packed in 120 (b) (4) ct bottles (b) (4) with CR caps. (b) (4) The design is generally similar to RLD.
RLD	NDA 20049 PENTASA by Takeda (formerly Shire). RS 500 mg approved Jul 08, 2004; 250 mg approved May 10, 1993). RLD label: https //dailymed nlm.nih gov/dailymed/drugInfo.cfm?setid=e39d9a3d-5d3a-4bb6-aab1-fdbb2a598606
Proposed Indication(s) including Intended Patient Population	Mesalamine Extended-Release Capsules are indicated for the treatment of mildly to moderately active **ulcerative colitis** (b) (4) **Mesalamine has** (b) (4) **anti-inflammatory effect on the colonic epithelial cells** (b) (4)
Duration of Treatment	Chronic
Maximum Daily Dose	Maximum total daily dose MDD: 4,000 mg/day (b) (4) (b) (4)
Alternative Methods of Administration	(b) (4) 'Mesalamine Extended-Release Capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. The capsules and capsule contents must not be crushed or chewed.

(b) (4)

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II. A. DP OVERALL RECOMMENDATION: Adequate

Drug Substance: **Adequate**

Mesalamine USP [5-ASA or 5-Aminosalicylic acid, EP Mesalazine]

The most current status of the DMF used for this application is listed in the table included in the "QUALITY ASSESSMENT DATA SHEET", section 1.A, page 3 of this document.

- The DMF (*DMF# 029575 by SUN PHARMA, Mumbai, India*) is currently adequate.

(b) (4)

[redacted]

Outstanding Issues as of Assessment cycle #R02:

- (b) (4)
-

Drug Product: Adequate

MESALAMINE ER Capsules, 500MG, USP (b) (4)

DP DESIGN & CRITICAL PROPERTIES

- The MESALAMINE ER CAPSULES 500mg consist of **ER pellets** (b) (4)
  (b) (4)
- The ANDA DP design is generally similar to RLD.
  (b) (4)

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(b) (4)

Outstanding Issues as of Assessment cycle #R01:

- minor clarifications requested regarding–
  - (b) (4)

Outstanding Issues as of Assessment cycle #R02:

- *Each of the outstanding issues from cycle R01 have been successfully addressed as of R02 (Seq0011/0012 submissions).*
- *No further issues are remaining.*

Labeling: Adequate

No labeling issue was identified per DPQ review assessment, as applicable per MOU

B. Manufacturing:

a. Process: Adequate

(b) (4)

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(b) (4)

b. **Facilities: Adequate**

Summary:

R02:
FACILITIES
The drug substance and drug product manufacturers, as well as analytical testing lab, are approval based on the manufacturing history and compliance status. (b) (4)

C. Biopharmaceutics: Adequate

BP adequate since R01.

The Applicant submitted ANDA 214585 for the marketing approval of Mesalamine Extended-Release Capsules (b) (4) 500 mg) in the US, indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis. The Applicant provided a bioequivalence study with the 500 mg strength (b) (4) (b) (4)

The proposed dissolution method is consistent with Test 1 in the Mesalamine Extended-Release Capsules USP Monograph. The Applicant has demonstrated the discriminating ability of the proposed dissolution method (Apparatus II, 100 rpm, 900mL of pH 7.5 phosphate buffer) (b) (4) (b) (4) through comparative dissolution studies (f2 <50).

The Applicant's originally proposed acceptance criteria were permissive, and, the Applicant was advised via TCIR to adopt the following acceptance criteria for all strengths: (b) (4) (b) (4).
The Applicant **counter proposed different acceptance criteria** with the same range but with different targets: (b) (4) **which are acceptable**.

It is noted that the **Applicant has added the statement "FDA approved dissolution test specifications differ from USP" and was recommended to petition the USP for a revision to the monograph**.

This Application, ANDA-214585-ORIG-1, is ADEQUATE and recommended for Approval from a Biopharmaceutics perspective

D. Microbiology: N/A

Not applicable. A stand-alone microbiology review was not conducted for this non-sterile oral drug product. (b) (4) (b) (4)

Application Technical Lead Name and Date: *Sanna T Sander, Ph.D., May 2022. For signature date, please see attached signature page in archived document*

Sanna Sander

Digitally signed by Sanna Sander
Date: 5/09/2022 09:43:34PM
GUID: 51dc6d2e0000c649fbc009a8f0773910

Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	214585
RLD/RS No.	020049
Applicant	SUN PHARMA INDUSTRIES LTD
Dosage	Capsule ER
Route	Oral
DP Name	MESALAMINE
Primary Assessor	Akhtar Siddiqui
Secondary Assessor	Sanna Sander

Discipline Executive Summary

Mesalamine CR capsules USP (b) (4) 500 mg are a generic version of Pentasa® (Mesalamine) CR Capsule 250 mg and 500 mg by Shire Development Inc. (N 020049).

(b) (4)

The drug product (DP) is indicated for ulcerative colitis in adults.
The MDD is 4000 mg/day.
ANDA DP basic design is similar to RLD, (b) (4)

(b) (4)

(b) (4)

Review Iteration						
Review Iteration		Assessor Decision	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date
1	Original Review	DRL	9/29/2021	Amendment Correspondence; Quality Amendment Correspondence; Labeling Amendment Correspondence; Filing Form 3674; New	5 4 3 2	7/1/2021 6/7/2021 5/20/2021 3/31/2021

2	DRL Response	Inadequate Minor	2/9/2022	Amendment Correspondence; Quality	8	10/27/2021
3	CR Response	Inadequate Minor	4/22/2022	Amendment Correspondence; Quality; Resubmission Amendment Correspondence; Quality	11 12	2/15/2022 2/25/2022
4	IR Response	IR	5/6/2022	Amendment Correspondence; Quality	13	4/28/2022
5	IR Response 2	Adequate	5/9/2022	Amendment Correspondence; Quality	14	5/4/2022

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(b) (4)

Labeling	
Description Section	
Is the information accurate?	Yes

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
(b) (4)		
Mesalamine, USP 500mg	25	"RL36" printed on both cap and body in black

		ink
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

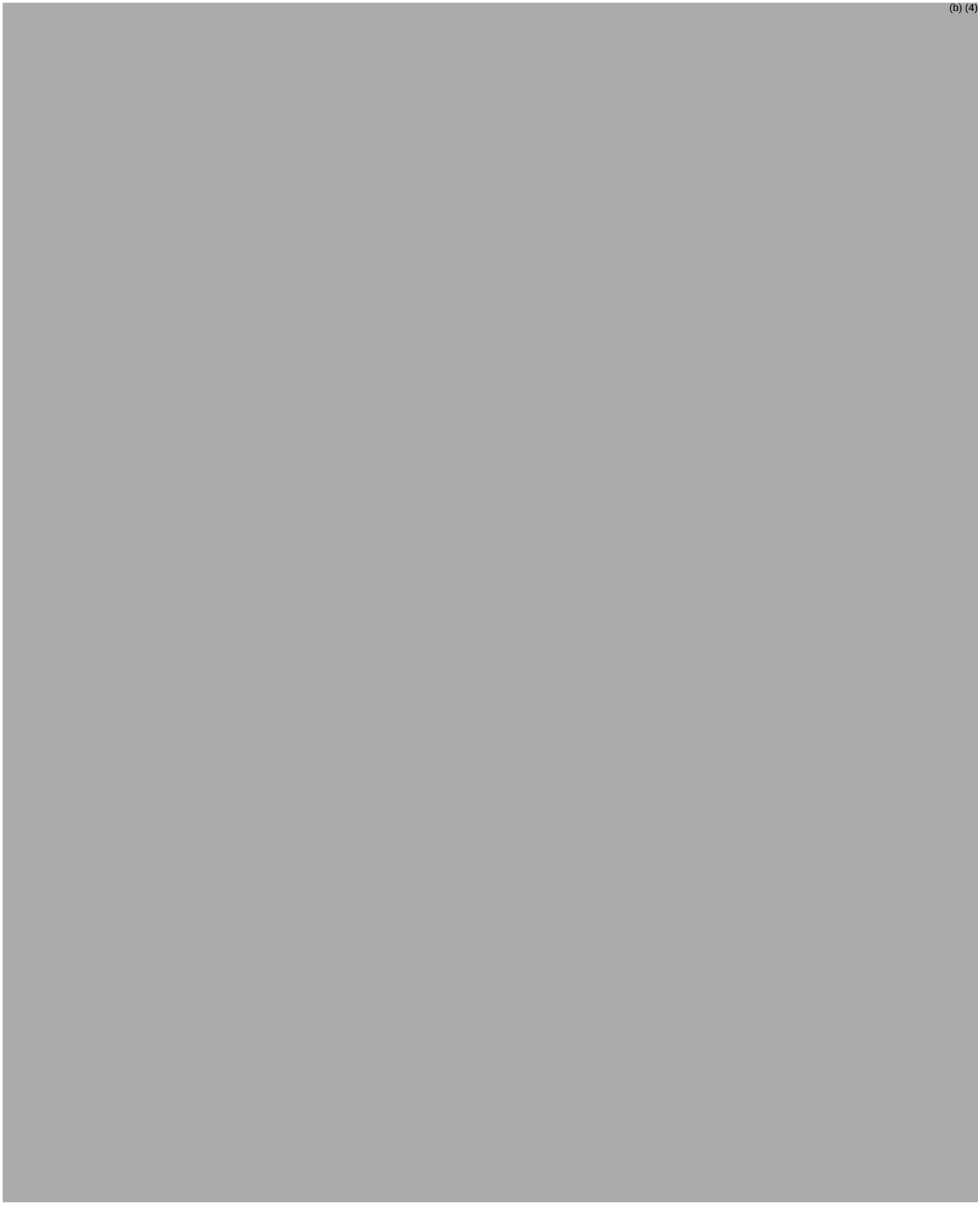
P.1.5 Unique Situations

L.1 Labeling

Knowledge-aided Assessment and Structured Application

P2. Drug Product Development

(b) (4)



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(b) (4)

Deficiencies

(b) (4)

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Knowledge-Aided Assessment and Structured Application

DEFICIENCIES

Drug Substance

MESALAMINE

No deficiencies to display

Akhtar Siddiqui

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Date: 5/09/2022 11:25:43AM
GUID: 539b2b530000210e771a688c6c56ebff

Sanna Sander

Digitally signed by Sanna Sander
Date: 5/09/2022 11:24:22AM
GUID: 51dc6d2e0000c649fbc009a8f0773910

Manufacturing Integrated Assessment

Overview

ANDA Basic Information	
ANDA No.	214585
Drug Product Name	MESALAMINE
Drug Product Strength(s)	MESALAMINE 500mg ; (b) (4)
RLD/RS Number.	020049
Applicant Name	SUN PHARMA INDUSTRIES LTD
Dosage Form	Capsule ER
Administration Route	Oral
Indication	Indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.
Primary Assessor	Chaoying Ma
Secondary Assessor	Shujun Chen

I. Manufacturing Summary	
Facility Assessment Recommendation	Adequate
Process Assessment Recommendation	Adequate

(b) (4)

[redacted]

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V. List of outstanding Information Request/Deficiencies

No deficiencies to display

Chaoying Ma

Digitally signed by Chaoying Ma
Date: 4/21/2022 02:42:41PM
GUID: 5463e4f2002198a810eed24f57d8b791

Shujun Chen

Digitally signed by Shujun Chen
Date: 4/21/2022 02:43:51PM
GUID: 54205154000196cff39c23804cad2165

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☒ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☐ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 *Choose this option when both of the following apply:* • *Quality is Adequate except for inspection deferred due to travel restriction AND* • *OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)*

(b) (4)

ANDA 214585
Assessment #01

Drug Product Name	Mesalamine Extended-Release Capsules, 500 mg
Dosage Form	Extended-Release Capsules
Strength	500mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	SUN PHARMA INDUSTRIES LTD
US agent, if applicable	Praveen Devakadaksham Sun Pharmaceutical Industries, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Quality/Response to Information Request	12/14/2021	Quality/Biopharm
Quality/Response to Discipline Review Letter	10/27/2021	Quality
Response to Information Request	07/01/2021	Quality
Original Submission	03/31/2021	Quality/ALL

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance/Drug Product	Akhtar Siddiqui	Sanna Sander
Manufacturing	Chaoying Ma	Shujun Chen
Microbiology	N/A	N/A
Biopharmaceutics	Nadia Ahmed	Kimberly Raines
Regulatory Business Process Manager	Maya Johnson-Nimo	
Application Technical Lead	Sanna Sander	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
029575	II	SUN PHARMACEUTICAL INDUSTRIES LTD	Mesalamine USP	Adequate	05/20/21	Ying Lin
Multiple	Other	Refer to Drug Product Quality assessment (P7), module 32P7 and 356h form				

B. Other Documents:

Document	Application Number	Description
RLD/RS	NDA 020049	PENTASA by Takeda (formerly Shire). RS 500 mg approved Jul 08, 2004; 250 mg approved May 10, 1993;).

2. CONSULTS - None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

For more details about the items in this template, please see the Abbreviated Executive Summary (CR Only) chapter of the ANDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete Response-Minor

This application is not recommended for approval based on outcome of IQA team review assessment cycle R01 as summarized in Section II.

Drug product and Manufacturing process review assessments are currently inadequate and include minor deficiencies. Manufacturing facility, and Biopharmaceutics review assessments are adequate as of this R01.

OPQ recommends issuing a Complete Response Letter –**Minor**

II. QUALITY ASSESSMENT OVERVIEW

Proposed Indication(s) including Intended Patient Population	Mesalamine Extended-Release Capsules are indicated for the treatment of mildly to moderately active **ulcerative colitis** (b) (4). NOTE: Mesalamine has (b) (4) anti-inflammatory effect on the colonic epithelial cells (b) (4) (b) (4) [1].
Duration of Treatment	Chronic
Maximum Daily Dose	Maximum total daily dose MDD : 4000 mg/day (b) (4) (b) (4)
Alternative Methods of Administration	(b) (4) : 'Mesalamine Extended-Release Capsules may be swallowed whole, or alternatively, the capsule may be opened and the entire contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. The capsules and capsule contents must not be crushed or chewed.

(b) (4)

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III. A. DP OVERALL RECOMMENDATION: Inadequate-Minor

Drug Substance: **Inadequate-Minor**

Mesalamine USP [5-ASA or 5-Aminosalicylic acid, EP Mesalazine]

The most current status of the DMF used for this application is listed in the table included in the "QUALITY ASSESSMENT DATA SHEET", section 1.A, page 3 of this document.

- The DMF (*DMF# 029575 by SUN PHARMA, Mumbai, India*) is currently adequate.

(b) (4)

[redacted]

Drug Product: Inadequate-Minor

MESALAMINE ER Capsules, 500MG, USP [redacted]

DP DESIGN & CRITICAL PROPERTIES

- The MESALAMINE ER CAPSULES [redacted] 500mg consist of **ER pellets** [redacted]
- The ANDA DP design is generally similar to RLD.

[redacted]

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

(b) (4)

Outstanding Issues as of Assessment cycle #R01:

- (b) (4)

Labeling: Adequate

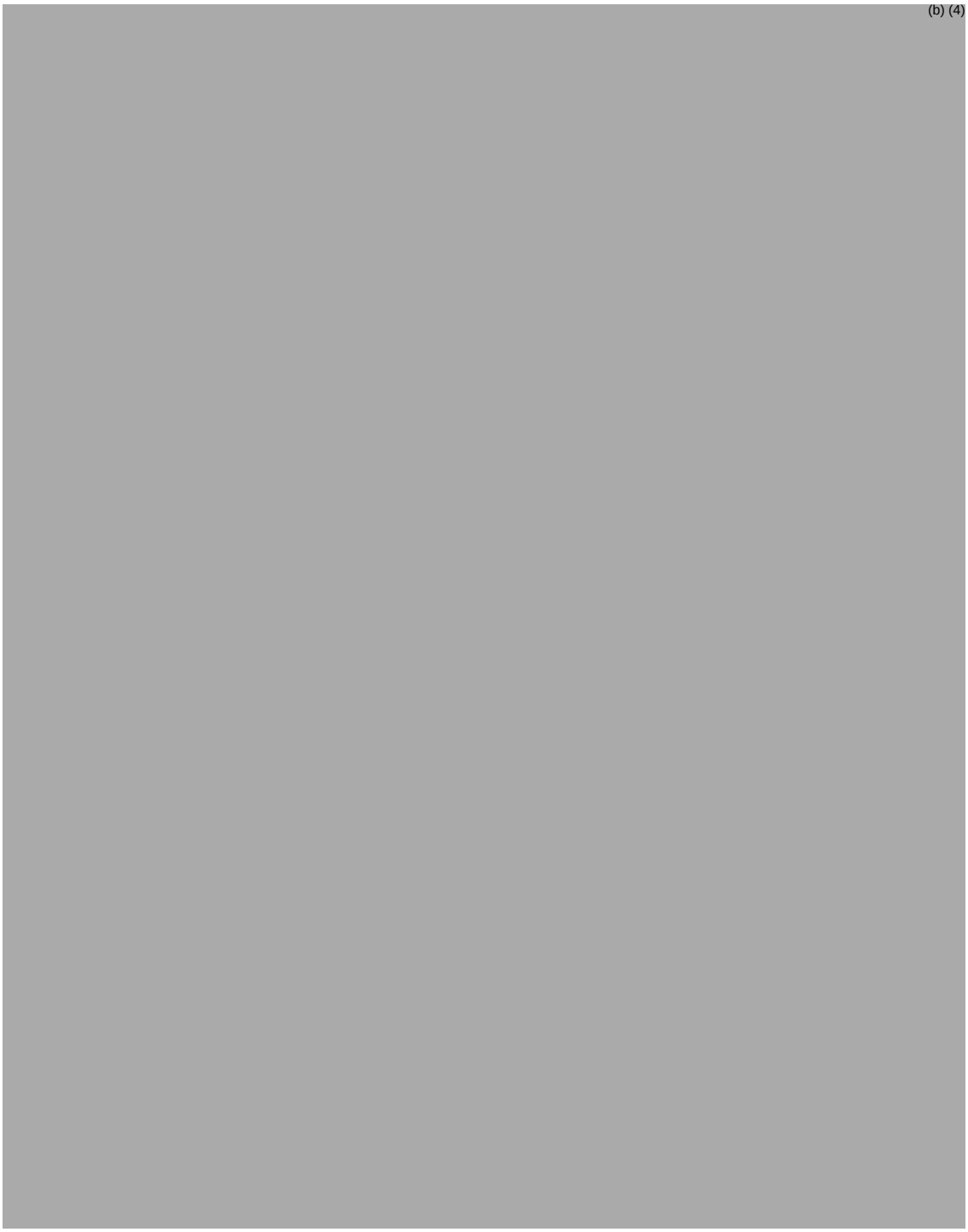
No labeling issue was identified per DPQ review assessment, as applicable per MOU

B. Manufacturing:

a. **Process: Inadequate-Minor**

(b) (4)

(b) (4)



b. **Facilities: Adequate**

(b) (4)

C. Biopharmaceutics: Adequate

The Applicant submitted ANDA 214585 for the marketing approval of Mesalamine Extended-Release Capsules (b) (4) 500 mg) in the US, indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis. The Applicant provided a bioequivalence study with the 500 mg strength (b) (4) (b) (4)

The proposed dissolution method is consistent with Test 1 in the Mesalamine Extended-Release Capsules USP Monograph. The Applicant has demonstrated the discriminating ability of the proposed dissolution method (Apparatus II, 100 rpm, 900mL of pH 7.5 phosphate buffer) (b) (4) through comparative dissolution studies (f2 <50).

The Applicant's originally proposed acceptance criteria were permissive, and, the Applicant was advised via TCIR to adopt the following acceptance criteria for all strengths: (b) (4) (b) (4)
The Applicant **counter proposed different acceptance criteria** with the same range but with different targets: (b) (4) (b) (4) **which are acceptable**.

It is noted that the **Applicant has added the statement "FDA approved dissolution test specifications differ from USP" and was recommended to petition the USP for a revision to the monograph**.

This Application, ANDA-214585-ORIG-1, is ADEQUATE and recommended for Approval from a Biopharmaceutics perspective

D. Microbiology: N/A

Not applicable. A stand-alone microbiology review was not conducted for this non-sterile oral drug product. (b) (4)

E. List of Deficiencies for Complete Response

Overall Quality Deficiencies - None

Drug Substance Deficiencies

1. (b) (4)

2.

Drug Product Deficiencies

1. (b) (4)

2.

3.

4. (b) (4)

5.

Labeling Deficiencies*: None*

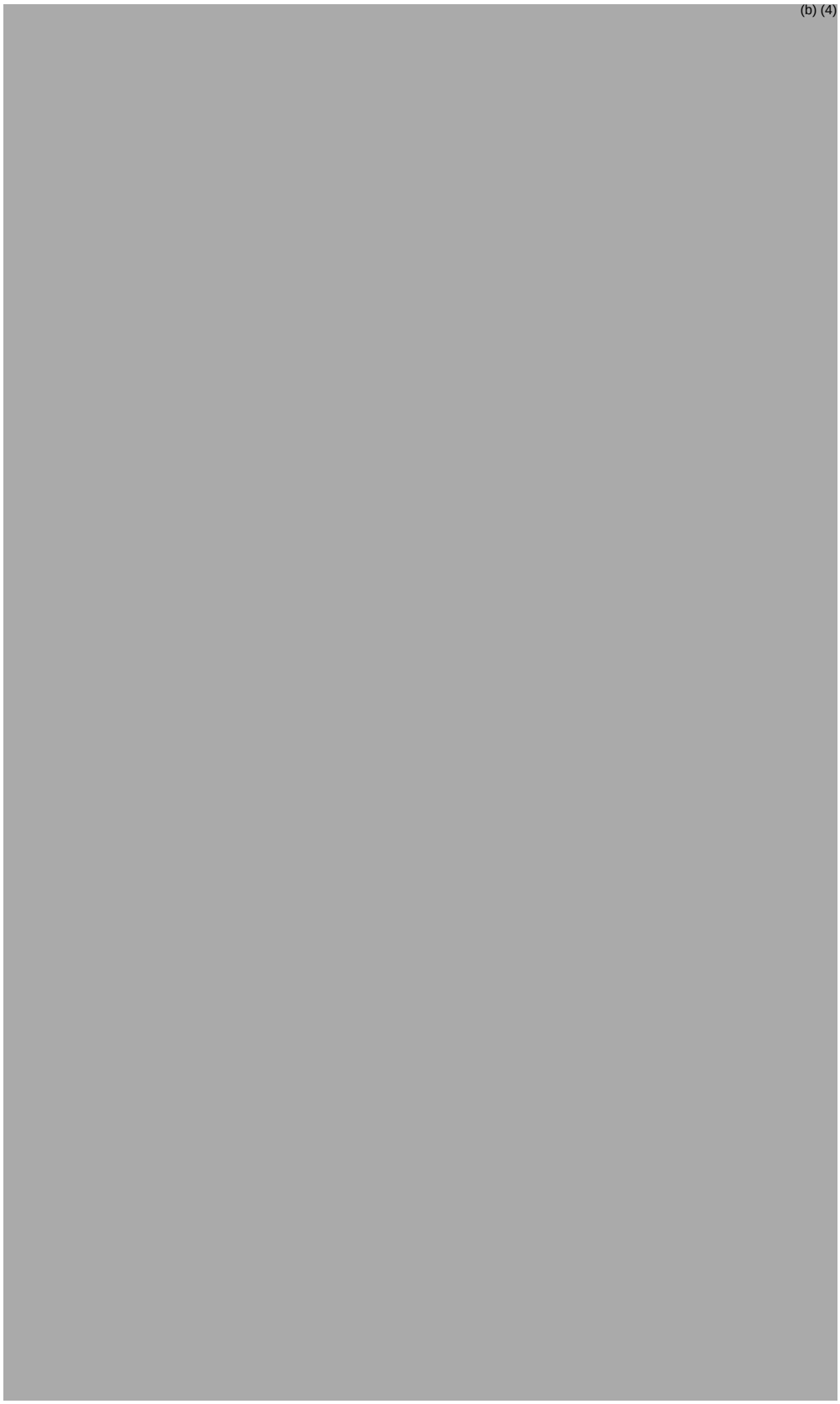
Manufacturing Deficiencies:

(b) (4)

(b) (4)

2.

3.



Biopharmaceutics Deficiencies: None

Microbiology Deficiencies: None

Other Deficiencies *(Specify discipline, such as Environmental):* ***None***

Application Technical Lead Name and Date: *Sanna T Sander, Ph.D.. For signature date, please see attached signature page in archived document*

Sanna Sander

Digitally signed by Sanna Sander
Date: 1/12/2022 11:35:22AM
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Knowledge-Aided Assessment and Structured Application Biopharmaceutics Assessment

Overview

ANDA Basic Information	
ANDA No.	214585
DP Name	MESALAMINE
RLD/RS No.	020049
Applicant	SUN PHARMA INDUSTRIES LTD
Dosage	Capsule ER
Route	Oral
Primary Assessor	Nadia Ahmed
Secondary Assessor	Kimberly Raines

Biopharmaceutics Executive Summary	
The Applicant submitted ANDA 214585 for the marketing approval of Mesalamine Extended-Release Capsules (b) (4) 500 mg) in the US, indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis. The Applicant provided a bioequivalence study with the 500 mg strength (b) (4) It is noted that the proposed dissolution method is consistent with Test 1 in the Mesalamine Extended-Release Capsules USP Monograph. The Applicant has demonstrated the discriminating ability of the proposed dissolution method (Apparatus II, 100 rpm, 900mL of pH 7.5 phosphate buffer) (b) (4) through comparative dissolution studies (f2 <50). However, the Applicant's originally proposed acceptance criteria were permissive. Therefore, the Applicant was advised via TCIR to adopt the following acceptance criteria for all strengths: (b) (4) The Applicant has counter proposed different acceptance criteria with the same range but with different targets: (b) (4) (b) (4) which are acceptable. It is noted that the Applicant has added the statement "FDA approved dissolution test specifications differ from USP" and was recommended to petition the USP for a revision to the monograph. This Application, ANDA-214585-ORIG-1, is ADEQUATE and recommended for Approval from a Biopharmaceutics perspective.	
Has OGD deemed the drug product BE to the RLD?	Pending

Drug Substance(s) and Drug Product				
	DS Name	**Strength Name (Active Moiety or Salt)**	**Therapeutic Area**	**Therapeutic Sub-Category**
1	MESALAMINE	Mesalamine	Gastroenterology	

DP Strength List		
	DS 1	
	mg	
Strength 1	500	
	(b) (4)	

Review Iteration						
	Review Iteration	**Assessor Decision**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
1	Original Review	IR	6/4/2021	Form 3674; New	2	3/31/2021
2	IR Response	Adequate	8/19/2021	Amendment Correspondence; Quality	5	7/1/2021
3	DRL Response	Adequate	12/16/2021	Amendment	8	10/27/2021

				Correspondence; Quality Amendment Correspondence; Quality	10	12/14/2021

Lifecycle Management for ANDA 214585	
Biopharmaceutics Risk Mitigation Strategy	
Supportive BA/BE	
Other Relevant Comment	

In Vitro Release Specification

MESALAMINE - Capsule ER

	Strength	Apparatus	Rotation Speed	Temperature	Medium / Volume (ml)	Acceptance Criteria
1	All Strengths	2-Paddle	100	37	pH 7.5 Phosphate Buffer - Volume: 900 ml	(b) (4)

Reference Biopharmaceutics Properties

RLD Basic Information	
NDA No.	020049
Non-proprietary DP Name	MESALAMINE 1 G TABLETS
Proprietary DP Name	PENTASA

RLD Reference Information	
Dosage and Administration	1 gram 4 times daily for a total daily dosage of 4 grams.
Equilibrium Solubility	Could not find this information
pKa	Could not find this information
Bioavailability	Mean Cmax after administration of suspension was 14.72 ug/mL for 5-ASA and 11.4 ug/mL for acetyl 5-ASA
Pharmacokinetics	Mean AUC is 1213 ng h/mL and Cmax is 423.4 ng/mL
BCS Classification	Could not find this information
DS/DP Characterization	Could not find this information
Other Relevant Biopharm Information	Could not find this information

Reference Documents		
URL Description	**URL**	**Init. Page**
RLD Biopharm Review	https://www.accessdata.fda.gov/drugsatfda_docs/nda/96/020049a_052292_biopharmrev.pdf	
RLD Label	https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=e39d9a3d-5d3a-4bb6-ab1-fdbb2a598606&type=pdf	

RLD Drug Substance(s) and Drug Product		
DS Name		**Strength Name (Active Moiety or Salt)**
1	MESALAMINE	Mesalamine

RLD DP Strength List		
	DS 1	
	mg	
Strength 1	250	
Strength 2	500	

Pilot BE Studies

Are there any submitted pilot studies evaluating the BE of several formulation variants for the test product?	Yes
Has an IVIVC or IVIVR (e.g. physiological based model with virtual BE) been established?	No
Pertinent BE / Clinical Evaluations Perspective	The data are not adequate to build a safe space
Reviewer Evaluation	The Applicant has conducted Pilot BE studies with the same formulation as the currently proposed formulation.

Drug Substance Information

MESALAMINE (ER)	
Drug Substance Information	
High Risk drug substance	No
BCS Solubility	Low
BCS Class Reported by Applicant	IV
Reviewer Evaluation	[redacted] (b) (4) Mesalamine is considered as a poorly soluble drug as per BCS classification.; BCS Solubility
Are there supportive BE studies (i.e. pilot BE studies evaluating formulation variants) to support the in vivo relevance of the dissolution test?	Yes
Reviewer Evaluation	The Applicant has conducted Pilot BE studies with the same formulation as the currently proposed formulation.

Initial Risk Assessment

MESALAMINE (ER) / BCS Solubility: Low	
Is in vitro dissolution independent of test condition (e.g., medium pH, rotation speed)?	No
Could Critical Bioavailability Attribute(s) be clearly identified, detected and controlled?	Yes
Initial Risk Ranking	Medium

Mitigation Strategies

MESALAMINE (ER) / BCS Solubility: Low / Initial Risk: Medium			
Recommended Biopharmaceutics Mitigation Strategies (Pertinent Critical Bioavailability Attribute(s) CBAs)			
Attributes	**Strength(s)**	**Proposed Control Limit**	**Comment**
Other: Extended Release Rate-Controlling Polymer	All Strengths		
Mitigated Biopharmaceutics Risk Level		**Reviewer Evaluation**	
Low		(b) (4)	

Drug Substance Dissolution Methods and Acceptance Criteria

MESALAMINE (Capsule ER)						
Proposed Dissolution Methods and Acceptance Criteria						
Strength	**Apparatus**	**Rotation Speed**	**Temp (°C)**	**Medium/Volume (mL)**	**Acceptance Criteria**	**Adequate**
All Strengths	2-Paddle	100 rpm	37	pH 7.5 Phosphate Buffer - Volume: 900 ml	(b) (4) [redacted]	Yes
Reviewer Evaluation	The Applicant's proposed dissolution method is consistent with Method 1 in the USP Monograph for Mesalamine Extended-Release Capsules. (b) (4) [redacted] However, the Applicant's originally proposed acceptance criteria were permissive. Therefore, the Applicant was recommended via TCIR to tighten their proposed acceptance criteria. The Applicant has counter proposed different acceptance criteria (with the same range but with different targets), which are acceptable. ; Exhibit Batch Dissolution					
Unique Situations						
Any unique situations not covered by KASA?	No					
Adequate	Yes					
Reviewer Evaluation						
Proposed Dissolution Testing						
FDA Dissolution Database						
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Pending					
Reviewer Evaluation	Pending as of 08/16/21					
Description of Links for Dissolution Methods	**URL Link**					
USP NF Monograph	https://online.uspnf.com/uspnf/document/1_GUID-F44B5678-F9F2-4E44-BCA1-5C3D5B0468D_3_en-US?source=Quick%20Search&highlight=mesalamine					
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	Yes					
Reviewer Evaluation						
Number of units tested meets the requirements (e.g. 12 units)	Yes					
Reviewer Evaluation						
Source of Dissolution Test Method	USP Monograph					
Does the proposed drug product meet the USP Monograph standards?	No					
Actions requested of the Applicant	Applicant has initiated a USP monograph revision					
Reviewer Evaluation	The Applicant has added the statement, "FDA approved dissolution test specifications differ from USP" and will petition the USP for a revision to the official monograph for mesalamine extended-release capsules.					

Deficiencies

Proposed Dissolution Methods and Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	(b) (4) [redacted]
			[Deficiency/IR]

			Based on the submitted in vitro dissolution data, the proposed dissolution acceptance criteria are permissive for your mesalamine extended-release capsules and NOT acceptable. The following data-driven dissolution acceptance criteria are recommended for all strengths: (b) (4) (b) (4) (Q)" for your proposed drug product at release and on stability. Implement these dissolution acceptance criteria for all strengths of your drug product at release and on stability and update the specifications of the drug product with the revised criteria for the dissolution test, accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet the revised dissolution acceptance criteria in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.
			[Summary of the applicant's response and reviewer comment]
IR Response	Solved	1	**[Summary of the applicant's response and reviewer comment]**
			The Applicant has counter proposed different acceptance criteria (with the same range but with different targets), which are acceptable.
			[Deficiency/IR Previous Iteration]

Recommended Dissolution Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
DRL Response	Solved	1	Petition the USP for a revision to the dissolution test methods
			[Deficiency/IR]
			We acknowledge that the FDA recommended dissolution acceptance criteria for your product, mesalamine extended release capsules, differ from the USP. Please initiate a revision to an official monograph for mesalamine extended release capsules to the USP under the USP Pending Monograph Process. Until your product is in alignment with the test or test method in the USP monograph, include the following statement in the Labeling, “FDA approved dissolution test specifications differ from USP”.
			[Summary of the applicant's response and reviewer comment]
			The Applicant has acknowledged and concurred with this recommendation.

Drug Product Exhibit Batch Dissolution Testing

Commercial batch size is within a factor of ten times the size of the biobatch	Yes
Reviewer Evaluation	
Testing was conducted using unexpired and/or fresh lots	Yes
Reviewer Evaluation	The Batches are approximately 10 months old at the time of testing.
Is the RLD drug product scored?	No

Deficiencies

No deficiencies to display

APPEARS THIS WAY ON ORIGINAL

Nadia Ahmed

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Date: 12/16/2021 07:56:56PM
GUID: 5e0e0b9100939fa4af29f1127f130ee2

Kimberly Raines

Digitally signed by Kimberly Raines
Date: 12/17/2021 06:20:48AM
GUID: 508da6fd000284a73fdbe11d01b3132f

Sanna Sander

Digitally signed by Sanna Sander
Date: 5/10/2022 11:19:14AM
GUID: 51dc6d2e0000c649fbc009a8f0773910

Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	214585
RLD/RS No.	020049
Applicant	SUN PHARMA INDUSTRIES LTD
Dosage	Capsule ER
Route	Oral
DP Name	MESALAMINE
Primary Assessor	Akhtar Siddiqui
Secondary Assessor	Sanna Sander

Discipline Executive Summary

Mesalamine CR capsules USP (b) (4) 500 mg are a generic version of Pentasa® (Mesalamine) CR Capsule 250 mg and 500 mg by Shire Development Inc. (N 020049).

(b) (4)

The drug product (DP) is indicated for ulcerative colitis in adults.
The MDD is 4000 mg/day.
ANDA DP basic design is similar to RLD, (b) (4)

(b) (4)

(b) (4)

Review Iteration						
Review Iteration		Assessor Decision	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date
1	Original Review	DRL	9/29/2021	Amendment Correspondence; Quality Amendment Correspondence; Labeling Amendment Correspondence; Filing Form 3674; New	5 4 3 2	7/1/2021 6/7/2021 5/20/2021 3/31/2021

2	DRL Response	Inadequate Minor	2/9/2022	Amendment Correspondence; Quality	8	10/27/2021
3	CR Response	Inadequate Minor	4/22/2022	Amendment Correspondence; Quality; Resubmission Amendment Correspondence; Quality	11 12	2/15/2022 2/25/2022
4	IR Response	IR	5/6/2022	Amendment Correspondence; Quality	13	4/28/2022
5	IR Response 2	Adequate	5/9/2022	Amendment Correspondence; Quality	14	5/4/2022

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(b) (4)

Labeling	
Description Section	
Is the information accurate?	Yes

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
(b) (4)		
Mesalamine, USP 500mg	25	"RL36" printed on both cap and body in black

		ink
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

P.1.5 Unique Situations

L.1 Labeling

Knowledge-aided Assessment and Structured Application

P2. Drug Product Development

(b) (4)

[redacted]

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(b) (4)

Deficiencies

(b) (4)

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Knowledge-Aided Assessment and Structured Application

DEFICIENCIES

Drug Substance

MESALAMINE

No deficiencies to display

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Akhtar Siddiqui

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Sanna Sander

Digitally signed by Sanna Sander
Date: 5/09/2022 11:24:22AM
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Manufacturing Integrated Assessment

Overview

ANDA Basic Information	
ANDA No.	214585
Drug Product Name	MESALAMINE
Drug Product Strength(s)	MESALAMINE 500mg ; (b) (4)
RLD/RS Number.	020049
Applicant Name	SUN PHARMA INDUSTRIES LTD
Dosage Form	Capsule ER
Administration Route	Oral
Indication	Indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.
Primary Assessor	Chaoying Ma
Secondary Assessor	Shujun Chen

I. Manufacturing Summary	
Facility Assessment Recommendation	Adequate
Process Assessment Recommendation	Adequate

(b) (4)

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V. List of outstanding Information Request/Deficiencies

No deficiencies to display

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Chaoying Ma

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Shujun Chen

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GUID: 54205154000196cff39c23804cad2165

Manufacturing Integrated Assessment

Overview

ANDA Basic Information	
ANDA No.	214585
Drug Product Name	MESALAMINE
Drug Product Strength(s)	MESALAMINE 500mg ; (b) (4)
RLD/RS Number.	020049
Applicant Name	SUN PHARMA INDUSTRIES LTD
Dosage Form	Capsule ER
Administration Route	Oral
Indication	Indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.
Primary Assessor	Chaoying Ma
Secondary Assessor	Shujun Chen

I. Manufacturing Summary	
Facility Assessment Recommendation	Adequate
Process Assessment Recommendation	Inadequate Minor

(b) (4)

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V. List of outstanding Information Request/Deficiencies

1. (b) (4)
2.
3.

Chaoying Ma

Digitally signed by Chaoying Ma
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Shujun Chen

Digitally signed by Shujun Chen
Date: 12/22/2021 10:50:38PM
GUID: 54205154000196cff39c23804cad2165

Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	214585
RLD/RS No.	020049
Applicant	SUN PHARMA INDUSTRIES LTD
Dosage	Capsule ER
Route	Oral
DP Name	MESALAMINE
Primary Assessor	Akhtar Siddiqui
Secondary Assessor	Sanna Sander

Discipline Executive Summary

Mesalamine controlled release capsules USP (b) (4) 500 mg are a generic version of Pentasa® (Mesalamine) Controlled-Release Capsule 250 mg and 500 mg by Shire Development Inc. (N 020049). (b) (4). The drug product (DP) is indicated for ulcerative colitis in adults. The MDD is 4000 mg/day. ANDA DP basic design is similar to RLD, (b) (4)

(b) (4)

Review Iteration					
Review Iteration	**Assessor Decision**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**

1	Original Review	DRL	9/29/2021	Amendment Correspondence; Quality Amendment Correspondence; Labeling Amendment Correspondence; Filing Form 3674; New	5 4 3 2	7/1/2021 6/7/2021 5/20/2021 3/31/2021
2	DRL Response	Inadequate Minor		Amendment Correspondence; Quality	8	10/27/2021

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(b) (4)

Labeling	
Description Section	
Is the information accurate?	Yes

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
		(b) (4)
Mesalamine, USP 500mg	25	"RL36" printed on both cap and body in black ink
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

P.1.5 Unique Situations

L.1 Labeling

Knowledge-aided Assessment and Structured Application

P2. Drug Product Development

(b) (4)

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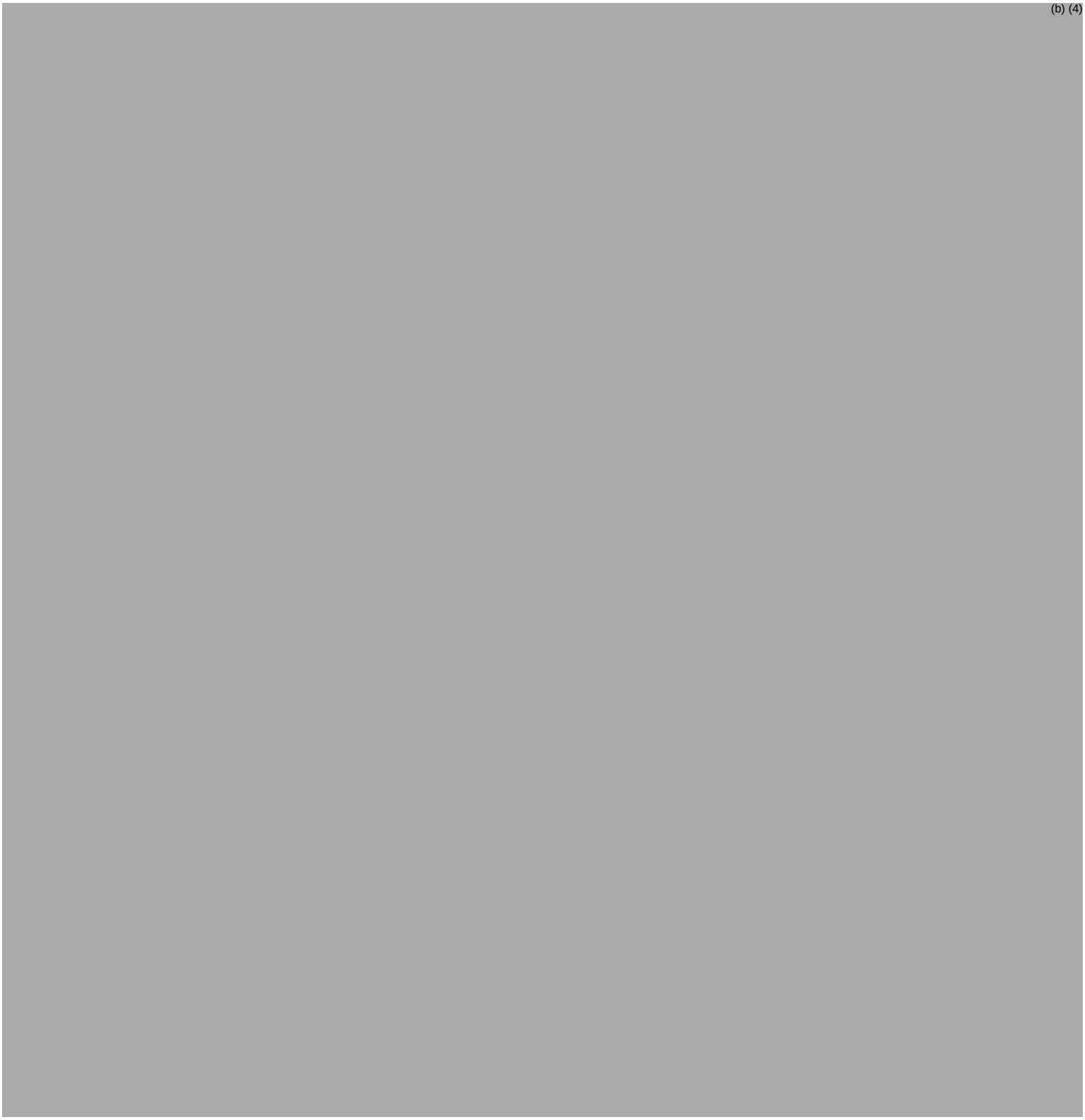
Deficiencies



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Knowledge-Aided Assessment and Structured Application

DEFICIENCIES

Drug Substance

MESALAMINE

Drug Product

Sanna Sander

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Date: 12/15/2021 03:47:53PM
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Akhtar Siddiqui

Digitally signed by Akhtar Siddiqui
Date: 12/15/2021 07:59:59PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214585Orig1s000

BIOEQUIVALENCE REVIEWS

Knowledge-Aided Assessment and Structured Application Biopharmaceutics Assessment

Overview

ANDA Basic Information	
ANDA No.	214585
DP Name	MESALAMINE
RLD/RS No.	020049
Applicant	SUN PHARMA INDUSTRIES LTD
Dosage	Capsule ER
Route	Oral
Primary Assessor	Nadia Ahmed
Secondary Assessor	Kimberly Raines

Biopharmaceutics Executive Summary	
The Applicant submitted ANDA 214585 for the marketing approval of Mesalamine Extended-Release Capsules (b) (4) 500 mg) in the US, indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis. The Applicant provided a bioequivalence study with the 500 mg strength (b) (4) It is noted that the proposed dissolution method is consistent with Test 1 in the Mesalamine Extended-Release Capsules USP Monograph. The Applicant has demonstrated the discriminating ability of the proposed dissolution method (Apparatus II, 100 rpm, 900mL of pH 7.5 phosphate buffer) (b) (4) through comparative dissolution studies (f2 <50). However, the Applicant's originally proposed acceptance criteria were permissive. Therefore, the Applicant was advised via TCIR to adopt the following acceptance criteria for all strengths: (b) (4) The Applicant has counter proposed different acceptance criteria with the same range but with different targets: (b) (4): (b) (4) which are acceptable. It is noted that the Applicant has added the statement "FDA approved dissolution test specifications differ from USP" and was recommended to petition the USP for a revision to the monograph. This Application, ANDA-214585-ORIG-1, is ADEQUATE and recommended for Approval from a Biopharmaceutics perspective.	
Has OGD deemed the drug product BE to the RLD?	Pending

Drug Substance(s) and Drug Product				
	DS Name	**Strength Name (Active Moiety or Salt)**	**Therapeutic Area**	**Therapeutic Sub-Category**
1	MESALAMINE	Mesalamine	Gastroenterology	

DP Strength List		
	DS 1	
	mg	
Strength 1	500	
	(b) (4)	

Review Iteration						
Review Iteration		**Assessor Decision**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
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3	DRL Response	Adequate	12/16/2021	Amendment	8	10/27/2021

				Correspondence; Quality Amendment Correspondence; Quality	10	12/14/2021

Lifecycle Management for ANDA 214585	
Biopharmaceutics Risk Mitigation Strategy	
Supportive BA/BE	
Other Relevant Comment	

In Vitro Release Specification

MESALAMINE - Capsule ER

	Strength	Apparatus	Rotation Speed	Temperature	Medium / Volume (ml)	Acceptance Criteria
1	All Strengths	2-Paddle	100	37	pH 7.5 Phosphate Buffer - Volume: 900 ml	(b) (4)

Reference Biopharmaceutics Properties

RLD Basic Information	
NDA No.	020049
Non-proprietary DP Name	MESALAMINE 1 G TABLETS
Proprietary DP Name	PENTASA

RLD Reference Information	
Dosage and Administration	1 gram 4 times daily for a total daily dosage of 4 grams.
Equilibrium Solubility	Could not find this information
pKa	Could not find this information
Bioavailability	Mean Cmax after administration of suspension was 14.72 ug/mL for 5-ASA and 11.4 ug/mL for acetyl 5-ASA
Pharmacokinetics	Mean AUC is 1213 ng h/mL and Cmax is 423.4 ng/mL
BCS Classification	Could not find this information
DS/DP Characterization	Could not find this information
Other Relevant Biopharm Information	Could not find this information

Reference Documents		
URL Description	**URL**	**Init. Page**
RLD Biopharm Review	https://www.accessdata.fda.gov/drugsatfda_docs/nda/96/020049a_052292_biopharmrev.pdf	
RLD Label	https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=e39d9a3d-5d3a-4bb6-ab1-fdbb2a598606&type=pdf	

RLD Drug Substance(s) and Drug Product		
DS Name		**Strength Name (Active Moiety or Salt)**
1	MESALAMINE	Mesalamine

RLD DP Strength List		
	DS 1	
	mg	
Strength 1	250	
Strength 2	500	

Pilot BE Studies

Are there any submitted pilot studies evaluating the BE of several formulation variants for the test product?	Yes
Has an IVIVC or IVIVR (e.g. physiological based model with virtual BE) been established?	No
Pertinent BE / Clinical Evaluations Perspective	The data are not adequate to build a safe space
Reviewer Evaluation	The Applicant has conducted Pilot BE studies with the same formulation as the currently proposed formulation.

Drug Substance Information

MESALAMINE (ER)	
Drug Substance Information	
High Risk drug substance	No
BCS Solubility	Low
BCS Class Reported by Applicant	IV
Reviewer Evaluation	(b) (4) Mesalamine is considered as a poorly soluble drug as per BCS classification.; BCS Solubility
Are there supportive BE studies (i.e. pilot BE studies evaluating formulation variants) to support the in vivo relevance of the dissolution test?	Yes
Reviewer Evaluation	The Applicant has conducted Pilot BE studies with the same formulation as the currently proposed formulation.

Initial Risk Assessment

MESALAMINE (ER) / BCS Solubility: Low	
Is in vitro dissolution independent of test condition (e.g., medium pH, rotation speed)?	No
Could Critical Bioavailability Attribute(s) be clearly identified, detected and controlled?	Yes
Initial Risk Ranking	Medium

Mitigation Strategies

MESALAMINE (ER) / BCS Solubility: Low / Initial Risk: Medium			
Recommended Biopharmaceutics Mitigation Strategies (Pertinent Critical Bioavailability Attribute(s) CBAs)			
Attributes	**Strength(s)**	**Proposed Control Limit**	**Comment**
Other: Extended Release Rate-Controlling Polymer	All Strengths		
Mitigated Biopharmaceutics Risk Level		**Reviewer Evaluation**	
Low		(b) (4)	

Drug Substance Dissolution Methods and Acceptance Criteria

MESALAMINE (Capsule ER)						
Proposed Dissolution Methods and Acceptance Criteria						
Strength	**Apparatus**	**Rotation Speed**	**Temp (°C)**	**Medium/Volume (mL)**	**Acceptance Criteria**	**Adequate**
All Strengths	2-Paddle	100 rpm	37	pH 7.5 Phosphate Buffer - Volume: 900 ml	(b) (4)	Yes
Reviewer Evaluation	The Applicant's proposed dissolution method is consistent with Method 1 in the USP Monograph for Mesalamine Extended-Release Capsules. The Applicant has demonstrated the discriminating ability of the proposed dissolution method through comparative dissolution studies (b) (4) (b) (4) ymer (f2 <50). However, the Applicant's originally proposed acceptance criteria were permissive. Therefore, the Applicant was recommended via TCIR to (b) (4) their proposed acceptance criteria. The Applicant has counter proposed different acceptance criteria (with the same range but with different targets), which are acceptable. ; Exhibit Batch Dissolution					
Unique Situations						
Any unique situations not covered by KASA?	No					
Adequate	Yes					
Reviewer Evaluation						
Proposed Dissolution Testing						
FDA Dissolution Database						
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Pending					
Reviewer Evaluation	Pending as of 08/16/21					
Description of Links for Dissolution Methods	**URL Link**					
USP NF Monograph	https://online.uspnf.com/uspnf/document/1_GUID-F44B5678-F9F2-4E44-BCA1-5C3D5B0468D_3_en-US?source=Quick%20Search&highlight=mesalamine					
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	Yes					
Reviewer Evaluation						
Number of units tested meets the requirements (e.g. 12 units)	Yes					
Reviewer Evaluation						
Source of Dissolution Test Method	USP Monograph					
Does the proposed drug product meet the USP Monograph standards?	No					
Actions requested of the Applicant	Applicant has initiated a USP monograph revision					
Reviewer Evaluation	The Applicant has added the statement, "FDA approved dissolution test specifications differ from USP" and will petition the USP for a revision to the official monograph for mesalamine extended-release capsules.					

Deficiencies

Proposed Dissolution Methods and Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	(b) (4)
			[Deficiency/IR]

			Based on the submitted in vitro dissolution data, the proposed dissolution acceptance criteria are permissive for your mesalamine extended-release capsules and NOT acceptable. The following data-driven dissolution acceptance criteria are recommended for all strengths: (b) (4) (b) (4) for your proposed drug product at release and on stability. Implement these dissolution acceptance criteria for all strengths of your drug product at release and on stability and update the specifications of the drug product with the revised criteria for the dissolution test, accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet the revised dissolution acceptance criteria in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.
			[Summary of the applicant's response and reviewer comment]
IR Response	Solved	1	**[Summary of the applicant's response and reviewer comment]**
			The Applicant has counter proposed different acceptance criteria (with the same range but with different targets), which are acceptable.
			[Deficiency/IR Previous Iteration]

Recommended Dissolution Acceptance Criteria

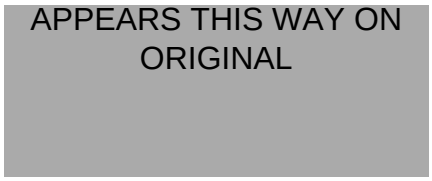
Iteration	Status	ID	[Issue Topic]
DRL Response	Solved	1	Petition the USP for a revision to the dissolution test methods
			[Deficiency/IR]
			We acknowledge that the FDA recommended dissolution acceptance criteria for your product, mesalamine extended release capsules, differ from the USP. Please initiate a revision to an official monograph for mesalamine extended release capsules to the USP under the USP Pending Monograph Process. Until your product is in alignment with the test or test method in the USP monograph, include the following statement in the Labeling, "FDA approved dissolution test specifications differ from USP".
			[Summary of the applicant's response and reviewer comment]
			The Applicant has acknowledged and concurred with this recommendation.

Drug Product Exhibit Batch Dissolution Testing

Commercial batch size is within a factor of ten times the size of the biobatch	Yes
Reviewer Evaluation	
Testing was conducted using unexpired and/or fresh lots	Yes
Reviewer Evaluation	The Batches are approximately 10 months old at the time of testing.
Is the RLD drug product scored?	No

Deficiencies

No deficiencies to display



Nadia Ahmed

Digitally signed by Nadia Ahmed
Date: 12/16/2021 07:56:56PM
GUID: 5e0e0b9100939fa4af29f1127f130ee2

Kimberly Raines

Digitally signed by Kimberly Raines
Date: 12/17/2021 06:20:48AM
GUID: 508da6fd000284a73fdbe11d01b3132f

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	214585
Drug Product Name	Mesalamine Extended-Release Capsules, USP
Strength(s)	(b) (4) 500 mg
Applicant Name	Sun Pharmaceutical Industries Limited
Applicant Address	Sun House, Plot No. 201 B/1 Western Express Highway, Goregaon (E) Mumbai, Maharashtra, India 400 063
US Contact Name and US Mailing Address	Praveen Devakadaksham Sun Pharmaceutical Industries, Inc. 2 Independence Way Princeton, NJ 08540 Email: Praveen.devakadaksham@sunpharma.com
US Contact Telephone Number	(b) (6)
US Contact Fax Number	(609) 720-8503
Original Submission Date(s)	03/31/2021
Submission Date(s) of Amendment(s) Under Review	N/A
Primary Reviewer	Jason Mao, Ph.D.
Secondary Reviewer	Yi Zhang, Ph.D.
Tertiary Reviewer	Wendy Cai, Ph.D.

Study Number(s)	BA19140130	MSM_1000C_0652_18	BA19140473
Study Type(s)	Fasting	Fed	Sprinkle-Fasting
Strength(s)	2 x 500 mg	2 x 500 mg	2 x 500 mg
Clinical Site	Cliantha Research Limited	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited	Cliantha Research Limited
Clinical Site Address	Property No 2A, Block A Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India.	Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India	Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India
Analytical Site	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited		
Analytical Site Address	Plot No. GP-5, Sector-18, HSIDC Old Delhi-Gurugram Road,		

	Gurugram 122 015, Haryana, India.			
Study Number(s)	PKD_18_099	MSM_1000C_0536_17	BA19140426	BA19140131
Study Type(s)	Fed (pilot)	Fed (pilot)	Fasting sprinkle (failed)	Fasting sprinkle (failed)
Strength(s)	2 x 500 mg	2 x 500 mg	2 x 500 mg	2 x 500 mg
Clinical Site	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited		Cliantha Research Limited	
Clinical Site Address	Near R. C. Patel Estate, Akota Road, Akota Vadodara- 390 020 (India)	Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India	Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India	
Analytical Site	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited			
Analytical Site Address	Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India			
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**		**Post October 1, 2014 ANDAs** ☐ **Pending** ☐ **Pending For Cause Inspection** ☒ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**			
QC Dissolution	☒ **Pending**[1] ☐ **Adequate** ☐ **Inadequate**			
Formulation	☒ **Adequate** ☐ **Inadequate**			
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**			
Deficiency Classification	☐ **Major** ☒ **Minor/DRL** ☐ **N/A**			
Major Deficiency Theme	**N/A**			
Justification for Major Designation	**N/A**			
Overall Review Result	☐ **Adequate** ☒ **Inadequate**			

[1] The quality control dissolution testing method for the (b) (4) 500 mg strengths will be reviewed separately the Office of Product Quality (OPQ).

Product Specific Guidance (PSG) Referenced in Review	**☒ Recommended/Latest Revision Date:** ***Recommended Sept 2012; Revised Jul 2014, Oct 2017*** **RLD/RS Number: NDA 020049** **☐ N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	**☐ YES ☒ NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
2	**Fasting**	**500 mg**	**☒ Adequate ☐ Inadequate**
2	**Fed**	**500 mg**	**☒ Adequate ☐ Inadequate**
2	**Sprinkle-Fasting**	**500 mg**	**☒ Adequate ☐ Inadequate**
2	**In vitro Comparative Dissolution**	**(b) (4) 500 mg**	**☐ Adequate ☒ Inadequate**
(b) (4)			

EXECUTIVE SUMMARY

This application contains the results of three in vivo bioequivalence (BE) studies (i.e., fasting, fed and fasting sprinkle studies) comparing a test product, Sun Pharmaceutical Industries Limited's Mesalamine Extended-Release (ER) Capsules, 500 mg, to the corresponding reference product, Shire Development Inc.'s Pentasa® (mesalamine) ER Capsules, 500 mg (NDA 020049). Each of the BE studies was designed as a single-dose, two-treatment, two-sequence, four-period, fully replicated crossover study in healthy male subjects. The results of the three studies calculated by the assessor are summarized in the tables below.

Summary of Statistical Analysis – Fasting BE Study

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Mesalamine ER Capsules, 500 mg (No of subjects completed=49) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – #BA19140130					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUC0-3hr (hr. ng/mL)	1226.00	1326.08	0.92	81.66	104.67
LAUC3-72hr (hr. ng/mL)	2195.63	2665.02	0.82	74.45	91.17
LAUC0-72hr (hr. ng/mL)	3640.88	4225.26	0.86	79.15	93.82
LCMAX (ng/mL)	1222.28	1336.90	0.91	81.05	103.13

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUC0-3hr (hr. ng/mL)	0.92	81.66	104.67	0.3439695	0.5864891	-0.192772	Scaled/PE	PASS
LAUC3-72hr (hr. ng/mL)	0.82	74.45	91.17	0.159084	0.3988534	-0.029945	Scaled/PE	PASS
LAUC0-72hr (hr. ng/mL)	0.86	79.15	93.82	0.1395863	0.3736125	-0.046109	Scaled/PE	PASS
LCMAX (ng/mL)	0.91	81.05	103.13	0.2446753	0.4946466	-0.127063	Scaled/PE	PASS

Summary of Statistical Analysis – Fed BE Study

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Mesalamine ER Capsules, 500 mg
(No of subjects completed=62)
Dose [1 × 1000 mg (2 Capsules of 500 mg)]
Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals
Fasting Bioequivalence Study – #MSM_1000C_0652_18

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUC0-3hr (hr. ng/mL)	47.14	51.32	0.92	80.71	104.55
LAUC3-72hr (hr. ng/mL)	193.84	192.55	1.01	86.99	116.50
LAUC0-72hr (hr. ng/mL)	255.26	266.19	0.96	84.53	108.78
LCMAX (ng/mL)	82.58	92.26	0.90	75.81	105.68

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUC0-3hr (hr. ng/mL)	0.98	80.71	104.55	0.423832	0.6510238	-0.256766	Scaled/PE	PASS
LAUC3-72hr (hr. ng/mL)	1.01	86.99	116.50	0.5222681	0.7226812	-0.317896	Scaled/PE	PASS
LAUC0-72hr (hr. ng/mL)	0.97	84.53	108.78	0.4029474	0.6347814	-0.24198	Scaled/PE	PASS
LCMAX (ng/mL)	0.90	75.81	105.68	0.7887945	0.888141	-0.456673	Scaled/PE	PASS

Summary of Statistical Analysis –Fasting Sprinkle BE Study

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Mesalamine ER Capsules, 500 mg
(No of subjects completed=141)
Dose [1 × 1000 mg (2 Capsules of 500 mg)]
Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals
Fasting Bioequivalence Study – #BA19140473

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUC0-3hr (hr. ng/mL)	1960.18	1727.63	1.13	106.13	121.29
LAUC3-72hr (hr. ng/mL)	2730.08	2710.63	1.01	95.31	106.44
LAUC0-72hr (hr. ng/mL)	5015.55	4753.34	1.06	100.87	110.38
LCMAX (ng/mL)	1746.58	1595.01	1.10	103.67	115.67

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUC0-3hr (hr. ng/mL)	1.13	106.13	121.29	0.205138	0.4529216	-0.112468	Scaled/PE	PASS
LAUC3-72hr (hr. ng/mL)	1.01	95.31	106.44	0.1298865	0.3603977	-0.085901	Scaled/PE	PASS
LAUC0-72hr (hr. ng/mL)	1.05	100.87	110.38	0.0914441	0.3023973	-0.055949	Scaled/PE	PASS
LCMAX (ng/mL)	1.10	103.67	115.67	0.1454749	0.3814118	-0.083869	Scaled/PE	PASS

Assessor's Note: The subjects were dosed in 3 groups in the fasting sprinkle study. As verified by assessor, no significant group-by-treatment interaction was observed for all PK parameters (P>0.1). Therefore, the final statistical analysis was performed with trt*grp term dropped (See section 4.1.3 for details).

As per the draft product-specific guidance (PSG)[2] for Mesalamine ER Capsules, for the pivotal fasting and fasting sprinkle BE studies, the data of partial AUCs (i.e., AUC0-3, AUC3-t), AUC0-t, and Cmax are recommended for BE evaluation. Based on the study results, in the pivotal fasting and fasting sprinkle BE studies, since the within-subject variability of the reference product (sWR) for pharmacokinetic (PK) parameters were all greater than 0.294, reference-scaled average BE approach was used, and statistical results met acceptance BE criteria for all PK parameters. Therefore, the pivotal fasting and sprinkle BE studies are acceptable.

For pivotal fed BE study, the PSG recommends AUC0-t and Cmax for BE evaluation, with submission of AUC0-3 and AUC3-t data as supportive evidence. The results of statistical analysis showed that the sWR for these PK parameters were greater than 0.294. Based on the assessor's calculation, the statistical results of AUC0-3, AUC3-t, AUC0-t and Cmax all met the reference-scaled average BE criteria. Therefore, the pivotal fed study is acceptable.

It should be noted that different batches of test and reference products were used in the pivotal fasting and fed BE studies (test bio-batch #3967425 and reference bio-batch #5783929) and fasting sprinkle study (test bio-batch #AB78176 and reference bio-batch #AK8368A) (See section 4.1.1.1.2 for details).

The applicant also conducted two failed pivotal fasting sprinkle studies [#BA19140131 (N = 47) and #BA19140426 (N = 89)], using the same test bio-batch (#3967425) as in the pivotal fasting

[2] PSG for Mesalamine Extended Release Capsules; https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20cap%20ER_RLD%2020049_RC10-17.pdf

and fed studies, and fully replicate study design in healthy male subjects. The applicant has only submitted 16 BE summary tables for these two failed studies. Per the applicant's own statistical analysis, in two failed sprinkle fasting studies, AUC0-3, AUC3-72, AUC0-72 and Cmax all failed to meet BE criteria except Cmax in study #BA19140131. It is noted that the T/R ratios in the failed fasting sprinkle studies were lower than 0.80 for most of PK parameters (74.51%, 79.63%, 71.23% and 80.05% in study #BA19140131 and 76.17%, 82.18%, 73.00% and 81.81% in study #BA19140426 for AUC0-t, AUC0-3, AUC3-t and Cmax, respectively). However, applicant did not submit the completed clinical, statistical and bioanalytical study reports and concentration/PK datasets for these two failed fasting sprinkle studies. The applicant will be asked to submit above mentioned information.

In addition, the applicant conducted two pilot fed studies (#PKD_18_099 and #MSM_1000C_0536_17). The formulation of test product (bio-batch #070-2018) in the pilot fed studies was the same as that in the pivotal studies. The applicant has submitted 16 BE summary tables for these two pilot studies. Both pilot fed studies failed to meet BE criteria. The applicant will be asked to provide the detailed information (e.g., severity) of adverse events (AEs) reported for these two pilot fed studies.

In addition to the *in vivo* BE studies, the applicant submitted *in vitro* comparative dissolution study in multi-media (i.e., 0.1N HCl, pH 4.5, pH 6.0, pH 6.5, pH 6.8, pH 7.2 and pH 7.5 buffers) on (b) (4) strengths (b) (4) 500 mg) of test and the reference listed drug (RLD) products as per the PSG, including two lots of the 500 mg strength (Batches #3967425 and #AB78176) (b) (4) (b) (4) of the test product. The dissolution profiles of the test product were comparable to those of the reference product for both strengths in all tested media of different pH conditions. However, based on the dissolution data, it is noted that the drug release was incomplete for both test and RLD products in pH 4.5 and 6.0 media at the last time point of 12 hours. The applicant will be asked to provide additional dissolution data showing complete release (> 80%) at these two pH conditions.

(b) (4)

The formulations of (b) (4) 500 mg strengths of test product are proportionally similar and acceptable. The dissolution testing will be reviewed separately for establishing the quality control method and specifications by the Office of Product Quality (OPQ).

Office of Study Integrity and Surveillance (OSIS) Inspections:

Per the EIR[3,4], the inspection at clinical sites (*Cliantha Research Limited, Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201301, Uttar Pradesh, India* and *Sun Pharmaceutical Industries, Ltd., Clinical Pharmacology Unit, Hakeem Abdul Hameed Centenary Hospital 2nd Floor, Jamia Hamdard a.k.a. Hamdard University, Hamdard Nagar, New Delhi 110062, India*) were classified as No Action Indicated (NAI). Per the EIR, Remote Record Review (RRR) was conducted for the analytical site[5] (*Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited, Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India*) for ANDA 214585 and concluded that an inspection is not warranted at this time. In addition, the study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. Thus, the overall OSIS inspection status of the current ANDA is complete.

The application is **inadequate**.

[3] https://panorama fda.gov/task/view?ID=6067826000403425e3bf625d556289e7
[4] https://panorama fda.gov/task/view?ID=6067829300404d4b81c633d2e2fb3d45
[5] https://panorama fda.gov/task/view?ID=606782860040483157b2428baa9fe5da

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3. SUBMISSION SUMMARY

3.1 Drug Product Information[6]

Test Drug Product and Strength(s)	Mesalamine Extended-Release Capsules, (b) (4) 500 mg
Reference Standard (RS) and Strength(s)	Pentasa® (mesalamine) Extended-Release Capsules, 500 mg
RS Holder; NDA/ANDA Number; Approval Date	Shire Development Inc.; N020049; July 8, 2004
Reference Listed Drug (RLD) and Strength(s)	Pentasa® (mesalamine) Extended-Release Capsules, 250 mg and 500 mg
RLD Holder; NDA/ANDA Number; Approval Date	Shire Development Inc.; N020049; May 10, 1993: for 250 mg strength July 8, 2004: for 500 mg strength

3.2 PK/PD Information[7]

Most recent RLD label (provide embedded document) Please check if an NG tube study is needed.	RLD-020049Orig1s034lbl.pdf Action date (Supplement-34): 10/29/2020 No NG tube study was mentioned.
Indication	PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.
Boxed warning	None
Bioavailability	Based on urinary excretion data, 20% to 30% of the mesalamine in PENTASA is absorbed. Plasma mesalamine concentration peaked at approximately 1 mcg/mL 3 hours following a 1-g PENTASA dose and declined in a biphasic manner. Oral mesalamine pharmacokinetics were nonlinear when PENTASA capsules were dosed from 250 mg to 1 g four times daily, with steady-state mesalamine plasma concentrations increasing about nine times, from 0.14 µg/mL to 1.21 µg/mL, suggesting saturable first-pass metabolism.

[6] https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020049#19912

[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020049Orig1s034lbl.pdf

Food Effect	PENTASA labeling does not provide any information on food effect.
Tmax	Mesalamine: 3 hours following a 1-g PENTASA dose.
Metabolism	N-acetyl-5-aminosalicylic acid, the major metabolite of mesalamine (5-aminosalicylic acid), peaked at approximately 3 hours at 1.8 µg/mL, and its concentration followed a biphasic decline. N-acetyl-5-aminosalicylic acid pharmacokinetics were linear. Pharmacological activities of N-acetylmesalamine are unknown, and other metabolites have not been identified.
Excretion	About 130 mg free mesalamine was recovered in the feces following a single 1-g PENTASA dose, which was comparable to the 140 mg of mesalamine recovered from the molar equivalent sulfasalazine tablet dose of 2.5 g. Elimination of free mesalamine and salicylates in feces increased proportionately with PENTASA dose. N-acetylmesalamine was the primary compound excreted in the urine (19% to 30%) following PENTASA dosing.
Half-life	The literature describes a mean terminal half-life of 42 minutes for mesalamine following intravenous administration. Because of the continuous release and *absorption of mesalamine from PENTASA throughout the gastrointestinal tract, the true elimination half-life cannot be determined after oral administration.* The mean elimination half-life at steady-state for both mesalamine and N-acetyl-5-ASA is 7-12 hours.[8]
Maximum Daily Dose	4 g. Safety and efficacy of PENTASA in pediatric patients have not been established.

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20cap%20ER_RLD%20020049_RC10-17.pdf Recommended Sept 2012; Revised Jul 2014, Oct 2017	
Summary of OGD or DB History	Approved ANDAs:	No[9]
	Pending ANDAs:	Yes (b) (4) A214585 for RLD's Pentase)

[8] Per http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=377&sec=monphar&t=0 ; accessed date: 05/06/2021

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

	Controls:	Yes[10] (See comments below)
	Protocols:	Yes[11] (None from the current applicant)
	Pending Citizen Petitions and other legal and regulatory issues: If yes, please comment.	☐ Yes ☒ No[12]

(b) (4)

[redacted]

[10] https://palantir.fda.gov/workspace/report/ri.report main.report.bafcd4b7-dd6d-4c22-8172-d52126bfe2ce
[11] https://ogd fda.gov/QDoc/RFS/Search
[12] https://fda.sharepoint.com/sites/CDER-OGD/OGDP%20DPAL%20Alert%20List/Forms/Active%20Docs.aspx

(b) (4)

[redacted]

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(b) (4)

3.4 Pre-Study Bioanalytical Method Validation

Results	
Bioanalytical method validation report location	**Module 5, 5.3.1.4, pdf file: Study No. BA19140130-ar-mv-report (MV648/17)**
Analyte	Mesalamine
Internal standard (ISTD)	Mesalamine D3
Method description	Ultra-High Performance Liquid Chromatography Tandem Mass Spectrometric Method for the Estimation of Mesalamine in Human K3EDTA Plasma using Mesalamine D3 as an Internal Standard. [Solid phase extraction technique] (MV648/17)
Limit of quantitation (ng/mL)	1.54 ng/mL
Average recovery of drug (%)	62.79% (%CV: 10.78), LQC: 55.04%, MQC: 65.79% and HQC: 67.55%
Recovery of ISTD (%)	77.15%
Standard Curve Concentration (ng/mL) (Nominal)	STDA: 1.54, STDA(DUP): 1.54, STDB: 4.41, STDC: 88.15, STDD: 220.38, STDE: 550.95, STDF: 1101.89, STDG 2203.79, STDH 4407.57, STDI: 5509.46, STDI(DUP): 5509.46 ng/mL
Standard curve concentrations (ng/mL) (Mean Value)	STDA: 1.553, STDA(DUP): 1.537, STDB: 4.300, STDC: 86.470, STDD: 220.807, STDE: 549.153, STDF: 1206.100, STDG: 2151.447, STDH: 4323.543, STDI: 5496.097, STDI(DUP) 5438.370 ng/mL
QC concentrations (ng/mL) (Nominal)	LOQQC – 1.55, LQC – 4.40, MQC –2202.01, HQC – 4404.02, D2QC-9370.26, D4QC-9370.26 ng/mL
QC concentrations (ng/mL) (Mean value)-Global statistics	LOQQC- 1.588, LQC- 4.239, MQC- 2116.483, HQC-4302.632, D2QC – 9270.080, D4QC – 9072.824 ng/mL
QC within batch accuracy range (%)	94.81 to 106.56
QC between batch accuracy range (%)	96.12 to 102.44
QC Intraday accuracy range (%)	95.70 to 103.28
QC within batch precision range (%)	LOQQC: 2.16 to 17.20 LQC: 0.75 to 3.11 MQC: 0.52 to 6.27 HQC: 0.85 to 4.88 D2QC: 0.76 to 5.85 D4QC: 1.73 to 3.74
QC between batch precision range (%)	2.71 to 10.49
QC Intraday precision range (%)	2.92 to 12.77
Bench-top stability in human plasma	8.25 hours, at room temperature, under low light

Stock solution stability of analyte (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
Stock solution stability of ISTD (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
In-injector stability (hours)	99.97 hours (10°C±1°C)
Freeze thaw stability (cycles)	Three cycles (frozen below -50°C and thawed at room temperature, under low light)
Dilution integrity*	Concentration diluted 2 and 4 times
Long Term Stability (days)	147 days in human plasma (stored below -50°C)
Selectivity	Six lots of normal human plasma, two lots of Heamolyzed human plasma and two lots of lipemic human plasma with K3EDTA as an anticoagulant were evaluated and none showed significant interfering peaks at the retention times of Mesalamine and Mesalamine D3 (ISTD).

*Dilution Integrity run with P& A evaluation.

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No SOP No: Bioanalytical Method Validation SOP022427[21]
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No K_3EDTA (human plasma)
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No The long-term stability data of 147 days below -50 ºC is sufficient to cover the storage time of the study samples from the fasting (46 days), fed (57 days) and sprinkle (100 days) BE studies below -50 °C.
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation:

- The plasma mesalamine for the fasting, fed and fasting sprinkle BE studies was measured using a validated Ultra-High Performance Liquid Chromatography Tandem Mass Spectrometric Method (UHPC-MS/MS) method. Mesalamine D3 was used as the internal standard (IS). The anticoagulant used in the method validation was tripotassium ethylene diamine tetraacetate (K_3EDTA). The same anticoagulant was used in the blood collection of samples in the BE studies.

- The mean percent recovery values of the analyte mesalamine and the internal standard mesalamine D3 were 62.79% and 77.15%, respectively. The mean % recovery values for analyte were 55.04% at LQC, 65.79% at MQC and 67.55% at HQC, similar

[21] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-ba19140130\study-ba19140130-ar-sop.pdf

recovery values at MQC and HQC level and ~10% lower in recovery at LQC level. It is also noted that the difference of mean recovery between analyte and IS was 14.36%. Overall, the observed difference in recovery is considered acceptable due to acceptable precision and accuracy in the pre-study method validation and sample analysis.

- The applicant stated that the mesalamine solution and samples were processed under low light condition and protected from light[22]. The same low light condition was used in the BE studies.

- The long-term storage stability was tested for 147 days below -50 °C which covers the study period of fasting (46 days), fed (57 days) and fasting sprinkle (100 days) studies below -50 °C.

The pre-study validation data for pregabalin is adequate.

[22] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-ba19140130\study-ba19140130-ar-mv-report.pdf Page 25 of 293

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route)[Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD) Mesalamine					Study Report Location
					C_{max} (ng/mL)	T_{max*} (hr)	AUC_{0-3} (ng hr/mL)	AUC_{3-t} (ng hr/mL)	AUC_{0-t} (ng hr/mL)	
BA19140130	Single dose oral bioequivalence study of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) and 'PENTASA®'(Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules) in healthy adult human subjects under fasting conditions	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose crossover fully replicate bioequivalence study in healthy adult human subjects under fasting condition. Study Type: Pivotal Study	**Reference product (R):** Pentasa® (Mesalamine) Controlled release capsules 500 mg, 2 Capsules, Oral [Batch. /Lot No. 5783929] **Test product (T):** Mesalamine Extended Release Capsules USP 500 mg, 2 Capsules, Oral [Batch. /Lot No. 3967425]	A total of 56 healthy, adult, male human subjects were enrolled in the study. 49 subjects completed the study. Mean age: 30 ± 6 years (Completed subjects) Range: 19 – 44 Years (Completed Subjects)	Reference (R1) 1641.412(± 919.8806/ 56.04) Reference (R2) 1471.146(± 884.2901/ 60.11) Test (T1) 1556.086(± 894.0198/ 57.45) Test (T2) 1427.579(± 922.8660/ 64.65)	Reference (R1) 2.667(0.667-7.000) Reference(R2) 2.333(0.667-6.000) Test (T1) 1.667 (0.667-6.000) Test (T2) 2.667(0.667-8.000)	Reference R1) 1681.4697 1062.68387/ 63.20) Reference (R2) 1657.0028(± 1162.32001/ 70.15) Test (T1) 1638.5413(± 1009.35265/ 61.60) Test (T2) 1582.3142(± 1195.98880/ 75.58)	Reference(R1) 3251.9458 1905.55379/ 58.60) Reference (R2) 2950.8758(± 1604.56227/ 54.38) Test (T1) 2696.0830(± 1640.17913/ 60.84) Test (T2) 2441.3896(± 1411.49317/ 57.82)	Reference (R1) 4933.4155 2610.33573/ 52.91) Reference (R2) 4607.8786(± 2410.83068/ 52.32) Test (T1) 4334.6243(± 2127.59800/ 49.08) Test (T2) 4023.7038(± 2301.56635/ 57.20)	Module 5, Section 5.3.1.2 (Study report body)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route)[Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD) Mesalamine					Study Report Location
					C_{max} (ng/mL)	T_{max*} (hr)	AUC_{0-3} (ng hr/mL)	AUC_{3-t} (ng hr/mL)	AUC_{0-t} (ng hr/mL)	
MSM_1000C_0652_18	Single dose four-way crossover fully replicate bioequivalence study on Mesalamine extended release capsules 500 mg (two capsules of 500 mg each; total dose 1000 mg) in healthy adult human subjects under fed condition.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, single dose, crossover fully replicate bioequivalence study in healthy adult human subjects under fed condition. Study Type: Pivotal Study	**Reference product (R):** Pentasa® (Mesalamine) Controlled release capsules 500 mg, 2 Capsules, Oral [Batch. /Lot No. 5783929] **Test product (T):** Mesalamine Extended Release Capsules USP 500 mg, 2 Capsules, Oral [Batch. /Lot No. 3967425]	A total of 84 healthy, adult, human male subjects were enrolled in the study. 62 male subjects completed the study. Mean age: 31.10 ± 6.22 years (Completed subjects) Range: 19 – 44 Years (Completed Subjects)	Reference (R1) 214.836 (± 379.8608/ 176.81) Reference (R2) 201.465 (± 351.7274/ 174.58) Test (T1) 176.638 (± 353.8930/ 200.35) Test (T2) 169.160 (± 251.9906/ 148.97)	Reference (R1) 3.667 (1.333 - 7.000) Reference (R2) 3.667 (1.667-12.000) Test (T1) 3.333 (1.000-8.000) Test (T2) 3.834 (1.667-8.000)	Reference (R1) 70.8645± 65.57190/ 92.53) Reference (R2) 77.4704 (± 90.24210/ 116.49) Test (T1) 78.1295 (± 97.32105/ 124.56) Test (T2) 75.2283 (± 84.79153/ 112.71)	Reference (R1) 331.1517± 378.81547/ 114.39) Reference (R2) 326.8802 (± 485.17889/ 148.43) Test (T1) 272.6403 (± 302.20370/ 110.84) Test (T2) 280.9248 (± 325.56630/ 115.89)	Reference (R1) 402.0162± 395.28293/ 98.33) Reference (R2) 404.3506 (± 519.30168/ 128.43) Test (T1) 350.7698 (± 350.10750/ 99.81) Test (T2) 356.1532 (± 374.88870/ 105.26)	Module 5, Section 5.3.1.2 (Study report body)

***Median range is provided.** R=R1=R2 T=T1=T2

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)					Study Report Location
					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-3} (ng hr/mL)	AUC_{3-t} (ng.hr/mL)	AUC_{0-t} (ng.hr/mL)	
Study No. BA191 40473	**Primary Objective:** To evaluate the oral bioequivalence of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules); manufactured by Sun Pharmaceutical Industries Limited, India with 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules); Manufactured for: Shire US Inc., USA, in healthy, adult, human subjects under fasting condition with contents sprinkled over applesauce. **Secondary Objective:** To monitor the safety of test product (T) and reference product (R) in healthy adult human subjects.	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover fully replicate bioequivalence study in healthy adult human subjects under fasting condition with contents sprinkled over applesauce.	Test product [Mesalamine Extended Release Capsules] (T=T1=T2) Strength: 500 mg Capsules Dose: (2 x 500 mg) Route: oral [Batch # AB78176] Ref. product [PENTASA®, (Mesalamine) Controlled-Release Capsules] (R=R1=R2) Strength: 500 mg Capsules Dose: (2 x 500 mg) Route: Oral [Lot # K8368A]	150 subjects enrolled in the study. No. of Subjects Completed (M)-:140 Healthy subjects mean age :30 (19-44)	Reference (R1) 1904.422 (± 1122.3408/ 58.93) Reference (R2) 1774.396 (± 906.6879/ 51.10) Test (T1) 2196.165 (± 1285.6236/ 58.54) Test (T2) 1853.351 (± 1080.0326/ 58.27)	Reference (R1) 1.667 (0.667-7.000) Reference(R2) 2.000 (0.667-8.000) Test (T1) 1.667 (0.667-6.500) Test (T2) 1.667 (0.667-8.000)	Reference R1) 2299.2380 (± 1725.28980 / 75.04) Reference (R2) 2033.0546 (± 1292.36434 / 63.57) Test (T1) 2652.1600 (± 1793.01888 / 67.61) Test (T2) 2233.1579 (± 1370.48466/ 61.37)	Reference(R1) 3077.6602 (± 1558.15820/ 50.63) Reference (R2) 3108.6370 (± 1546.83469/ 49.76) Test (T1) 3223.9236 (± 1508.46672/ 46.79) Test (T2) 2968.7589 (± 1503.42525/ 50.64)	Reference (R1) 5376.8982 (± 2546.73088 / 47.36) Reference (R2) 5141.6916 (± 2269.56507 / 44.14) Test (T1) 5876.0836 (± 2684.73845 / 45.69) Test (T2) 5201.9168 (± 2366.77360/ 45.50)	Module 5, Section 5.3.1.2 (Study report body)

***Median range is provided.** R=R1=R2, T=T1=T

4. APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	BA19140130
Study Title	Single dose oral bioequivalence study of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) and 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules) in healthy adult human subjects under fasting conditions.
Study Type	☑In Vivo BE ☐In Vitro BE ☐Permeability ☐Other
Submission Location: o **Study Report** o **Validation Report** o **Bioanalytical Report**	Module 5, 5.3.1.2, study- BA19140130-body Module 5, 5.3.1.4, study- BA19140130-ar-mv Module 5, 5.3.1.4, study- BA19140130-ar
Clinical Site (Name, Address, Phone #, Fax #)	Cliantha Research Limited Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201301, Uttar Pradesh, India. Tel# +91-120-6122100 FEI: 3013167427 DUNS: 871407072
Principal Clinical Investigator (Name, Email)	Dr. Sanjay Basumatary, MBBS sbasumatary@cliantha.com
Dosing Dates	P1: 05/21/2019 P2: 05/28/2019 P3: 06/04/2019 P4: 06/11/2019
Analytical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited., Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India Tel : (91-124) 4768005, 4768199 Fax: N/AP
Principal Analytical Investigator (Name, Email)	Mr. Bala Krishna Panigrahy, BalaKrishna.Panigrahy@sunpharma.com
Analytical Dates	06/15/2019-07/05/2019*
Sample Storage :	46 days

(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20° C to -80° C)	The samples were stored at clinical (-70 ± 10° C) and analytical site below -50°C (Operational Range -500 C to - 800 C)
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	147 days in human plasma (Stored below -50°C) for Mesalamine
LTSS Data Location	Module 5, 5.3.1.4, study- BA19140130-ar-mv-report, Section 9, subsection 9.3, PDF page No.232

***Assessor's Note**: 6/15/2019 was the date of receipt of samples and 07/05/2019 was the date of last run of study samples[23].

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	(T)=T1=T2	(R)=R1=R2
Product Name	Mesalamine Extended Release Capsules USP 500 mg	Pentasa® (Mesalamine) Controlled release capsules 500 mg
Manufacturer	Sun Pharmaceutical Ind. Ltd, SEZ Unit - 1, Plot no. A-41, Industrial Area, Phase VIII A, S.A.S Nagar (Mohali) – 160071, Punjab	Manufactured For: Shire US Inc., 300 Shire Way, Lexington, MA 02421, USA
Distributed By	-	-
Batch/Lot No.	3967425	5783929
Manufacture Date	08/2018	N/AP
Expiration Date	07/2020	03/2021
Strength	500 mg	500 mg
Dosage Form	Extended-Release Capsules	Controlled-Release Capsules
Bio-batch Size	(b) (4) Capsules	-
Production Batch Size	Capsules	-
Potency	100.1 % w/w	102.0 % w/w
Content Uniformity (mean, %CV)	Mean - 100.1 (%CV - 1.4)	-
Dose Administered	02 Capsules	02 Capsules
Route of Administration	Oral	Oral

[23] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-ba19140130\study-ba19140130-ar.pdf Page 108 of 113.

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment.	☐ Yes ☒ No (Please see comment below)
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment.	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes ☐ No

Assessor's Note: The applicant used two batches of test product (i.e., Lot# 3967425 for pivotal fasting and fed studies, and Lot# AB78176 for pivotal fasting sprinkle study) and RLD (i.e., Lot# 5783929 for pivotal fasting and fed studies, and Lot# AK8368A for pivotal fasting sprinkle study) in the pivotal BE studies and dissolution testing. Per product information tables submitted, the two exhibit batches of test product were manufactured with the same batch size. The two batches of test or RLD were within expiration dates when respective BE study was conducted. It is noted that the test Lot# 3967425 was expired when the pivotal fasting sprinkle study (#BA19140473) was conducted on 09/2020 (See section 4.1.3). The potency and dissolution profiles of two test batches or two RLD batches in QC media were similar (Please see Section 4.3 for details). In addition, as communicated with the OPQ review team[24], they did not find any significant deviations from the predeterminate acceptance ranges for both bio-batches of test products per their preliminary evaluation.

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 56 + 3 Dosed: 56 (P1); 49 (P2, P3 and P4) Completed: 49 Samples Analyzed: 56 Statistically Analyzed: 49
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No (b) (6)

[24] V:\DIVISION\BIO\BIO3\Email Communications\ANDA 214585-Mesalamine ER Capsules

	(b) (6)
Blood Sampling Times	0 (Pre-dose), 0.333, 0.667, 1.00, 1.333, 1.667, 2.00, 2.333, 2.667, 3.00, 3.333, 3.667, 4.00, 4.333, 4.667, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 9.00, 10.00, 12.00, 14.000, 16.00, 20.00, 24.00, 30.00, 36.00, 48.00 and 72.00 hours post-dose.
IRB Approval	☒ Yes Date: 04/22/2019 ☐ No
Informed Consent	☒ Yes Date: 04/22/2019 ☐ No
Length of Fasting	Subjects were fasted overnight for at least 10 hours.
Length of Confinement	Subjects were housed in the clinic from at least 11 hours prior to dosing until at least 72 hours post dose in each period.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design:

- The applicant conducted a randomized, single dose, four-period, fully replicated study in healthy subjects under fasting conditions. The PSG for Mesalamine ER Capsules[25] recommends two-way crossover study design, and also recommends an option of using reference-scaled BE approach if high variability (i.e., within-subject variability > 30%) is observed.

- Per the RLD labeling[26], the elimination half-life at steady-state is about 7-12 hours. Per Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (December 2013)[27], *an adequate washout period (e.g., ≥ 5 half-lives of the moieties to be measured) should separate each treatment*. Therefore, the washout period of at least 7 days, which is more than 5 half-lives of mesalamine, is sufficient for the drug to be cleared from the systemic circulation before the next dose administration in the next period.

- Per the RLD labeling, Tmax is 3 hours. The study samples were collected every 20 minutes between 0 to 5 hours after dosing, which is in line with the PSG recommendation (extensive sampling points around Tmax to accurate estimate Cmax and Tmax, and at least four non-zero measurements of concentration are recommended for each partial AUC).

[25] PSG for Mesalamine ER Capsules;https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20cap%20ER_RLD%2020049_RC10-17.pdf
[26] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020049Orig1s034lbl.pdf
[27] https://www.fda.gov/media/87219/download

- The sample storage duration was 46 days for the fasting study, which was within LTSS of 147 days below -50 ºC provided by the applicant.

- The study design is adequate.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. BA19140130			
		Treatment Groups	
		Test Product (T) N = 49	Reference Product (R) N = 49
Age (years)	Mean ± SD	30 (± 6)	30 (± 6)
	Range	19 - 44	19 - 44
Age Groups	< 18	00 (0%)	00 (0%)
	18 – 40	45 (91.84%)	45 (91.84%)
	41 – 64	04 (08.16%)	04 (08.16%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	49 (100.0%)	49 (100.0%)
	Female	00 (0.0%)	00 (0.0%)
Race	Asian	49 (100%)	49 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m^2)	Mean ± SD	22.2 (± 2.6)	22.2 (± 2.6)
	Range	18.7 – 29.2	18.7 – 29.2
Tobacco users/Smokers	Yes	00 (0.0%)	00 (0.0%)
	No	49 (100.0%)	49 (100.0%)
Other Factors		-	-

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. BA19140130				
Subject No	**Reason for dropout/replacement[11]**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Reason: Withdraw Consent Date: (b) (6) Time: NA	NA	Yes	(b) (6)
	Reason: Withdraw Consent Date: (b) (6) Time: NA	NA	Yes	
	Reason: Withdraw Consent Date: (b) (6) Time: NA	NA	Yes	
	Reason: Own accord Date: (b) (6) Time: 1825 Last Treatment Received: Test(T)	Period I	No	
	Reason: Own accord Date: (b) (6) Time: 1423 Last Treatment Received: Test(T)	Period I	No	
	Reason: Medical Ground (Vomiting) Date: (b) (6) Time: 1635 Last Treatment Received: Reference(R)	Period I	No	
	Reason: Own accord Date: (b) (6) Time: 1802 Last Treatment Received: Test(T)	Period I	No	
	Reason: Own accord Date: (b) (6) Time: 1830 Last Treatment Received: Reference(R)	Period I	No	
	Reason: Own accord Date: (b) (6) Time: 1242 Last Treatment Received: Reference(R)	Period I	No	
	Reason: Medical Ground (Vomiting) Date: (b) (6) Time: 1535 Last Treatment Received: Test(T)	Period I	No	

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.1.2.3 Study Adverse Events

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups Fasted Bioequivalence Study Study No. BA19140130	
	Test (T) (2) N=53 (3) n (%)	Reference (R) (2) N=52 (3) n (%)
Gastrointestinal disorders		
Vomiting	01 (1.89%)	01 (1.92 %)
Gastrointestinal disorders		
Diarrhoea	-	02 (3.85 %)
Gastrointestinal disorders		
Abdominal pain	-	01 (1.92 %)
Skin and subcutaneous tissue disorders		
Rash	01 (1.89 %)	-
Investigations		
Aspartate aminotransferase increased	01 (1.89%)	-
Alanine aminotransferase increased	01 (1.89 %)	-
Total	03 (5.66%)	02 (3.85%)

(1) MedDRA Version 22.0
(2) N=Number of subjects dosed for each treatment
(3) n= Number of subjects reporting at least one incidence of respective adverse event; (%)= percentage of subjects reporting at least one incidence of respective adverse event

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	Reference	P1	(b) (6)		6 hrs 40 mins
	Test	P1			6 hrs 4 mins

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A Both subjects were withdrawn during P1.
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No

If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.2 Protocol Deviations

Study No. BA19140130		
Type	**Subject #s (Test) (T)**	**Subject #s (Reference) (R)**
Blood draw time point deviations, Period I		(b) (6)
Missing Samples, Period I		
Blood draw time point deviations, Period II		
Missing Samples, Period II		
Blood draw time point deviations, Period III		
Missing Samples, Period III		
Blood draw time point deviations, Period IV		
Missing Samples, Period IV		
In Period II, concomitant medication [ORS] was given to the subject 48 for resolution of adverse event.		
In Period III, concomitant medication [Cetirizine 10 mg tablet] was given to the subject (b) (6) for resolution of adverse event.		
In Period-I, post-dose separated plasma was not divided into two aliquots for subject (b) (6) at time at 3.00 hrs.		
In Period-III, post-dose separated plasma was not divided into two Aliquots for subject (b) (6) at time point 0.333hrs.		
In P-IV blood sample should be centrifuged within 45 min of collection. However, same was not followed for Sub (b) (6) at 0.000 hrs blood sample of Sub (b) (6) were placed in centrifuge with a deviation of 08 min.		
End study procedure (Clinical examination and laboratory tests) was not followed for the subject (b) (6) and 11 as they did not report to the facility and declared as lost to follow up.		

Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results:

Dropouts:
There were 59 subjects enrolled and 56 dosed in the fasting study with 49 subjects completing all 4 periods in the study. Subjects (b) (6) were withdrawn before Period 1 dosing and replaced with three other subjects E1 (allotted Subject (b) (6), E2 (allotted Subject (b) (6) and E3 (allotted Subject (b) (6) respectively. Five subjects (Subject (b) (6) (b) (6) were withdrawn due to personal reason after doing in P1. Two subjects (i.e., Subjects (b) (6) were withdrawn from the study due to vomiting in Period 1. Therefore, a total of 49 subjects' data was included in PK and statistical analysis. The subjects who missed at least one period are tabulated below.

Subject #	Sequence	Period 1	Period 2	Period 3	Period 4	Included in statistical analysis (either ABE or RSABE)?
(b) (6)	TRTR	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	RTRT	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	RTRT	✓	X	X	X	No
	RTRT	✓	X	X	X	No
	TRTR	✓	X	X	X	No

Adverse Events:
Per the list of adverse events[28], a total of 8 adverse events (4 for Test and 4 for Reference) were reported within 5 subjects during the entire course of the study.

Subject (b) (6) experienced vomiting in P1 about 6 hours 40 minutes and 6 hours 4 minutes after dosing and were discontinued. Per Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations[29], in the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval should be deleted. Although the vomiting in current study occurred slightly after the dosing interval (6 hours) stated in the RLD labeling[30], the withdrawal is in line with the pre-established SOP[31] as it stated that

[28] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-ba19140130\fast-16-2-7-adverse-event-listings.pdf
[29] https://www.fda.gov/files/drugs/published/Guidance-for-Industry-Bioavailability-and-Bioequivalence-Studies-for-Orally-Administered-Drug-Products---General-Considerations.PDF
[30] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020049Orig1s034lbl.pdf
[31] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-msm-1000c-0652-18\study-msm-1000c-0652-18-protocol.pdf

"any subject who experiences vomiting post-dose at any time during the sample collection schedule in any of the period will be withdrawn from the study."

The reported adverse events were all mild in severity. There were no reports of deaths or serious AEs during the study. Overall, the occurrence of AEs is comparable in test product and RLD-treated groups.

Protocol Deviations:
As seen from above table, there were some sampling collection deviations and procedure deviations. The mentioned deviations were considered not to have an impact on the overall statistical outcome of the fasting study as the analysis is conducted with actual times.

Overall, the firm's handling of "Dropouts/Adverse Events/Protocol Deviations" is **adequate** as per the comments above.

The applicant evaluated 11 different concomitant medications (Acetaminophen, Diclofenac, Amoxicillin, Clavulanic acid, Caffeine, Nicotine, Ciprofloxacin, Tinidazole, Ranitidine, Cetirizine and Domperidone) in its pre-study method validation and none showed significant interfering at the retention time of Mesalamine and Mesalamine-D3 (ISTD). The applicant did not evaluate the impact of Oral rehydration solution (ORS; Containing-Sodium chloride Dextrose Potassium chloride Sodium Citrate), Ondansetron and Loperamide, which were administered as concomitant medication. However, the subjects (i.e., Subject (b) (6) who took concomitant medications (ORS, Ondansetron

and Loperamide) were withdrawn. The applicant did not evaluate the impact of concomitant medication for Subject (b) (6) who was administered ORS during sampling. However, ORS is a saline rehydration solution only containing mixture of Sodium Chloride, Dextrose Potassium Chloride and Sodium Citrate. The impact on PK and bioanalysis should be minimal because only the last two samples could be affected as the medication was administered 46 hours after dosing.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
SOP025099, Version No. 1.0 (Legacy document No.: OP005713, Version No. 6.0)	14 Dec 2018	Repeat Analysis
SOP022444 Version No. 5.0	07/05/2018	Incurred Sample Reanalysis
SOP022429 Version 2.0	09/05/2019	Chromatographic acceptance criteria and review of chromatograms
SOP022428 Version 2.0	04/11/2019	Preparation of Calibration Standards and Quality Control Samples; Analytical Run Organization and Its Acceptance Criteria

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. BA19140130 **Mesalamine**									
Parameter									
Standard Curve Samples									
Nominal Concentration (ng/mL)	1.56	4.25	31.48	92.60	231.49	578.73	1446.82	3617.05	4521.31
Mean Concentration (ng/mL)	1.577	4.132	30.869	93.056	227.161	567.456	1485.179	3703.959	4606.900
Inter day Precision (%CV)	1.10	2.94	2.43	2.32	2.82	1.98	2.04	2.55	3.04
Inter day Accuracy (%Nominal)	101.11	97.22	98.06	100.49	98.13	98.05	102.65	102.40	101.89
Linearity (Range of r values)	0.9958 – 0.9999								

Linearity Range (ng/mL)	1.56– 4521.31			
Sensitivity/ LOQ (ng/mL)	1.56			
Bioequivalence Study No. BA19140130 **Mesalamine**				
Parameter				
Quality Control Samples				
Nominal Concentration (ng/mL)	4.28	90.99	1444.27	3610.66
Mean Concentration (ng/mL)	4.121	92.742	1473.498	3695.521
Inter day Precision (% CV)	5.01	3.93	3.53	3.25
Inter day Accuracy (%Nominal)	96.28	101.93	102.02	102.35

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially (b) (6) ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 In Reanalysis of Study Samples

Study No. BA19140130 Additional information: Module 5, 5.3.1.4				
Reason why assay was repeated	**Number of samples reanalyzed**		**Number of recalculated values used after reanalysis**	
	Mesalamine			
	Actual number	**% of total assays[#]**	**Actual number**	**% of total assays[#]**

	Test (T)	Ref (R)	Test (T)	Ref (R)	Test (T)	Ref (R)	Test (T)	Ref (R)
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code IR Repeats: Internal Standard Related	5	5	0.08	0.08	5	5	0.08	0.08
Code PR Repeats: Processing Related	0	1	0.00	0.02	0	1	0.00	0.02
Total	5	6	0.08	0.09	5	6	0.08	0.09

#: % of total assay were calculated by dividing the number of samples reanalyzed with total number of samples analyzed

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

Comments on Bioanalytical Results:

Rejected and Reinjected Runs:

- The applicant reported 6 re-injected and 5 rejected runs of study sample analysis in the fasting study as shown below.

Batch ID	Rejected/Re-injected	Reason for Rejection/Re-injection
(b) (4), (b) (6)	Re-injected	SIL ERR LINK TIME OUT error
	Re-injected	Stopped at data file 260619\AR29\109, due to error-SIL No Rack ID
	Re-injected	Stopped at sample name (b) (4) due to error-"Device Fault detected in (b) (4) LC controller"
	Re-injected	Stopped during the acquisition of sample name: (b) (4), due to Communication Error "A Connection to the instrument controller has not been established".
	Re-injected	Stopped during the acquisition of sample name: (b) (4), due to Error "GPS High Voltage error".
	Re-injected	For Validation of Instrument # MS-24
	Rejected	Single blank sample rejected due to ISTD variation
	Rejected	All the LQCs were failed in accuracy
	Rejected	The peak area response at the RT of analyte in double and single blank sample was more than 20% of the peak area response of LOQ standard
	Rejected	ULOQ standard failed in accuracy [ULOQ standard (STD I) failed in accuracy and also next lower calibration standard to ULOQ (STD H) failed in accuracy therefore

(b) (4), (b) (6)		calibration curve could not be truncated. Analytical run was not acceptable]
	Rejected	5 out of 6 LQC's samples were failed in accuracy

Repeat Analysis:

- A total of 11 samples (5 samples following treatment with Test product and 6 with Reference product) out of 6445 samples (0.2%) were reanalyzed[32].

- Ten samples were reanalyzed under the reason of "*Internal Standard Related*". According to the raw numerical data, as verified by assessor, the internal standard response of these samples varied beyond 40 to 180% of mean ISTD area response of accepted calibration standards and quality control samples in each run as specified in its repeat SOP# 025099. The repeat analysis of these samples per its SOP# 025099 is considered acceptable.

(b) (6)

- One sample (Subject (b) (6) at 24 hrs in P4) was reanalyzed under the reason of "*Processing Related*" due to the reason of sample interchange. Normally, the "processing related" repeat analysis is considered as PK repeat. However, based on the applicant's explanation, it is considered acceptable as 1) the QC sample 130ME/M1QC#144 and 130ME/S28P4-24.000HR(A1) were next to each other; and 2) the calculated concentration for QC sample 130ME/M1QC#144 was 0.25 ng/mL, which was significantly different from its nominal value of 90.99 ng/mL and the calculated concentration for other M1QC samples 130ME/M1QC#142 (91.62 ng/mL) and 130ME/M1QC#143 (93.44 ng/mL) in the same run. Therefore, the reanalysis of this sample is considered acceptable.

[32] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-ba19140130\study-ba19140130-ar.pdf Page 63-64 of 113

- There was no sample re-integration reported during study sample analysis.

- Per the applicant's SOP on reanalysis of incurred samples (SOP OP005714), "*For studies with total number of subject/ animal samples > 1000: A minimum 10% of 1000 samples + at least 5% of the remaining samples*" A total of 398 out of 6445 (6.18%) samples were repeated for ISR. Per the current FDA Guidance for Industry - Bioanalytical Method Validation (May 2018), the ISR reanalysis should be conducted with 10% of the first 1000 samples and 5% of the remaining samples. The ISR sample size met this requirement (1000*10% + 5445*5% =373). Out of total 398 ISR samples, 373 (93.7%) samples met the acceptance criteria (at least 67% of samples were NMT 20% for each sample). Therefore, the ISR results are acceptable.

- The bioanalytical results are acceptable.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters

ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUC0-3	ng hr/mL	1610.428	68.38	85.78	5599.30	1669.236	66.37	144.83	5196.51	0.96
AUC3-T	ng hr/mL	2568.736	59.47	660.10	8340.58	3101.411	56.71	820.64	9181.78	0.83
AUCt	ng hr/mL	4180.285	52.93	772.09	10912.38	4770.326	52.51	1477.82	13370.84	0.88
CMAX	ng/mL	1491.832	60.74	188.74	4436.01	1556.279	57.94	292.84	4045.22	0.96
TMAX	hr	2.333	.	0.67	8.00	2.667	.	0.67	7.00	0.87

** Tmax values are presented as median, range

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Reference Scaled Average Bioequivalence Approach Used	☑Yes ☐ No
If No, then complete Table 3A only	
If Yes, then complete Tables 3A and 3B	

Mesalamine (No of subjects completed=49)
Dose [1 × 1000 mg (2 Capsules of 500 mg)]
Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals
Fasting Bioequivalence Study – BA19140130

Parameter	Test (T)	N	Reference (R)	N	Ratio (%) (T/R)	90% CI (T/R)
AUC_{0-t} (ng.h/mL)	N/AP	N/AP	N/AP	N/AP	86.15	N/AP
AUC_{0-3} (ng h/mL)	N/AP	N/AP	N/AP	N/AP	92.45	N/AP
AUC_{3-t} (ng.h/mL)	N/AP	N/AP	N/AP	N/AP	82.38	N/AP
C_{max} (ng/mL)	N/AP	N/AP	N/AP	N/AP	91.42	N/AP

Reference-Scaled Average BE Studies- Mesalamine fasting Study

Mesalamine (No of subjects completed=49)
Dose [1 × 1000 mg (2 Capsules of 500 mg)]
Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals
Fasting Bioequivalence Study – BA19140130

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2WR	sWR	Criteria Bound#	Method Used	Outcome
AUC_{0-t} (ng h/mL)	86.15	N/AP	N/AP	0.13952	0.37353	-0.04	RSAB	Bioequivalent
AUC_{0-3} (ng h/mL)	92.45	N/AP	N/AP	0.34397	0.58649	-0.19	RSAB	Bioequivalent
AUC_{3-t} (ng h/mL)	82.38	N/AP	N/AP	0.15908	0.39885	-0.02	RSAB	Bioequivalent
C_{max} (ng/mL)	91.42	N/AP	N/AP	0.2447	0.4947	-0.12	RSAB	Bioequivalent

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Mesalamine (No of subjects completed=49)
Dose [1 × 1000 mg (2 Capsules of 500 mg)]
Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals
Fasting Bioequivalence Study – BA19140130

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUC0-3 (hr. ng/mL)	1226.00	1326.08	0.92	81.66	104.67
LAUC3-72 (hr. ng/mL)	2195.63	2665.02	0.82	74.45	91.17
LAUC0-72 (hr. ng/mL)	3640.88	4225.26	0.86	79.15	93.82

LCMAX (ng/mL)	1222.28	1336.90	0.91	81.05	103.13

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUC0-3 (hr. ng/mL)	0.92	81.66	104.67	0.3439695	0.5864891	-0.192772	Scaled/PE	PASS
LAUC3-72 (hr. ng/mL)	0.82	74.45	91.17	0.159084	0.3988534	-0.029945	Scaled/PE	PASS
LAUC0-72 (hr. ng/mL)	0.86	79.15	93.82	0.1395863	0.3736125	-0.046109	Scaled/PE	PASS
LCMAX (ng/mL)	0.91	81.05	103.13	0.2446753	0.4946466	-0.127063	Scaled/PE	PASS

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	Please see the sWR above.
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No Test: 2.333 hrs (0.67 -8.0 hrs) RLD: 2.667 hrs (0.67-7.0 hrs) T/R ratio: 0.87
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first-time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	N/A	N/A	N/A	N/A
Reference	N/A	N/A	N/A	N/A
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A (AUC∞ is not calculated)			

Comments on PK results:

- Per the PSG, at least four non-zero measurements of concentration are recommended for each partial AUC calculation. For the current fasting BE study, the assessor verified that all subjects exhibited at least four non-zero measurable concentrations for all 4 periods before 3 hrs after dosing. Therefore, data from all subjects were included in the BE evaluation.

- As per the PSG for Mesalamine ER Capsules, partial AUC data (i.e., pAUC0-3 and pAUC3-72), AUC0-72 and Cmax were evaluated.

- The assessor performed the statistical analysis using HVScale4Period.SAS program (18 March 2009) to obtain the results of the PK parameters, pAUC0-3, pAUC3-72, AUC0-t and Cmax.

- The results of statistical analysis show that the within-subject variability of the reference product (sWR) for AUC0-3, AUC3-72, AUC0-72 and Cmax pharmacokinetic (PK) parameters are all greater than 0.294. Therefore, statistical data of AUC0-3, AUC3-t, AUC0-72 and Cmax for mesalamine in the fasting BE study meet the reference scaled average BE criteria as shown in the table above.

- The test/reference ratios for LnAUC0-3, LnAUC3-72, LnAUC0-72, and LnCmax fall within the acceptance range of 0.80-1.25. The 95% upper confidence bound for LnAUC0-3, LnAUC3-72, LnAUC0-72, and LnCmax is all negative.

- It is noted that the concentration profiles of both test and RLD showed double peaks, which may be due to absorption along the GI tract and the difference of drug product release rate in the GI tract.

- Therefore, the fasting BE study is adequate.

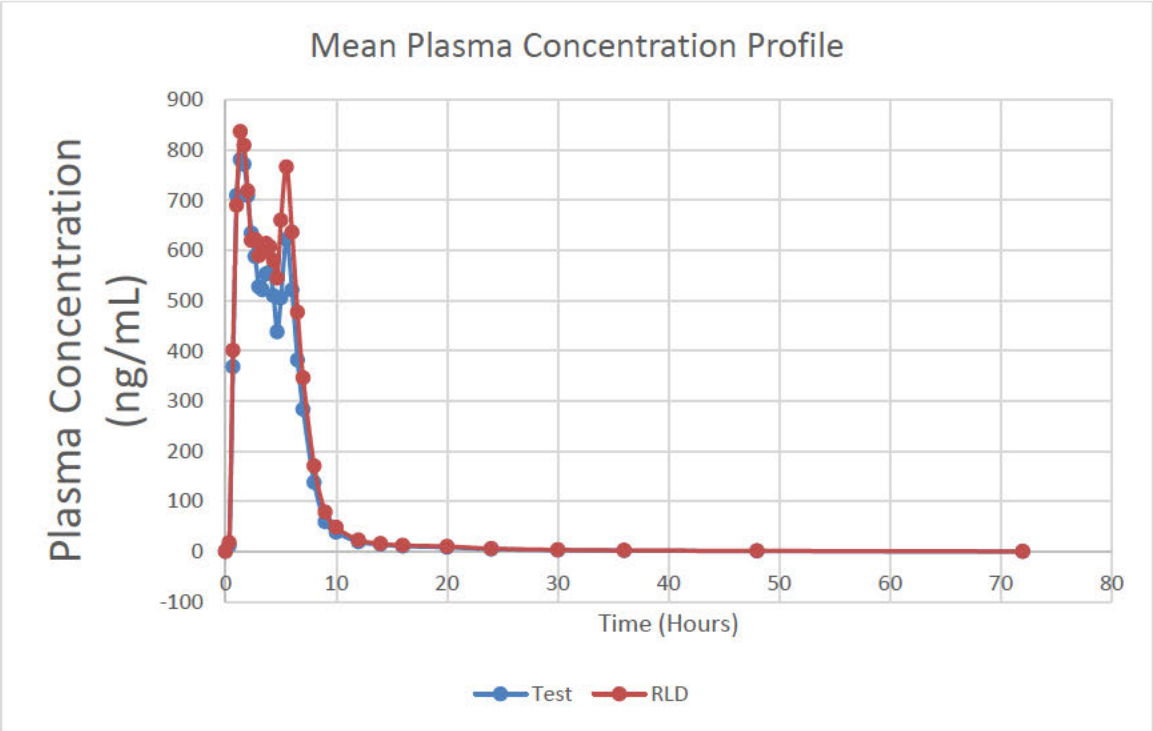
4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Treatment A		Treatment B		
Time	**Mean (ng/mL)**	**CV%**	**Mean (ng/mL)**	**CV%**	**T/R Ratio**
0	0	.	0	.	
0.333	11.34	225.91	17.45	237.78	0.65
0.667	367.88	99.7	400.86	101.11	0.92
1	709.5	102.18	689.81	77.1	1.03
1.333	780.67	93.59	836.69	96.35	0.93
1.667	771.55	91.11	809.31	101.21	0.95
2	708.95	103.35	718.45	90.7	0.99
2.333	634.33	100.37	619.53	86.14	1.02
2.667	587.54	97.17	621.83	96.08	0.94
3	527.44	80.87	589.19	79.23	0.90
3.333	521.36	73.12	596.16	66.55	0.87
3.667	553.03	89.29	613.8	65.09	0.90
4	556.31	88.05	606.99	61.14	0.92
4.333	509.89	77.27	579.66	67.2	0.88
4.667	437.67	88.1	544.69	89.11	0.80
5	505	86.98	660.06	96.55	0.77
5.5	622.1	92.97	766.32	86.54	0.81
6	521.06	92.98	636.1	80.37	0.82
6.5	381.27	101.09	476.79	85.55	0.80
7	283.2	109.43	345.96	90.64	0.82
8	137.53	122.44	170.42	106.95	0.81
9	59.04	81.65	78.65	102.66	0.75
10	38.21	100.53	48.07	81.26	0.79
12	19.09	101.52	22.79	62.66	0.84
14	14.02	111.2	15.75	62.72	0.89
16	10.47	83.12	12.29	70.05	0.85
20	8.38	101.83	10.08	100.08	0.83
24	4.64	103.96	5.82	92	0.80
30	2.67	144.63	3.3	153.31	0.81
36	1.66	198.53	2.19	204.98	0.76
48	0.71	254.47	1.27	272.51	0.56
72	0.09	438.91	0.17	556.26	0.53

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Stud



4.1.2 Single-Dose Fed Bioequivalence Study

4.1.2.3 Study Design

4.1.2.3.1 Study Information

Study Number	MSM_1000C_0652_18			
Study Title	Single dose four-way crossover fully replicate bioequivalence study on Mesalamine extended release capsules 500 mg (two capsules of 500 mg each; total dose 1000 mg) in healthy adult human subjects under fed condition.			
Study Type	☑ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other
Submission Location:				
Study Report	**Module 5, 5.3.1.2, study- MSM_1000C_0652_18-body**			
Validation Report	**Module 5, 5.3.1.4, study- MSM_1000C_0652_18-ar-mv**			
Bioanalytical Report	**Module 5, 5.3.1.4, study- MSM_1000C_0652_18-ar**			
Clinical Site (Name, Address, Phone #, Fax #)	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India Tel: (91-11) 2995-8529, 2995-6721 (Office) Fax: (91-11) 2605-9879			
Principal Clinical Investigator(s) (Name, Email)	Dr. Niraj Sharma E-mail: Niraj.Sharma1@sunpharma.com			
Dosing Dates	P1: 03/09/2019 P2: 03/17/2019 P3: 03/25/2019 P4: 04/02/2019			
Analytical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited., Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India Tel: (91-124) 4768134 Fax: N/AP			
Principal Analytical Investigator (Name, Email)	Dr. Sanjeev Mishra sanjeev.mishra2@sunpharma.com			
Analysis Dates	04/05/2019-05/30/2019			
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)**	**57 days**			
	The samples were stored at clinical and analytical site below -50°C (Operational Range -50^0 C to - 85^0 C)			

(b) Temperature Range (eg, -20°C to -80°C)	
Long-Term Storage Stability Coverage (no. days@ temp °C)	147 days in human plasma (Stored below -50°C) for Mesalamine
LTSS Data Location	Module 5, 5.3.1.4, study-msm-1000c-0652-18-ar-mv-report, Section 9, subsection 9.3, PDF page No.232

4.1.2.3.2 Product Information

Same as the pivotal fasting study (Section 4.1.1.1.2).

4.1.2.3.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 84 Dosed: 84 (P1); 76 (P2); 68 (P3); 64 (P4) Completed: 62 Samples Analyzed: 84 Statistically Analyzed: 76
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	8 days
Randomization	☒ Yes ☐ No (b) (6)
Blood Sampling Times	0 (pre-dose), 0.333, 0.667, 1.00, 1.333, 1.667, 2.00, 2.333, 2.667, 3.00, 3.333, 3.667, 4.00, 4.333, 4.667, 5.00, 5.333, 5.667, 6.00, 6.333, 6.667, 7.00, 7.50, 8.00, 9.00, 10.00, 12.00, 16.00, 20.00, 24.00, 30.00, 36.00, 48.00 and 72.00 hours post-dose.
IRB Approval	☒ Yes Date: 02/13/2019 ☐ No
Informed Consent	☒ Yes Date: 02/13/2019 ☐ No
Length of Fasting	at least 10 hours fasting condition before start of high fat high calorie breakfast was met
Length of Confinement	Subjects were admitted and housed in the Clinical Pharmacology Unit well in time so as to ensure that the requirement of at least 10 hours fasting condition before start of high fat high calorie breakfast was met and were discharged approximately 72 hours after administration of either of the test (T) or reference (R) product during each period of the study.

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Standard FDA Meal Used?	☒ Yes ☐ No
If No, then meal components and composition is listed in the tables below	

Comments on Study Design:

- The applicant conducted a randomized, single dose, four-period, fully replicated study in healthy subjects under fed condition. The PSG for Mesalamine ER Capsules, recommends two-way crossover study, however, also provides an option of other study designs if appropriate.

- The washout period of 8 days is sufficient considering the half-life of the drug product (7-12 hours per the Clinical Pharmacology website)[33].

- The applicant used an FDA-recommended standard high-fat high calorie breakfast in the fed bioequivalence study.[34]

- The long-term storage stability was tested for 147 days below -50 °C which covers the study period of 57 days for fed study below -50 °C.

- The study design is adequate.

4.1.2.4 Clinical Results

4.1.2.4.1 Demographic Profile of Subjects

Study No. MSM_1000C_0652_18			
		Treatment Groups	
		Test Product N = 62	**Reference Product N = 62**
Age (years)	**Mean ± SD**	31.10 ± 6.22	31.10 ± 6.22
	Range	19 - 44	19 - 44
Age Groups	**< 18**	0 (0.00)%	0 (0.00)%
	18 – 40	59 (95.16 %)	59 (95.16 %)
	41 – 64	03 (4.84 %)	03 (4.84 %)
	65 – 75	0 (0.00)%	0 (0.00)%
	> 75	0 (0.00)%	0 (0.00)%

[33] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020049Orig1s034lbl.pdf
[34] FDA Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies; Issued December 2002.

Sex	**Male**	62 (100 %)	62 (100 %)
	Female	0 (0.00)%	0 (0.00)%
Race	**Asian**	62 (100 %)	62 (100 %)
	Black	0 (0.00)%	0 (0.00)%
	Caucasian	0 (0.00)%	0 (0.00)%
	Hispanic	0 (0.00)%	0 (0.00)%
	Other	0 (0.00)%	0 (0.00)%
BMI (Kg/m^2)	**Mean ± SD**	23.39 ± 2.73	23.39 ± 2.73
	Range	18.60 – 28.36	18.60 – 28.36
Smokers	**Yes**	09 (14.52)%	09 (14.52)%
	No	53 (85.48 %)	53 (85.48 %)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?	☒ Yes ☐ No

4.1.2.4.2 Dropout Information

Study No. MSM_1000C_0652_18				
Subject No	**Reason for dropout/ Replacement[11]**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject withdrawn from the study in period I on (b) (6) (b) (6) due to adverse event of "Pain & Swelling left knee" and was last dosed with test product (T) in period I.	I	No	NAP
	Subject withdrawn from the study in period I on (b) (6) (b) (6) due to adverse event of "Dog Bite" and was last dosed with reference product (R) in period I.	I	No	NAP
	Subject withdrawn from the study in period I on (b) (6) (b) (6) Reason –Subject was misbehaving and non-cooperative - Inadequate cooperation and was last dosed with reference product (R) in period I.	I	No	NAP
	Subject withdrawn from the study in period I on (b) (6) (b) (6) due to adverse event of "Dog Bite" and was last dosed with test product (T) in period I.	I	No	NAP
	Subject withdrawn from the study in period I on (b) (6) (b) (6) due to adverse event of "Emesis" and was last dosed with reference product (R) in period I.	I	No	NAP
	Subject withdrawn from the study in period I on (b) (6) (b) (6) due to adverse event of "Trauma, Right index finger" and was last dosed with test product (T) in period I.	I	No	NAP
	Subject withdrawn from the study in period I on (b) (6) (b) (6) due to adverse event of "Emesis" and was last dosed with reference product (R) in period I.	I	No	NAP

(b) (6)	Subject dropped out from the study in Period II on (b) (6) (b) (6) due to personal reasons last dosed with test product (T) in period I.	II	No	NAP
	Subject withdrawn from the study in period II on (b) (6) (b) (6) due to adverse event of "Dog Bite" and was last dosed with reference product (R) in period II.	II	No	NAP
	Subject dropped out from the study in Period III on (b) (6) (b) (6) (Reason – Subject was not contactable) and was last dosed with test product (T) in period II.	III	No	NAP
	Subject dropped out from the study in Period III on (b) (6) (b) (6) (Reason – Personal Reasons) and was last dosed with test product (T) in period II.	III	No	NAP
	Subject dropped out from the study in Period III on (b) (6) (b) (6) (Reason –Subject did not report) and was last dosed with test product (T) in period II.	III	No	NAP
	Subject dropped out from the study in Period III on (b) (6) (b) (6) (Reason – Personal Reasons) and was last dosed with reference product (R) in period II.	III	No	NAP
	Subject withdrawn from the study in period III on (b) (6) (b) (6) due to adverse event of "Myalgia" and was last dosed with reference product (R) in period II.	III	No	NAP
	Subject dropped out from the study in Period III on (b) (6) (b) (6) (Reason – Subject was not contactable) and was last dosed with test product (T) in period II.	III	No	NAP
	Subject dropped out from the study in Period III on (b) (6) (b) (6) (Reason – Personal Reasons) and was last dosed with test product (T) in period II.	III	No	NAP
	Subject withdrawn from the study in period III on (b) (6) (b) (6) due to adverse event of "Varicella with secondary infection" and was last dosed with test product (T) in period III.	III	No	NAP
	Subject withdrawn from the study in period III on (b) (6) (b) (6) due to adverse event of "Varicella" and was last dosed with test product (T) in period III.	III	No	NAP
	Subject withdrawn from the study in period III on (b) (6) (b) (6) due to adverse event of "Emesis" and was last dosed with reference product (R) in period III.	III	No	NAP
	Subject withdrawn from the study in period IV on (b) (6) (b) (6) due to adverse event of "Emesis" and was last dosed with reference product (R) in period IV.	IV	No	NAP
	Subject withdrawn from the study in period IV on (b) (6) (b) (6) due to adverse event of "Rashes" and was last dosed with reference product (R) in period IV.	IV	No	NAP
	Subject dropped out from the study in Period IV on (b) (6) (b) (6) (Reason – Subject was not contactable) and was last dosed with test product (T) in period III.	IV	No	NAP

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.2.4.3 Study Adverse Events

Body system/Adverse Event	Reported Incidence by Treatment Groups[#]	
	Fed Bioequivalence Study Study No. MSM_1000C_0652_18	
	Test T (N=147)	Reference R (N=145)
Gastrointestinal Disorder		
Loose Stools	0	1
Emesis	0	4
Epigastric Pain	0	1
Gastritis	1	0
Pain Abdomen	1	0
General Disorder and administration site condition		
Fever	1	1
Skin and subcutaneous tissue disorders		
Generalized Itching	0	1
Rash	5	2
Urticaria	0	1
Nervous system disorders		
Headache	1	1
Eye disorders		
Itching in Right Eye	0	1
Musculoskeletal and connective tissue disorders		
Myalgia	0	1
Infections and infestations		
Varicella	1	1
Varicella with secondary infection	1	0
Laboratory Abnormality		
Increased AST	0	1
Increased ALT	0	1
Increased urine glucose	0	1
Increased Urine RBC	2	2
Musculoskeletal and connective tissue disorders		
Pain & swelling in Right Finger	0	1
Pain & Swelling Left knee	1	0
Injury, poisoning and procedural complications		
Dog Bite	1	2
Trauma Right index finger	1	0
Total	**16 (10.88%)**	**23 (15.86%)**

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)

(b) (6)	RLD	P1	(b) (6)	25 hrs 53 mins
	RLD	P1		30 hrs 17 mins
	RLD	P3		28 hrs 19 mins
	RLD	P4		2 hrs 26 mins

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A Subjects were withdrawn from the study.
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.2.4.4 Protocol Deviations

Study No. MSM_1000C_0652_18		
Type	**Subjects # Test (T)**	**Subjects # Reference (R)**
Sample collection at time point 3.667 hours was delayed by +03 minutes due to difficulty with veins in period I	(b) (6)	
Sample collection at time point 4.333 hours was delayed by +03 minutes due to difficulty with veins in period I		
Sample collection at time point 72.000 hours was delayed by +03 minutes due to difficulty with veins in period I		
Pre-dose blood sample was collected beyond 1.5 hours before dosing due to oversight in Period I.		
Sample collection at time point 2.333 hours was delayed by +03 minutes due to difficulty with veins in period II		
Sample collection at time point 6.667 hours was delayed by +03 minutes due to difficulty with veins in period III		
Sample collection at time point 6.000 hours was delayed by +03 minutes due to difficulty with veins in period III		
Sample collection at time point 2.333 hours was delayed by +05 minutes due to difficulty with veins in period IV		
Sample collection at time point 7.500 hours was delayed by +03 minutes due to difficulty with veins in period IV		

Sample collection at time point 72.000 hours was delayed by +06 minutes due to difficulty with veins in period IV	(b) (6)
Sample collection at time point 72.000 hours was delayed by +03 minutes due to preceding draw in period IV	
Sample collection at time point 72.000 hours was delayed by +03 minutes due to difficulty with veins in period IV	

Other Protocol deviations:

1. As per section 11.1, laboratory parameters of hepatic Profile (AST, ALT), biochemistry (BUN, Creatinine), urinalysis and hematology will be repeated at the end of the study at approximately 72.000 hours post dose of Period IV or at the discretion of principal investigator, however the same was not done for subject number (b) (6) as they were not reported to CPU for their end of study safety assessment sample.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

Dropouts:

There were 84 subjects enrolled and dosed in the fed study with 62 subjects completing all 4 periods in the study. The dropout/withdrawal subject is shown in the table:

Subject No.	Withdrawn/Dropout	Date	Period	Reason
(b) (6)	Withdrawn	(b) (6)	I	Due to adverse event of " Pain and swelling left knee"
	Withdrawn		I	Due to adverse event of " Dog bite "
	Withdrawn		I	Subject was misbehaving and non-cooperative - Inadequate cooperation
	Withdrawn		I	Due to adverse event of " Dog bite "
	Withdrawn		I	Due to adverse event of "emesis"
	Withdrawn		I	Due to adverse event of " Trauma, Right index finger "
	Withdrawn		I	Due to adverse event of "emesis"
	Dropout		II	Personal reason
	Withdrawn		II	Due to adverse event of " Dog bite "
	Dropout		III	Subject not contactable
	Dropout		III	Personal reason
	Dropout		III	Subject did not reported
	Dropout		III	Personal reason
	Withdrawn		III	Due to adverse event of "Myalgia "
	Dropout		III	Subject not contactable
	Dropout		III	Personal reason
	Withdrawn		III	Due to adverse event of "Varicella with secondary infection"
	Withdrawn		III	Due to adverse event of "Varicella"
	Withdrawn		III	Due to adverse event of "emesis"
	Withdrawn		IV	Due to adverse event of "emesis"
	Withdrawn		IV	Due to adverse event of "Rashes"
	Dropout		IV	Subject not contactable

(b) (6)

(b) (6)

A total of 76 subjects' data was included in PK and statistical analysis. The subjects who missed at least one period (with dosed period highlighted in yellow) are tabulated below.

Subject #	Sequence	Period 1	Period 2	Period 3	Period 4	Included in statistical analysis (either ABE or RSABE)?
(b) (6)	TRTR	✓/X	X	X	X	No
	RTRT	✓/X	X	X	X	No
	RTRT	✓/X	X	X	X	No
	TRTR	✓/X	X	X	X	No
	RTRT	✓/X	X	X	X	No
	TRTR	✓/X	X	X	X	No
	RTRT	✓/X	X	X	X	No
	TRTR	✓	✓/X	X	X	No
	TRTR	✓	✓/X	X	X	Yes
	RTRT	✓	✓	X	X	Yes
	RTRT	✓	✓	X	X	Yes
	RTRT	✓	✓	X	X	Yes
	TRTR	✓	✓	X	X	Yes
	TRTR	✓	✓	X	X	Yes
	RTRT	✓	✓	X	X	Yes
	RTRT	✓	✓	X	X	Yes
	TRTR	✓	✓	✓/X	X	Yes
	TRTR	✓	✓	✓/X	X	Yes
	RTRT	✓	✓	✓/X	X	Yes

(b) (6)	TRTR	✓	✓	✓	✓/X	Yes
	TRTR	✓	✓	✓	✓/X	Yes
	TRTR	✓	✓	✓	X	Yes

"✓" indicated that the subject was dosed. "X" indicated that the subject was withdrawn/dropout in that period.

Adverse Events:
Per the list of adverse events[35], a total of 39 adverse events (Test 16 and Reference 23) were reported within 23 subjects during the entire course of the study.

Subject (b) (6) experienced vomiting about 25 hours 53 minutes and 30 hours 17 minutes in P1, 28 hours 19 minutes in P3 and 2 hours 26 minutes in P4, respectively, after dosing. They were all discontinued, which was in line with the pre-established SOP[36].

The reported adverse events were all mild or moderate in severity. There were no reports of deaths or serious AEs during the study.

Protocol Deviations:
As seen from above table, there were some sampling collection deviations and procedure deviations. The mentioned deviations were considered not to have an impact on the overall statistical outcome of the fed study as the analysis is conducted with actual times.

Additionally, the applicant reported an incidence that in Period I approximately after 50 minutes of dosing (b) (6) study personal observed a floating capsule (which was identified as "Reference") in a washroom.[37] No untoward event/incident including any unreported adverse event during that period could be elicited from those subjects despite detailed questioning. Among the identified 14 subjects, 08 subject (Subject Nos. (b) (6) had received reference treatment in period – I. Subject (b) (6) had an episode of emesis on the next day (b) (6) (b) (6) and was withdrawn from the study. No responsible subject could be identified for this occurrence. As verified by assessor, none of these subjects were reported with "0" drug plasma concentrations at all time points during P1. The applicant also conducted statistics with data including or excluding these 7 subjects and the study results were meeting the bioequivalence criteria as per study protocol after inclusion and exclusion of all these 7 subjects. The assessor would not pursue this use further.

Overall, the applicant's handling of "Dropouts/Adverse Events/Protocol Deviations" is **adequate** as per the comments above.

(b) (4)

[35] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-ba19140130\fast-16-2-7-adverse-event-listings.pdf
[36] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-msm-1000c-0652-18\study-msm-1000c-0652-18-protocol.pdf
[37] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-msm-1000c-0652-18\study-msm-1000c-0652-18-body.pdf Page 38 of 317
[38] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-msm-1000c-0652-18\study-msm-1000c-0652-18-body.pdf Page 238 of 317

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(b) (6)

The applicant evaluated 11 different concomitant medications (Acetaminophen, Diclofenac, Amoxicillin, Clavulanic acid, Caffeine, Nicotine, Ciprofloxacin, Tinidazole, Ranitidine, Cetirizine and Domperidone) during the pre-study method validation and none showed significant interfering at the retention time of Mesalamine and Mesalamine-D3 (ISTD). The applicant also performed extra specificity testing in presence of concomitant medications (Ondansetron, Drotavarine, Levocetirizine, Pheniramine maleate and Pantoprazole) and found acceptable in the Analytical Report during sample analysis[39]. Paracetamol is acetaminophen[40].

However, the applicant did not evaluate the impact of Tetanus toxoid, Serratiopeptidase, Diethylamine, Linseed oil, Methyl Salicylate, Menthol, Chlorzoxazone, methyl prednisolone, Aceclofenac, Lactic acid bacillus spores, calamine, Diphenhydramine hydrochloride, Valacyclovir, Azithromycin, and Caladryl lotion, which were administered as concomitant medication. As twelve subjects (i.e., Subjects (b) (6) who were given with concomitant medication were withdrawn/dropout and the data after co-medication from these subjects (affected periods) were not included in statistical analysis, the co-medication in these subjects should have no impact on BE analysis. In addition, Caladryl lotion[41], Calamine[42] and Diphenhydramine hydrochloride are topical product and were applied topically on the affected area, it is not expected the application of them would have any impact on BE analysis.

As summarized by the assessor in the table above, the only concern is for Subject (b) (6) (P2) who was given Vizylac (Lactic acid bacillus 120 x 10^6 spores) one capsule for the treatment of loose stools. Lactic acid bacillus spores is a probiotics. There is no report of drug-drug interaction for mesalamine and Lactic acid bacillus spores in RLD labeling [43]. The impact of concomitant medications of Lactic acid bacillus spores on PK and/or sample analysis is not known as the applicant did not provide validation data to support this comedication and the (b) (6) P2 data were still included in the PK and statistical analysis. The assessor conducted a SAS analysis with excluding data for (b) (6) P2, and the statistical still meet the BE acceptance criteria. Therefore, the assessor will not pursue this issue further (Please see details in Section 4.1.2.6.4).

[39] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-msm-1000c-0652-18\study-msm-1000c-0652-18-ar.pdf Page 16-18 of 125.
[40] https://www.drugs.com/paracetamol.html
[41] https://www.webmd.com/drugs/2/drug-16219/caladryl-topical/details
[42] https://www.webmd.com/drugs/2/drug-14271/calamine-topical/details
[43] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020049s035lbl.pdf

4.1.2.5 Bioanalytical Results

4.1.2.5.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as under the fasting study.

4.1.2.5.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. MSM_1000C_0652_18 **Mesalamine**											
Parameter											
Standard Curve Samples											
Nominal Concentration (ng/mL)	1.56	1.56	4.15	25.59	63.97	159.92	319.83	639.66	1279.32	1599.15	1599.15
Mean Concentration (ng/mL)	1.575	1.556	4.051	25.290	63.772	157.928	320.910	647.937	1296.142	1617.890	1605.538
Inter day Precision (%CV)	1.22	2.67	2.98	2.16	2.01	1.93	2.14	1.86	3.06	2.75	5.75
Inter day Accuracy (%Nominal)	100.99	99.74	97.61	98.83	99.69	98.75	100.34	101.29	101.31	101.17	100.40
Linearity (Range of r values)	0.9962 – 1.000										
Linearity Range (ng/mL)	1.56– 1599.15										
Sensitivity/ LOQ (ng/mL)	1.56										

Bioequivalence Study No. MSM_1000C_0652_18 **Mesalamine**						
Parameter						
Quality Control Samples						
Nominal Concentration (ng/mL)	4.29	10.05	61.31	510.95	1264.72	2714.00 (DQC)
Mean Concentration (ng/mL)	4.211	9.594	61.787	520.960	1288.563	2993.933
Inter day Precision (% CV)	7.08	2.80	4.22	2.89	3.84	3.90
Inter day Accuracy	98.16	95.46	100.78	101.96	101.89	110.31

(%Nominal)						

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially (subjects (b) (6) (b) (6) ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.2.5.3 Reanalysis of Study Samples

Study No. MSM_1000C_0652_18 Additional information: Module 5, 5.3.1.4								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Mesalamine							
	Actual number		**% of total assays#**		**Actual number**		**% of total assays#**	
	Test (T)	**Ref (R)**	**Test (T)**	**Ref (R)**	**Test (T)**	**Ref (R)**	**Test (T)**	**Ref (R)**
Pharmacokinetic[8]	0	0	0.00	0.00	0	0	0.00	0.00
Code IR Repeats : Internal Standard Related	10	35	0.10	0.35	8&	35	0.08	0.35
Code BR Repeats: Blank Related	1	1	0.01	0.01	0	0	0.00	0.00
Code HR Repeats: Highest calibration Related	2	5	0.02	0.05	2	5	0.02	0.05
Code PR Repeats: Processing Related	0	2	0.00	0.02	0	1	0.00	0.01
Total	13	43	0.13	0.44	10	41	0.10	0.42

#: % of total assay were calculated by dividing the number of samples reanalyzed with total number of samples analyzed
[7]Provide a separate table for each analyte measured for each in vivo study.
[8]If no repeats were performed for pharmacokinetic reasons, insert "0.0"
&Two samples for Subject (b) (6) were not used for PK analysis as subject (b) (6) did not complete the period.

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

Comments on Bioanalytical Results:

Rejected and Reinjected Runs:

- The applicant reported 4 re-injected and 6 rejected runs of study sample analysis in the fed study as shown below.

Batch ID	Rejected/Re-injected	Reason for Rejection/Re-injection
(b) (4), (b) (6)	Re-injected	Stopped at sample name (b) (4) due to error "Device fault detected in Mass Spectrometer"
	Re-injected	Stopped at sample name (b) (4)' due to error 'Device fault detected in Mass Spectrometer'
	Re-injected	Stopped at sample name (b) (4) due to error 'Device fault detected in (b) (4) LC Controller'.
	Re-injected	Stopped at sample name (b) (4)' due to error 'Device fault detected in (b) (4) LC Controller'
	Rejected	17 out of 24 QC's failed in accuracy
	Rejected	Peak area response at the RT of analyte in single blank sample was more than 20% of the peak area response of LOQ standard
	Rejected	20 out of 24 QC's failed in accuracy
	Rejected	Peak area response at the RT of analyte in single blank sample was more than 20% of the peak area response of LOQ standard
	Rejected	ACQ error device fault detected in the (b) (4) LC controller and Pmax error encountered
	Rejected	Peak area response at the RT of analyte in double blank sample (ID: LS2407245A vial no. 02) was more than 20% of the mean peak area response of analyte of processed LOQ samples.

Repeat Analysis:

- A total of 56 samples (13 samples following treatment with Test product and 43 with Reference product) out of 9869 samples (0.57%) were reanalyzed.

- Forty-five samples were reanalyzed under the reason of "*Internal Standard Related*". According to the raw numerical data, as verified by assessor, the internal standard response of these samples varied beyond 40 to 180% of mean ISTD area response of accepted calibration standards and quality control samples in each run. The repeat analysis of these samples per its SOP OP005713 is considered acceptable.

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(b) (6)

- Two samples were reanalyzed under the reason of "*Blank related*". Per SOP OP005713, "*Sample(s) shall be identified under Code BR when subject blank and/or subject zero/non-clinical Pre-dose (Day 0) sample fails to meet acceptance criteria as significant Peak Area Response at RT of ISTD in Subject Blank (Pre-dose) Sample or Quantifiable Concentration in Subject Zero (Pre-dose + ISTD) Sample/non-clinical Pre-dose (Day 0) sample was observed.*"

(b) (6)

In both double blank samples, significant peak area response at RT of ISTD was observed. The repeat analysis of these samples per its SOP OP005713 is considered acceptable.

(b) (6)

The initial values for these samples exceeded the highest calibration curve standard concentration (ULOQ: 1599.15 ng/mL). The applicant conducted dilution integrity study during its method validation with dilution factor of 2 and 4. All the repeat values were more than 85% of ULOQ (1359.3 ng/mL). The repeat analysis is acceptable.

- Two samples were reanalyzed under the reason of "*Processing Related*".

Based on the applicant's explanation, the reanalysis is considered acceptable for Sample of Subject (b) (6) at 36 hrs in P2 as 1) the QC sample 0652ME/HQC#244 and 0652ME/S53P2-36.000HR(A1) were next to each other; and 2) the calculated concentration for QC sample 0652ME/HQC#244 was 2.05 ng/mL, which was significantly different from its nominal value of 1264.72 ng/mL and the calculated concentration for other HQC samples 0652ME/HQC#243 (1276.65 ng/mL) and 0652ME/HQC#245 (1309.83 ng/mL) in the same run. Therefore, the reanalysis of this sample is considered acceptable.

For sample of Subject (b) (6) at 0 hr in P1 (repeat for the secondary time), the applicant's explanation is acceptable and the repeat value is the same as the original value.

- There was no re-integration reported during study sample analysis.

- Per the firm's SOP on reanalysis of incurred samples (SOP OP005714), "*For studies with total number of subject/ animal samples > 1000: A minimum 10% of 1000 samples + at least 5% of the remaining samples*" A total of 568 out of 9869 (5.76%) samples were repeated for ISR. Per the current FDA Guidance for Industry - Bioanalytical Method Validation (May 2018), the ISR reanalysis should be conducted with 10% of the first 1000 samples and 5% of the remaining samples. The ISR sample size met this requirement (1000*10% + 8869*5% =543). Out of total 568 ISR samples, 557 (98.06%) samples met the acceptance criteria (at least 67% of samples were NMT 20% for each sample). Therefore, the ISR results are acceptable.

- The bioanalytical results are acceptable.

4.1.2.6 Pharmacokinetic Results

4.1.2.6.1 Arithmetic Mean Pharmacokinetic Parameters

ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUC0-3	ng hr/mL	76.781	119.04	6.76	573.94	73.832	104.83	9.52	589.35	1.04
AUC3-T	ng hr/mL	276.491	112.91	43.80	2182.88	329.233	130.07	16.73	3022.54	0.84
AUCt	ng hr/mL	353.289	102.04	66.81	2257.88	402.936	112.50	37.24	3104.60	0.88
CMAX	ng/mL	173.162	178.84	9.78	2836.54	208.828	175.37	8.62	2372.09	0.83
TMAX	hr	3.500	.	1.00	8.00	3.667	.	1.33	12.00	0.95

** Tmax values are presented as median, range

4.1.2.6.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Reference Scaled Average Bioequivalence Approach Used			☑Yes	☐ No		
If No, then complete Table 3A only						
If Yes, then complete Tables 3A and 3B						
Mesalamine (No of subjects completed=62*) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fed Bioequivalence Study – MSM 1000C 0652 18						
Parameter	**Test (T)**	**N**	**Reference (R)**	**N**	**Ratio (%) (T/R)**	**90% CI (T/R)**
C_{max} (ng/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{0-t} (ng h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{0-3} (ng.h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{3-t} (ng h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP

Reference-Scaled Average BE Studies- Mesalamine fed Study

Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s^2WR**	**sWR**	**Criteria Bound#**	**Method Used**	**Outcome**
Including Subject (b) (6)								
AUC_{0-t} (ng h/mL)	96.75	N/AP	N/AP	0.40315	0.63494	-0.24	RSAB	Bioequivalent
AUC_{0-3} (ng h/mL)**	97.83	N/AP	N/AP	0.42383	0.65102	-0.25	RSAB	N/AP
AUC_{3-t} (ng h/mL)**	101.03	N/AP	N/AP	0.52227	0.72268	-0.31	RSAB	N/AP
C_{max} (ng/mL)	90.02	N/AP	N/AP	0.7888	0.8881	-0.45	RSAB	Bioequivalent
Excluding Subject (b) (6)								
AUC_{0-t} (ng h/mL)	98.76	N/AP	N/AP	0.40112	0.63334	-0.23	RSAB	Bioequivalent

AUC_{0-3} (ng h/mL)**	96.92	N/AP	N/AP	0.45237	0.67259	-0.26	RSAB	N/AP
AUC_{3-t} (ng h/mL)**	103.83	N/AP	N/AP	0.51287	0.71615	-0.30	RSAB	N/AP
C_{max} (ng/mL)	95.07	N/AP	N/AP	0.7818	0.8842	-0.46	RSAB	Bioequivalent

4.1.2.6.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Mesalamine (No of subjects completed=62) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – MSM_1000C_0652_18					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUC0-3 (hr. ng/mL)	47.14	51.32	0.92	80.71	104.55
LAUC3-72 (hr. ng/mL)	193.84	192.55	1.01	86.99	116.50
LAUC0-72 (hr. ng/mL)	255.26	266.19	0.96	84.53	108.78
LCMAX (ng/mL)	82.58	92.26	0.90	75.81	105.68

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUC0-3 (hr. ng/mL)	0.98	80.71	104.55	0.423832	0.6510238	-0.256766	Scaled/PE	PASS
LAUC3-72 (hr. ng/mL)	1.01	86.99	116.50	0.5222681	0.7226812	-0.317896	Scaled/PE	PASS
LAUC0-72 (hr. ng/mL)	0.97	84.53	108.78	0.4029474	0.6347814	-0.24198	Scaled/PE	PASS
LCMAX (ng/mL)	0.90	75.81	105.68	0.7887945	0.888141	-0.456673	Scaled/PE	PASS

Assessor's Note: The data used for analysis included the 62 subject who completed all four periods and 14 subjects who completed two or three periods with at least one test and one RLD. The assessor did not conduct additional analysis by excluding data from subjects (Subject (b) (6) (b) (6) who were possibly involved in the incident discussed in Section 4.1.2.4 as the applicant investigated the incidence conducted analysis by excluding these subjects, and the results obtained by the assessor were the same as the applicant's with inclusion of these subjects.

4.1.2.6.4 Additional Information for the Study

Root Mean Square Error	Please see the sWR above.
Is there a Tmax difference between Test and Reference?	☐ Yes ☒ No

If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)	Test: 3.5 hrs (1.0-8.0 hrs) RLD: 3.667 hrs (1.33-12.0 hrs) T/R ratio: 0.95
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first-time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Comments on PK results: **Adequate**

- As per the PSG for Mesalamine ER Capsules, for the fed study, the following PK parameters were evaluated: Log-transformed AUC0-t and Cmax. AUC0-3 and AUC3-t data were also evaluated as supportive evidence of comparable therapeutic outcome.

- The assessor performed the statistical analysis using HVScale4Period.SAS program (18 March 2009) to obtain the results of the PK parameters, pAUC0-3, pAUC3-72, AUC0-t and Cmax.

- The results of statistical analysis show that the within-subject variability of the reference product (sWR) for AUC0-3, AUC3-72, AUC0-72 and Cmax PK parameters are greater than 0.294. Therefore, statistical data of AUC0-3, AUC3-t, AUC0-72 and Cmax for mesalamine in the fed BE study meet the reference scaled average BE criteria as shown in the table above.

- The test/reference ratios for LnAUC0-3, LnAUC3-72, LnAUC0-72, and LnCmax fall within the acceptance range of 0.80-1.25. The 95% upper confidence bounds for LnAUC0-3, LnAUC3-72, LnAUC0-72, and LnCmax are all negative.

- As discussed early in Section 4.1.2.4.4, Subject (b) (6) was administered concomitant medication (Lactic acid bacillus 120 x 10^6 spores) in P2 but the impact of concomitant medications of Lactic acid bacillus spores on PK and/or sample analysis was not evaluated by the applicant. Therefore, the assessor conducted a SAS analysis with excluding data for S74 P2. The outcome indicates that the PK parameters still meet the BE criteria as shown below.

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	255.31	266.64	0.96	84.32	108.73
LCMAX	82.56	92.12	0.90	75.84	105.91

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.97	84.32	108.73	0.4029474	0.6347814	-0.24198	Scaled/PE	PASS
LCMAX	0.90	75.84	105.91	0.7887945	0.888141	-0.456673	Scaled/PE	PASS

- PENTASA labeling does not provide any information on food effect. However, it is noted that food decreases AUCs and Cmax values significantly as shown in the table below.

Parameter	Unit	Fasting	Fed	% Decrease	Fasting	Fed	% Decrease
		Test			RLD		
AUC0-3	ng hr/mL	1610.428	76.781	- 95.23	1669.236	73.832	- 95.58
AUC3-T	ng hr/mL	2568.736	276.491	- 89.24	3101.411	329.233	- 89.38
AUCt	ng hr/mL	4180.285	353.289	- 91.55	4770.326	402.936	- 91.55
CMAX	ng/mL	1491.832	173.162	- 88.39	1556.279	208.828	- 86.58

- The pharmacokinetic results are adequate.

4.1.2.7 Overall Comment

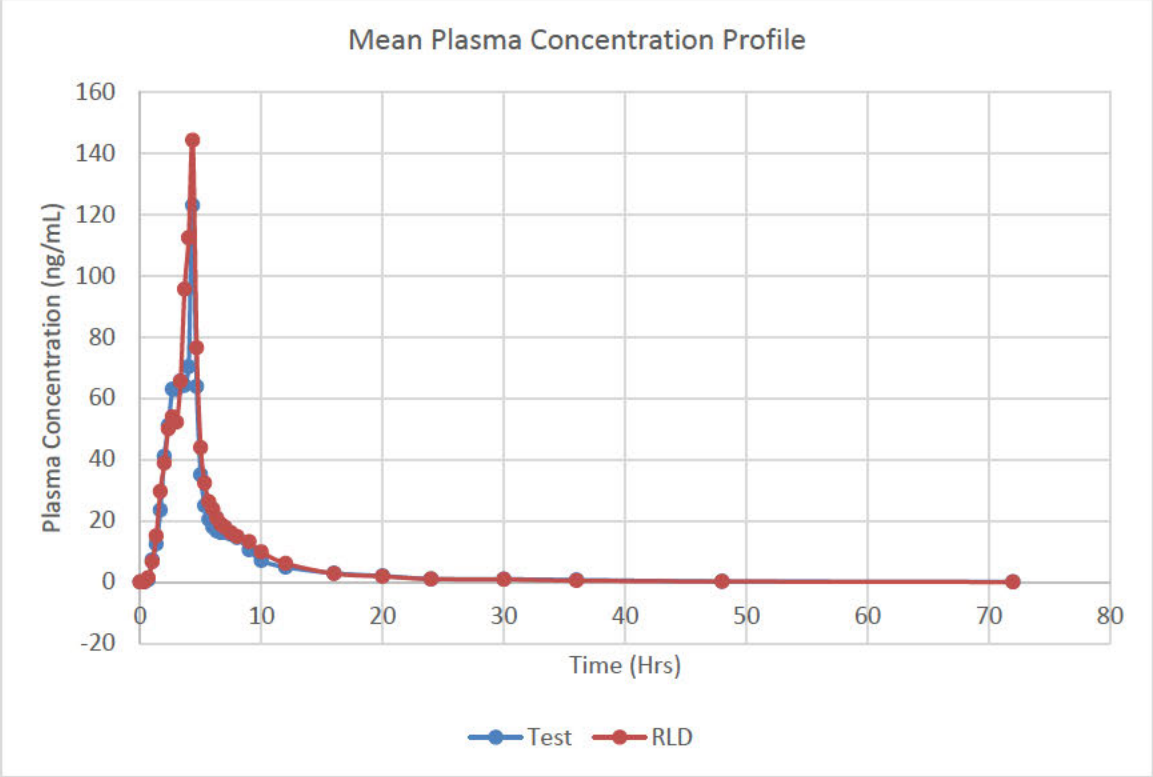
Was the fed bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Treatment A		Treatment B		T/R Ratio
Time	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0	0	.	0	.	
0.333	0.02	1191.64	0.01	1174.73	2.00
0.667	0.75	230.22	1.4	139.56	0.54
1	7.22	423.75	6.6	157.46	1.09
1.333	12.42	302.66	15.04	128.28	0.83
1.667	23.45	153.35	29.56	152.04	0.79
2	41.06	145.61	38.85	127.07	1.06
2.333	51.11	130.36	49.98	140.56	1.02
2.667	62.96	139.99	53.94	141.03	1.17
3	62.87	143.49	52.19	140.16	1.20
3.333	65.67	170.6	65.5	143.7	1.00
3.667	64.13	156.49	95.57	209.76	0.67
4	70.24	183.56	112.34	261.73	0.63
4.333	122.95	242.75	144.21	230.09	0.85
4.667	63.86	251.23	76.49	218.11	0.83
5	35.03	190.9	43.87	164.61	0.80
5.333	24.94	152.4	32.3	142.27	0.77
5.667	20.52	119.91	26.23	135.43	0.78
6	17.95	107.37	23.82	142.32	0.75
6.333	16.68	105.13	20.87	139.24	0.80
6.667	16.11	112.84	18.81	156.58	0.86
7	16.11	131.36	17.86	180.88	0.90
7.5	15.53	125.21	16.07	176.82	0.97
8	14.51	126.53	14.85	175.25	0.98
9	10.53	110.3	13.17	160.68	0.80
10	7.04	86.78	9.84	159.93	0.72
12	4.85	79.5	6.1	192.6	0.80
16	2.88	72.18	2.75	77.38	1.05
20	1.99	79.09	1.84	88.83	1.08
24	1.04	129.69	0.98	154.59	1.06
30	0.95	169.13	0.85	196	1.12
36	0.7	192.02	0.47	235.65	1.49
48	0.22	415.25	0.18	413.71	1.22
72	0.07	1191.64	0	.-	-

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Assessor's Generated Figure



4.1.3 Single-dose Sprinkled Fasting Bioequivalence Study

4.1.3.3 Study Design

4.1.3.3 Study Information

Study Number	BA19140473
Study Title	Single dose oral bioequivalence study of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) and 'PENTASA®' (Mesalamine) Controlled-Releasle Capsules 500 mg (2 x 500 mg capsules) in healthy adult human subjects under fasting condition with contents sprinkled over applesauce.
Study Type	☑In Vivo BE □In Vitro BE □Permeability □Other
Submission Location: o **Study Report** o **Validation Report** o **Bioanalytical Report**	 Module 5, 5.3.1.2, study- BA19140473-body Module 5, 5.3.1.4, study- BA19140473-ar-mv Module 5, 5.3.1.4, study- BA19140473-ar
Clinical Site (Name, Address, Phone #, Fax #)	Cliantha Research Limited Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201301, Uttar Pradesh, India. Tel#+91-120-6122100 FEI: 3013167427 DUNS: 871407072
Principal Clinical Investigator (Name, Email)	Dr. Mitisha, MD mkjain@cliantha.com
Dosing Dates	Group 1: P1: 09/01/2020 P2: 09/08/2020 P3: 09/15/2020 P4: 09/22/2020 Group 2: P1: 09/29/2020 P2: 10/06/2020 P3: 10/13/2020 P4: 10/20/2020 Group 3: P1: 10/08/2020 P2: 10/15/2020 P3: 10/22/2020 P4: 10/29/2020
Analytical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited., Plot No. GP-5, Sector 18, HSIDC, Udyog Vihar Industrial Area Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India Tel: (91-124) 4768005 Fax: N/AP
Principal Analytical Investigator (Name, Email)	Mr. Bala Krishna Panigrahy, BalaKrishna.Panigrahy@sunpharma.com

Analytical Dates	10/15/2020-12/28/2020
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., (-20°C to -80°C)**	100 days The samples were stored at clinical (-70 ± 10° C) and analytical site below -50°C (Operational Range -500 C to - 800 C)
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	147 days in human plasma (Stored below -50°C) for Mesalamine
LTSS Data Location	Module 5, 5.3.1.4, study- BA19140473-ar-mv-report, Section 9, subsection 9.3, PDF page No.232

4.1.3.3.1 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	**(T)=T1=T2**	**(R)=R1=R2**
Product Name	Mesalamine Extended Release Capsules USP 500 mg	Pentasa® (Mesalamine) Controlled release capsules 500 mg
Manufacturer	Sun Pharmaceutical Ind. Ltd, SEZ Unit - 1, Plot no. A-41, Industrial Area, Phase VIII A, S.A.S Nagar (Mohali) – 160071, Punjab	Manufactured For: Shire US Inc., 300 Shire Way, Lexington, MA 02421, USA
Distributed By	-	-
Batch/Lot No.	AB78176	AK8368A
Manufacture Date	07/2020	N/AP
Expiration Date	06/2022	10/2022
Strength	500 mg	500 mg
Dosage Form	Extended-Release Capsules	Controlled-Release Capsules
Bio-batch Size	(b) (4) Capsules	-
Production Batch Size	Capsules	-
Potency	97.5 % w/w	101.0 % w/w
Content Uniformity (mean, %CV)	Average- 97.5 AV-2.4 (By Weight Variation)	-
Dose Administered	02 Capsules	02 Capsules
Route of Administration	Oral	Oral

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies?	☐ Yes ☒ No

If No, please comment.	(Please see comment in Section 4.1.1.1.2)
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment.**	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? **If No, please comment.**	☒ Yes ☐ No

4.1.3.3.2 Study Design, Single-Dose Sprinkled Fasting Bioequivalence Study

Number of Subjects	Enrolled: 150 Dosed: 150 (P1), 141 (P2), 140 (P3) and 139 (P4) Completed: 139 Samples Analyzed: 150 Statistically Analyzed: 141
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	3
Washout Period	7 days
Randomization	☒ Yes ☐ No (b) (6)
Blood Sampling Times	0 (pre-dose), 0.333, 0.667, 1.0, 1.333, 1.667, 2.0, 2.333, 2.667, 3.0, 3.333, 3.667, 4.0, 4.333, 4.667, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 30.0, 36.0, 48.0 and 72.0 hours post dose
IRB Approval	☒ Yes Date: 08/28/2020 ☐ No
Informed Consent	☒ Yes Date: 08/28/2020 ☐ No
Length of Fasting	Subjects were fasted for at least 10 hours prior to dosing until at least 4 hours post-dose in each period
Length of Confinement	Subjects were housed at least 10 hours prior to drug administration and checked-out from the clinical facility after 72 hours from dosing in each study period.
Was the drug product administered per labeling	☒ Yes ☐ No ☐ N/A

for specialized dosage forms e.g. ODT)?	
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design:

- The applicant conducted a randomized, single dose, four-period, fully replicated study in healthy subjects under sprinkled-fasting condition. The PSG for Mesalamine ER Capsules[44], recommends two-way crossover study, however, also provides an option to conduct other study designs if appropriate.

- Per study protocol, after an overnight fast of at least 10 hours, a single oral dose (two capsules) content of either test product (1) or reference product (R) will be sprinkled over one serving spoon containing applesauce (approximately 05 grams) at room temperature and will be administered immediately to the subjects as per the randomization schedule in a sitting posture with about 240 mL of drinking water at an ambient temperature under supervision of trained study personnel in each period often study. The applesauce with sprinkled content of investigational products (Test or Reference) must be swallowed whole without chewing or crushing. The study personnel shall ensure that there are no pellets left over on the serving spoon or on the subject's tongue by thorough examination of the oral cavity.

- The washout period of 7 days is sufficient considering the half-life of the drug product (7-12 hours)[45].

- Per the RLD labeling, Tmax is 3 hours. The study sampled every 20 minutes between 0 to 5 hours after dosing, which is in line with the PSG recommendation.

- Per study protocol, sample size calculation is based on applicant's in-house study data on Mesalamine Extended-release capsules, a T/R ratio of 90-110% and high pharmacokinetic variability of the drug product (~45%) and possible dropouts and/or withdrawals. Total of 150 subjects were dosed in three groups on different dates, 9-29 days apart.

- The bio-batches of test and RLD products used in the pivotal sprinkle study were different from the ones used in pivotal fasting and fed studies. It is noted that the test batch used in the pivotal fasting and fed studies was expired at the time of the pivotal fasting sprinkle study started (although the RLD batch was not expired).

- The long-term storage stability was tested for 147 days below -50 °C which covers the study period of 100 days below -50 °C for fasting sprinkle study.

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[44] PSG for Mesalamine ER Capsules; https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20cap%20ER_RLD%20020049_RC10-17.pdf

[45] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020049Orig1s034lbl.pdf

4.1.3.4 Clinical Results

4.1.3.4.1 Demographic Profile of Subjects

Study No. BA19140473			
		Treatment Groups	
		Test Product (T) N = 140	Reference Product (R) N = 140
Age (years)	Mean ± SD	30 (± 6)	30 (± 6)
	Range	19 - 44	19 - 44
Age Groups	< 18	00 (0%)	00 (0%)
	18 – 40	132 (94.29%)	132 (94.29%)
	41 – 64	08 (05.71%)	08 (05.71%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	140 (100%)	140 (100%)
	Female	00 (0%)	00 (0%)
Race	Asian	140 (100%)	140 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m^2)	Mean ± SD	22.9 (± 2.8)	22.9 (± 2.8)
	Range	18.6 – 29.4	18.6 – 29.4
Tobacco users/Smokers	Yes	00 (0%)	00 (0%)
	No	140 (100%)	140 (100%)
Other Factors		-	-

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.3.4.2 Dropout Information

Study No. BA19140473				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Reason: Did not report for subsequent periods of the study Date: (b) (6)	Period I	No	NA

(b) (6)	Time: 2100 hrs Last Treatment Received: Reference			
	Reason: Withdrawal by subject Date: (b) (6) Time: 1200 hrs Last Treatment Received: Reference	Period I	No	NA
	Reason: Adverse Event (Vomiting) Date (b) (6) Time: 1719 hrs Last Treatment Received: Test	Period I	No	NA
	Reason: Did not report for subsequent periods of the study Date: (b) (6) Time: 2102 hrs Last Treatment Received: Test	Period I	No	NA
	Reason: Adverse Event (Vomiting) Date: (b) (6) Time: 1514 hrs Last Treatment Received: Reference	Period I	No	NA
	Reason: Adverse Event (Vomiting) Date: (b) (6) Time: 1657 hrs Last Treatment Received: Test	Period I	No	NA
	Reason: Did not report for subsequent periods of the study Date: (b) (6) Time: 2130 hrs Last Treatment Received: Test	Period I	No	NA
	Reason: Did not report for subsequent periods of the study Date: (b) (6) 0 Time: 2102 hrs Last Treatment Received: Test	Period I	No	NA
	Reason: Did not report for subsequent periods of the study Date: (b) (6) Time: 2104 hrs Last Treatment Received: Test	Period I	No	NA
	Reason: Adverse Event (Vomiting) Date: (b) (6) Time: 0908 hrs Last Treatment Received: Test	Period III	No	NA

- Subject (b) (6) was discontinued for particular period IV due to Adverse Event (Rash and Pruritus) on (b) (6) at 1530 hrs.
- Subject (b) (6) was discontinued for particular period III as he did not report for P-III check-in (b) (6) (b) (6) at 2230 hrs.
- Subject (b) (6) was discontinued on (b) (6) at 0903 hrs. for particular period II due to Incomplete IP administration.
- Subject (b) (6) was discontinued for period II due to Adverse Event (Diarrhoea) on (b) (6) at 1815 hrs. and for particular period III as he did not report for Period -III check-in on (b) (6) at 2102 hrs.

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.3.4.3 Study Adverse Events

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. BA19140473	
	Test (T) (2) N=147 (3) n (%)	Reference (R) (2) N=144 (3) n (%)
Skin and subcutaneous tissue disorders		
Rash	01 (0.68%)	-
Pruritus	01 (0.68%)	-
Gastrointestinal disorders		
Vomiting	03 (2.04%)	01 (0.69%)
Diarrhoea	-	02 (01.39%)
Nausea	-	01 (0.69%)
Investigations		
Alanine aminotransferase increased	01 (0.68%)	01 (0.69%)
Aspartate aminotransferase increased	02 (1.36%)	01 (0.69%)
Platelet count decreased	-	01 (0.69%)
Blood alkaline phosphatase increased	-	01 (0.69%)
General disorders and administration site condition		
Catheter site pain	01 (0.68%)	-
Swelling	-	01 (0.69%)
Musculoskeletal and connective tissue disorders		
Pain in extremity	-	01 (0.69%)
Total	07 (4.76%)*	07 (4.86%)*

* Two subjects (b) (6) were common who reported AE in both test and reference arm.

(1) MedDRA Version 23.1
(2) N=Number of subjects dosed for each treatment
(3) n= Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	Test	1		(b) (6)	8 hrs 5 mins

(b) (6)	RLD	1	(b) (6)	5 hrs 56 mins
	Test	1		7 hrs 37 mins
	Test	3		3 mins

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A Subjects were withdrawn from the study.
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.3.4.4 Protocol Deviations

Study No. BA19140473		
Type	**Subject #s (Test) (T)**	**Subject #s (Reference) (R)**
Blood draw time point deviations, Period I	(b) (6)	
Missing Samples, Period I		
Blood draw time point deviations, Period II		
Missing Samples, Period II		
Blood draw time point deviations, Period III		
Missing Samples, Period III		
Blood draw time point deviations, Period IV		
Missing Samples, Period IV		
In Period-IV, Subject (b) (6) dosed with additional 30mL of drinking water to ensure complete consumption of Investigational product.		
Due to emergency at home, subject (b) (6) left the facility after 48.0 hrs. of sample on Investigator's discretion. Although, he visited the facility for 72.0 hrs. sample. Subject was checked-out at 1021 hrs. dated (b) (6) he completed 48 hours + 77 minutes of housing. Duration of housing deviation was 22 hours + 43 minutes.		
In Period-I, Subject (b) (6) was dosed with additional 30mL of drinking water to ensure complete consumption of Investigational product.		

In Period-IV, Subject (b) (6) was dosed with additional 90mL of drinking water to ensure complete consumption of Investigational product.		(b) (6)
During IP administration, few granules along with applesauce were accidentally dropped down on the ground leading to incomplete administration of IP for Subject (b) (6) in Period-II.		
The IP was administered with approx. 180 ml of water instead of 240 ml of water, for Subject (b) (6) in Group III Period II as the subject complained of nausea at the time of drinking water post IP administration.		
In Group-III, Subject (b) (6) did not turn up to provide end study sample. He was telephonically contacted and refused to visit for End study sample. Hence considered lost to follow up.		
In Period-I, for subject (b) (6) 0.000 hrs. sample collection was done at 0746 hrs. and stored at 0919 hrs. due to oversight of the concerned study person, leading to a deviation of 93 minutes.		
Study was being conducted in 3 groups with 50 subjects in each group completing the clinical phase with 150 subjects. However, considering the total number of samples and logistic requirements for the same, samples were shipped after completion of each group instead of whole clinical phase.		
Due to oversight blood sample of 0.000 hrs. for Subject (b) (6) were centrifuged within 54 min and 46min of collection instead of 45 min. .		
Subject (b) (6) was given concomitant medication Paracetamol 325 mg+ Ibuprofen 400 mg in P-II.		
Subject (b) (6) was given concomitant medication Heparin Sodium 50 IU + Benzyl nicotinate 2mg in P-II.		
Subject (b) (6) was given concomitant medication 2.6 g Sodium chloride + 1.5 g Potassium chloride + 2.9 g Sodium citrate + 13.5 g Dextrose in P-II.		
Subject (b) (6) was given concomitant medication Diclofenac diethylamine 1.16% w/w in P-IV.		
Subject (b) (6) was given concomitant medication Ibuprofen 400mg + Paracetamol 325 mg in P-IV.		
Subject (b) (6) was given concomitant medication Trypsin-chymotrypsin 100000 armour units in P-IV.		

Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

Deviation: As per section 15.0 of protocol, in all cases if any subject dropped out after dosing and no post dose samples are collected, then pre-dose sample of that period of such subject will not be analyzed.

However for subject (b) (6) which was withdrawn / dropout in period 3 after dosing and no post dose samples were collected for that period, inadvertently pre-dose sample of period 3 was analyzed along with other samples due of over sight.

Impact Assessment: Deviation does not have any impact on study out come because this sample was analyzed additionally and not used for any calculation as conclusion drawn.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results:

Dropouts:

There were 150 subjects enrolled and 150 dosed in the sprinkle fasting study with 137 subjects completing all 4 periods of the study. Subjects (b) (6) dropped out after P1 due to not reporting for subsequent periods of study. Subject (b) (6) withdrew after P1 due to personal reason. Subjects (b) (6) were withdrawn due to vomiting in P1 or P3. Subject (b) (6) was discontinued for particular period IV due to Adverse Event (Rash and Pruritus). Subject (b) (6) was discontinued for particular period III as he did not report for Period-III check-in. Subject (b) (6) was discontinued on (b) (6) at 0903 hrs. for particular period II due to incomplete investigation product administration. Per study protocol[46], data from all subjects completing at least two periods of the study will be included in the pharmacokinetic analysis. Therefore, a total of 49 subjects' data was included in PK and statistical analysis. The subjects who missed at least one period (highlighted in yellow) are tabulated below.

Subject #	Sequence	Period 1	Period 2	Period 3	Period 4	Included in statistical analysis (either ABE or RSABE)?
(b) (6)	TRTR	✓	✓	✓	X	Yes
	RTRT	✓	X	X	X	No
	RTRT	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	RTRT	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	TRTR	✓	X	X	X	No
	RTRT	✓	✓	X	✓	Yes
	RTRT	✓	X	✓	✓	Yes
	TRTR	✓	✓	X	X	Yes

Adverse Events:

[46] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-ba19140473\fast-16-1-1-protocol-amendments.pdf

Per the list of adverse events[47], a total of 19 adverse events (Test 9 and Reference 10) were reported within 12 subjects during the entire course of the study.

Subjects (b) (6) experienced vomiting in P1 about 8, 6 and 7 hours and in P3 3 minutes after dosing and were discontinued from the study. Per Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations[48], in the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval should be deleted. Although two vomiting in the current study occurred slightly after the dosing interval (6 hours) stated in the RLD labeling[49], the withdrawals are in line with the applicant's pre-established SOP[50] as it stated that "any subject who experiences vomiting post -dose at any time during the sample collection schedule in any of the period will be withdrawn from the study."

The reported adverse events were all mild in severity. There were no reports of deaths or serious AEs during the study. Overall, the occurrence of AEs is comparable in test product and RLD-treated groups.

Protocol Deviations:
As seen from above table, there were some sampling collection deviations and procedure deviations. The mentioned deviations were considered not to have an impact on the overall statistical outcome of the fasting sprinkle study as the analysis is conducted with actual times.

Overall, the applicant's handling of "Dropouts/Adverse Events/Protocol Deviations" is **adequate** as per the comments above.

(b) (6)

[47] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-ba19140473\fast-16-2-7-adverse-event-listings.pdf
[48] https://www.fda.gov/files/drugs/published/Guidance-for-Industry-Bioavailability-and-Bioequivalence-Studies-for-Orally-Administered-Drug-Products---General-Considerations.PDF
[49] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020049Orig1s034lbl.pdf
[50] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-ba19140473\fast-16-1-1-protocol-amendments.pdf

Following this page, 1 Page Withheld in Full as (b)(6)

The applicant evaluated 11 different concomitant medications (Acetaminophen/paracetamol, Diclofenac, Amoxicillin, Clavulanic acid, Caffeine, Nicotine, Ciprofloxacin, Tinidazole, Ranitidine, Cetirizine and Domperidone) in the pre-study method validation and none showed significant interfering at the retention time of Mesalamine and Mesalamine-D3 (ISTD). The applicant also demonstrated that ibuprofen had no impact on analysis of Mesalamine. The applicant did not evaluate the impact of Sodium chloride Dextrose Potassium chloride Sodium Citrate, Calamine, diphenhydramine, Heparin Sodium, Benzyl nicotinate, Diethylamine and Trypsin-Chemotrypsin, which were administered as concomitant medication. However, Subject (b) (6) who was administered with concomitant medications (ORS Containing-Sodium chloride Dextrose Potassium chloride Sodium Citrate) was withdrawn. The concomitant medications may have no impact on statistical analysis as the concomitant medications (Calamine diphenhydramine, Heparin Sodium and Benzyl nicotinate, and Diclofenac diethylamine) were locally administered to Subject (b) (6). Sodium chloride Dextrose Potassium chloride Sodium Citrate is a product used to replace fluids and minerals loss and Trypsin-Chemotrypsin is an enzyme. It is very unlikely that either of them may have any impact on Subject (b) (6) in P2 and (b) (6) in P4 as Sodium chloride Dextrose Potassium chloride Sodium Citrate is just a saline solution and trypsin-chemotrypsin is a protein orally administered. Although the applicant did not evaluate the impact of these concomitant medications on PK for these subjects, the assessor will not further pursue this issue as the impact on bioequivalence is minimal.

4.1.3.5 Bioanalytical Results

4.1.3.5.1 SOPs dealing with Sample Analysis including Repeat Analysis

As under fasting conditions

4.1.3.5.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. BA19140473 **Mesalamine**									
Parameter									
Standard Curve Samples									
Nominal Concentration (ng/mL)	1.56	4.23	31.34	92.17	230.43	576.07	1440.18	3600.45	4500.56
Mean Concentration (ng/mL)	1.564	4.201	31.207	91.550	229.813	575.513	1448.775	3633.097	4517.514
Inter day Precision (%CV)	0.98	2.54	1.76	1.60	1.72	1.68	1.65	2.24	2.57
Inter day Accuracy (%Nominal)	100.27	99.32	99.58	99.33	99.73	99.90	100.60	100.91	100.38

Linearity (Range of r values)	0.9986 –1.0000
Linearity Range (ng/mL)	1.56– 4500.56
Sensitivity/ LOQ (ng/mL)	1.56

Bioequivalence Study No. BA19140473 **Mesalamine**					
Parameter					
Quality Control Samples					
Nominal Concentration (ng/mL)	4.46	85.85	1430.83	3577.08	7861.71
Mean Concentration (ng/mL)	4.423	86.678	1469.390	3585.541	8552.330
Inter day Precision (% CV)	3.71	3.25	3.22	2.79	4.35
Inter day Accuracy (%Nominal)	99.18	100.96	102.69	100.24	108.78

Assessor's Note: QCs are LQC, M1QC, MQC, HQC and DQC. DQC: Diluted Quality Control sample.

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially (Subjects (b) (6) (b) (6) ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.3.5.3 Reanalysis of Study Sample

Study No. BA19140473 **Additional information: Module 5, 5.3.1.4**		
Reason why assay was repeated	**Number of samples reanalyzed**	**Number of recalculated values used after reanalysis**

	Mesalamine							
	Actual number		% of total assays#		Actual number		% of total assays#	
	Test (T)	Ref (R)	Test (T)	Ref (R)	Test (T)	Ref (R)	Test (T)	Ref (R)
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code IR Repeats: Internal Standard Related	15	21	0.08	0.12	15	21	0.08	0.12
Code HR Repeats: Highest Calibration Related	17	11	0.09	0.06	17	11	0.09	0.06
Code PR Repeats: Processing Related	9	2	0.05	0.01	9	2	0.05	0.01
Code BR Repeats: Blank Related	2	1	0.01	0.01	2	1	0.01	0.01
Total	43	35	0.24	0.19	43	35	0.24	0.19

#: % of total assay were calculated by dividing the number of samples reanalyzed with total number of samples analyzed

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

Comments on Bioanalytical Results:

Rejected and Reinjected Runs:

- The applicant reported 4 re-injected and 8 rejected runs of study sample analysis in the fasting sprinkle study as shown below.

Batch ID	Rejected/Re-injected	Reason for Rejection/Re-injection
(b) (6)	Rejected	Peak area response of blank sample > 20% of LOQ
	Rejected	Blank sample rejected due to ISTD variation
	Rejected	Peak area response of blank sample > 20% of LOQ
	Rejected	Error in preparation of ISTD working solution
	Rejected	Error in preparation of ISTD working solution
	Rejected	Peak area response of blank sample > 20% of LOQ
	Rejected	All LQC samples failed in accuracy
	Rejected	Peak area response of blank sample > 20% of LOQ
	Re-injection	Stopped due to the "missing vial#6001" error
	Re-injection	For system validation

(b) (6)	Re-injection	Stopped at data file: 251120\AR94\059 due to error "VIERROR status received during run" observed due to Pmax error
	Re-injection	Stopped at sample name: 31-93-36 due to VIERROR error observed due to Pmax error in UHPLC pump

Repeat Analysis:

- A total of 78 samples (43 samples following treatment with Test product and 35 with Reference product) out of 18140 samples (0.43%) were reanalyzed.

- Thirty-six samples were reanalyzed under the reason of "*Internal Standard Related*". According to the raw numerical data, as verified by assessor, the internal standard response of these samples varied beyond 40 to 180% of mean ISTD area response of accepted calibration standards and quality control samples in each run. The repeat analysis of these samples per its SOP# 025099 is considered acceptable.

- Twenty-eight samples were reanalyzed under the reason of "*Highest calibration Related*".

The initial values for these samples exceeded the highest calibration curve standard concentration (ULOQ: 4500.56 ng/mL). The applicant conducted dilution integrity study during its method validation with dilution factor of 2 and 4. All the repeat values were more than 85% of ULOQ (3825.48 mg/mL). The repeat analysis is acceptable.

- Three samples were reanalyzed under the reason of "*Blank related*". Per SOP OP005713, "*Sample(s) shall be identified under Code BR when subject blank and/or subject zero/non-clinical Pre-dose (Day 0) sample fails to meet acceptance criteria as significant Peak Area Response at RT of ISTD in Subject Blank (Pre-dose) Sample or Quantifiable Concentration in Subject Zero (Pre-dose + ISTD) Sample/non-clinical Pre-dose (Day 0) sample was observed.*"

In two of the double blank samples ((b) (6) pre-dose in P3 and (b) (6) predose in P3), significant peak area response at RT of ISTD was observed. For sample of Subject (b) (6) pre-dose in P2, quantifiable concentration in subject zero (pre-dose + ISTD)

sample was observed. The repeat analysis of these samples per its SOP OP005713 is considered acceptable.

Based on applicant's explanation, the reanalysis is considered acceptable for Samples of Subject (b) (6) at 12 hrs and Subject (b) (6) at 7 hrs in P4 and Subject (b) (6) at 2 hrs in P1 as 1) the test and corresponding QC samples (MQC for sample of Subject (b) (6) P4 12 hrs and HQC for sample of Subject (b) (6) P4 7hrs) were next to each other; and 2) the calculated concentrations (6.76 and 201.37 ng/mL) for QC samples was significantly different from the nominal values (1430.83 ng/mL and 3577.08 ng/mL) and calculated concentration for QC samples of the same nominal concentration in the same run. Therefore, the reanalysis of this sample is considered acceptable.

For the 8 samples of Subject (b) (6) at 0 to 2.333 hr in P1, the initial samples were lost as reported. The applicant's explanation is acceptable.

- There was re-integration reported for 7 samples due to chromatographic peak shift during study sample analysis. As verified by assessor, comparison of the original and reintegrated chromatograms indicated that the re-integration is acceptable.

- Per the applicant's SOP on reanalysis of incurred samples (SOP OP005714), "*For studies with total number of subject/ animal samples > 1000: A minimum 10% of 1000 samples + at least 5% of the remaining samples*". A total of 1061 out of 18140 (5.85%) samples were repeated for ISR. Per the current FDA Guidance for Industry - Bioanalytical Method Validation (May 2018), the ISR reanalysis should be conducted with 10% of the first 1000 samples and 5% of the remaining samples. The ISR sample size met this requirement (1000*10% + 17140*5% =957). Out of the 1061 ISR samples, 1047 (98.68%) samples met the acceptance criteria (at least 67% of samples were NMT 20% for each sample). Therefore, the ISR results are acceptable.

- The bioanalytical results are acceptable.

4.1.3.6 Pharmacokinetic Results

4.1.3.6.1 Arithmetic Mean Pharmacokinetic Parameters

ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUC0-3	ng hr/mL	2442.659	65.78	38.17	10449.20	2167.577	70.57	147.55	13737.40	1.13
AUC3-T	ng hr/mL	3096.341	48.72	687.02	8294.66	3092.982	50.11	109.62	8538.75	1.00
AUCt	ng hr/mL	5538.941	46.01	1325.44	16292.72	5260.652	45.85	326.78	18611.96	1.05
CMAX	ng/mL	2024.758	59.14	435.22	7777.78	1840.108	55.52	205.84	8236.61	1.10
TMAX	hr	1.667	.	0.67	8.00	2.000	.	0.67	8.00	0.83

* Tmax values are presented as median, range.

4.1.3.6.2 Geometric Means and 90% Confidence Intervals - <u>Applicant Calculated</u>

Reference-Scaled Average BE Studies

Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s^2WR**	**sWR**	**Criteria Bound#**	**Method Used**	**Outcome**
Including Interaction effect								
AUC_{0-t} (ng.h/mL)	105.49	N/AP	N/AP	0.09018	0.30030	-0.05	RSAB	Bioequivalent
AUC_{0-3} (ng h/mL)	113.44	N/AP	N/AP	0.20345	0.45106	-0.11	RSAB	Bioequivalent
AUC_{3-t} (ng.h/mL)	100.62	N/AP	N/AP	0.12823	0.35809	-0.08	RSAB	Bioequivalent
C_{max} (ng/mL)	109.75	N/AP	N/AP	0.1457	0.3817	-0.08	RSAB	Bioequivalent
Excluding Interaction effect								
AUC_{0-t} (ng.h/mL)	105.48	N/AP	N/AP	0.09018	0.30030	-0.05	RSAB	Bioequivalent
AUC_{0-3} (ng h/mL)	113.43	N/AP	N/AP	0.20345	0.45106	-0.11	RSAB	Bioequivalent
AUC_{3-t} (ng.h/mL)	100.61	N/AP	N/AP	0.12823	0.35809	-0.08	RSAB	Bioequivalent
C_{max} (ng/mL)	109.74	N/AP	N/AP	0.1457	0.3817	-0.08	RSAB	Bioequivalent

Assessor's Note: As the subjects were dosed in three groups, the applicant conducted its statistical analysis including or excluding trt*grp interaction effect.

4.1.3.6.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Mesalamine (No =141) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – BA19140473					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUC0-3 (hr. ng/mL)	1960.18	1727.63	1.13	106.13	121.29
LAUC3-72 (hr. ng/mL)	2730.08	2710.63	1.01	95.31	106.44
LAUC0-72 (hr. ng/mL)	5015.55	4753.34	1.06	100.87	110.38
LCMAX (ng/mL)	1746.58	1595.01	1.10	103.67	115.67

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUC0-3 (hr. ng/mL)	1.13	106.13	121.29	0.205138	0.4529216	-0.112468	Scaled/PE	PASS
LAUC3-72 (hr. ng/mL)	1.01	95.31	106.44	0.1298865	0.3603977	-0.085901	Scaled/PE	PASS
LAUC0-72 (hr. ng/mL)	1.05	100.87	110.38	0.0914441	0.3023973	-0.055949	Scaled/PE	PASS
LCMAX (ng/mL)	1.10	103.67	115.67	0.1454749	0.3814118	-0.083869	Scaled/PE	PASS

Assessor's Note: As verified by the assessor's, no significant group-by-treatment interaction was observed for all PK parameters (P>0.1), the statistical analysis was only performed with trt*grp term dropped (using trt*grp=2).

4.1.3.6.4 Additional Information for the Study

Root Mean Square Error	Please see the sWR above.
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☒ Yes ☐ No See information provided below
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☒ Yes ☐ No Subject (b) (6) at P2 showed measurable concentration (5.85 ng/mL) at 0 h. But the concentration is less than 5% of Cmax (4080.9*5%=204.045 ng/mL) in this period

	for this subject. The subject was included in the BE analysis per FDA general guidance.
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first-time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Comments on PK results: **Adequate**

- Per the PSG, at least four non-zero measurements of concentration are recommended for each partial AUC calculation. For the current fasting sprinkle BE study, as verified by assessor that all subjects exhibited at least four non-zero measurable concentrations for all 4 periods before 3 hrs after dosing. Therefore, data from all subjects were included in the BE evaluation.

- As per the PSG for Mesalamine ER Capsules, partial AUC (i.e., pAUC0-3. pAUC3-72), AUC0-t, and Cmax were evaluated.

- As the subjects were dosed in three groups, the assessor performed PK analysis with a SAS code (HVScale4Period-group effect.SAS, with estimate statement updated in the PROC MIXED model). As verified by Dr. Devvrat Patel, the OB/DBIII consultant for statistical analysis, no significant treatment*group effect was found ($p>0.1$) for the PK parameters Cmax ($p=0.1484$), AUC0-3 ($p=0.4409$), AUC3-72 ($p=0.9095$), and AUCT ($p=0.5558$). The results of the PK parameters, AUC0-3, AUC3-t, AUC0-t and Cmax, are presented above.

- The result of statistical analysis shows that the within-subject variability values of the reference product (sWR) for AUC0-3, AUC3-72, AUC0-t and Cmax PK parameters are greater than 0.294. Therefore, Reference-Scaled Average BE approach was used to determine BE. The outcome of the statistical analysis for AUC0-3, AUC3-72, AUC0-t and Cmax PK parameters using Reference Scaled Average Bioequivalence Approach meet the reference scaled average BE criteria as shown in the table above.

- The test/reference ratios for LnAUC0-3, LnAUC3-72, LnAUC0-t, and LnCmax fall within the acceptance range of 0.80-1.25. The 95% upper confidence bounds for LnAUC0-3, LnAUC3-72, LnAUC0-t, and LnCmax are all negative.

- Therefore, the sprinkle fasting BE study is adequate.

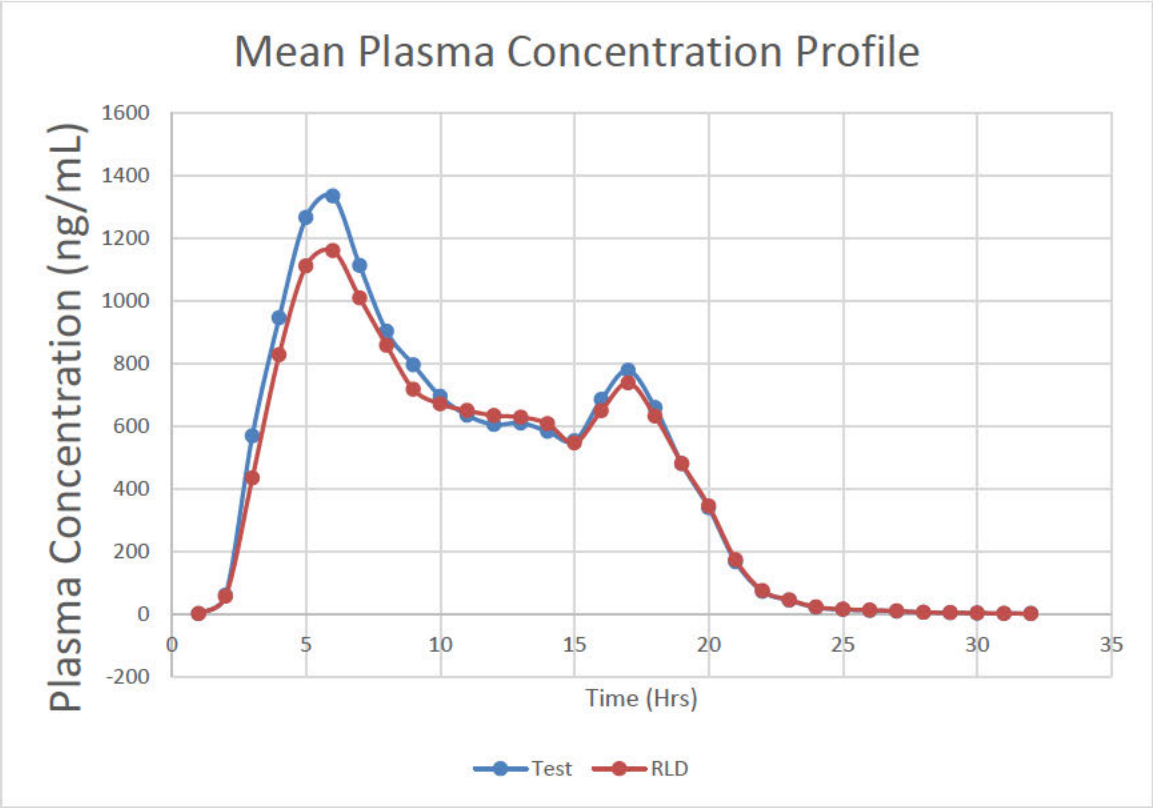
4.1.3.7 Overall Comment

Was the Sprinkle-fasting bioequivalence study acceptable? Acceptable.

Mean Plasma Concentrations, Single-Dose Fasting Sprinkle Bioequivalence Study

	Treatment A		Treatment B		
Time	**Mean (ng/mL)**	**CV%**	**Mean (ng/mL)**	**CV%**	**T/R Ratio**
0	0.02	1673.32	0	.	#DIV/0!
0.333	58.76	418.46	55.18	394.94	1.06
0.667	568.18	99.99	433.45	126.8	1.31
1	945.41	87.25	827.21	104.37	1.14
1.333	1265.72	91.09	1110.69	90.79	1.14
1.667	1334.03	90	1159.83	82.6	1.15
2	1112.12	81.43	1008.83	84.69	1.10
2.333	902.15	77.02	857.25	89.09	1.05
2.667	795.04	76.09	716.56	78.11	1.11
3	694.41	75.4	669.99	72.99	1.04
3.333	633.94	68.08	649.08	73.09	0.98
3.667	604.28	68.55	633	69.98	0.95
4	609.13	69.78	627.95	64.14	0.97
4.333	582.4	60.51	606.75	61.2	0.96
4.667	552.02	63.68	545.61	66.89	1.01
5	684.49	68.06	648.4	70.26	1.06
5.5	777.41	69.1	737.44	72.53	1.05
6	658.46	76.34	631.1	76.31	1.04
6.5	479.03	78.77	479.83	85.66	1.00
7	338.62	84.14	344.18	92.41	0.98
8	165.95	104.76	172.33	108.18	0.96
9	71.37	112.54	73.58	117.77	0.97
10	42.83	102.49	44.26	109.26	0.97
12	19.94	74.29	21.45	85.45	0.93
14	13.5	56.37	14.66	81.53	0.92
16	10.19	58.82	11.28	87.97	0.90
C27	8.03	66.97	8.66	90.46	0.93
24	4.18	102.36	4.28	88.79	0.98
30	3.12	140.74	3.09	132.33	1.01
36	1.83	153.64	1.94	162.93	0.94
48	0.61	257.78	0.73	251.77	0.84
72	0.65	1575.14	0.06	558.4	10.83

Mean Plasma Concentrations, Single-Dose Sprinkle-Fasting Bioequivalence Study



4.1.4 Single-dose Sprinkled Fasting Bioequivalence Study (BA19140131, failed)

In addition to the three pivotal studies, i.e., fasting (BA19140130), fed (MSM_1000C_0652_18) and fasting sprinkle (BA19140473), the applicant also submitted 16 BE summary tables for two failed sprinkle fasting studies, i.e., #BA19140131 and #BA19140426, and two pilot fed studies, i.e., #PKD_18_099 and #MSM_1000C_0536_17. Different batches of test product were used for pivotal, failed and pilot studies, but the formulations were the same as per the summary tables submitted.

(b) (4)

Assessor's Note: All three test batches' formulations were the same.

Study Information

Study Number	BA19140131
Study Title	Single dose oral bioequivalence study of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) and 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules) in healthy adult human subjects under fasting condition with contents sprinkled over applesauce.
Study Type	☑In Vivo BE □In Vitro BE □Permeability □Other
Submission Location: o **Study Report** o **Validation Report** o **Bioanalytical Report**	N/AP
Clinical Site (Name, Address, Phone #, Fax #)	Cliantha Research Limited Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201301, Uttar Pradesh, India. Tel#+91-120-6122100 FEI: 3013167427 DUNS: 871407072
Principal Clinical Investigator (Name, Email)	Dr. Sanjay Basumatary, MBBS sbasumatary@cliantha.com
Analytical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited., Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India Tel: (91-124) 4768005, 4768199 Fax: N/AP
Principal Analytical Investigator (Name, Email)	Mr. Bala Krishna Panigrahy (Study Director) [Mail ID: BalaKrishna.Panigrahy@sunpharma.com]
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20° C to -80° C)**	50 Days The samples were stored at clinical site between -70 ± 10° C and analytical site below -50°C (Operational Range -50^0 C to - 80^0 C)
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	147 days in human plasma (Stored below -50°C) for Mesalamine
LTSS Data Location	N/AP

Product Information

Product	**Test**	**Reference**	**Reference**
Treatment ID	**(T)=T1=T2**	**(R)=R1=R2**	**(R)=R1=R2**

Product Name	Mesalamine Extended Release Capsules USP 500 mg	Pentasa® (Mesalamine) Controlled release capsules 500 mg	Pentasa® (Mesalamine) Controlled release capsules 500 mg
Manufacturer	Sun Pharmaceutical Ind. Ltd, SEZ Unit - 1, Plot no. A-41, Industrial Area, Phase VIII A, S.A.S Nagar (Mohali) – 160071, Punjab	Manufactured For: Shire US Inc., 300 Shire Way, Lexington, MA 02421, USA	Manufactured For: Shire US Inc., 300 Shire Way, Lexington, MA 02421, USA
Distributed By	-	-	-
Batch/Lot No.	3967425	5783929	AK8368A
Manufacture Date	08/2018	N/AP	N/AP
Expiration Date	07/2020	03/2021	10/2022
Strength	500 mg	500 mg	500 mg
Dosage Form	Extended-Release Capsules	Controlled-Release Capsules	Controlled-Release Capsules
Bio-batch Size	(b) (4) Capsules	-	-
Production Batch Size	Capsules	-	-
Potency	100.1 % w/w	102.0 % w/w	101.0 % w/w
Content Uniformity (mean, %CV)	Average- 100.1 AV-1.4 (By Weight Variation)	-	-
Dose Administered	02 Capsules	02 Capsules	02 Capsules
Route of Administration	Oral	Oral	Oral

Comments on the study Information:

The applicant conducted the failed pivotal fasting sprinkle studies (study No. BA19140131 and BA19140426) with test formulation (Batch # 3967425) and batch of RLD product (Lot # 5783929 and AK8368A. It could not be determined which RLD batch was used in this study based on information submitted). The test batch used in the failed fasting sprinkle BE studies is the same as that used in the passed pivotal fasting (#BA19140130) but different from that used in passed pivotal fasting sprinkle (#BA19140473) studies.

Demographic Profile of Subjects Completing the Bioequivalence Study

Study No. BA19140131			
		Treatment Groups	
		Test Product (T) N = 47	**Reference Product (R) N = 47**
Age (years)	Mean ± SD	29 (± 6)	29 (± 6)
	Range	19 - 44	19 - 44
Age Groups	< 18	00 (0%)	00 (0%)
	18 – 40	46 (97.87%)	46 (97.87%)

	41 – 64	01 (02.13%)	01 (02.13%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	47 (100%)	47 (100%)
	Female	00 (0%)	00 (0%)
Race	Asian	47 (100%)	47 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m^2)	Mean ± SD	23.2 (± 2.8)	23.2 (± 2.8)
	Range	18.8 – 29.8	18.8 – 29.8
Tobacco users/Smokers	Yes	02 (04.26%)	02 (04.26%)
	No	45 (95.74%)	45 (95.74%)
Other Factors		-	-

Dropout Information

Study No. BA19140131				
Subject No	**Reason for dropout/replacement[11]**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Reason: Withdrew Consent Date: (b) (6) Time: NA	NA	Yes	Subject (b) (6) (b) (6)
	Reason: Withdrew Consent Date: (b) (6) Time: 1700 Last Treatment Received: Reference	Period I	No	NA
	Reason: Withdrew Consent Date: (b) (6) Time: 1800 Last Treatment Received: Test	Period I	No	NA
	Reason: Did not report for subsequent periods of the study Date: (b) (6) Time: 1810 Last Treatment Received: Reference	Period I	No	NA
	Reason: Adverse Event (Vomiting) Date (b) (6) Time: 1949 Last Treatment Received: Test	Period II	No	NA
	Reason: Did not report for subsequent periods of the study Date: (b) (6) Time: 2002 Last Treatment Received: Test	Period III	No	NA

(b) (6)	Reason: Protocol Violation (UDS Positive) Date: (b) (6) Time: 1500 Last Treatment Received: Test	Period III	No	NA
	Reason: Protocol Violation (UDS Positive for THC) Date: (b) (6) Time: 1230 Last Treatment Received: Test	Period III	No	NA
	Reason: Did not report for subsequent periods of the study Date: (b) (6) Time: 2004 Last Treatment Received: Reference	Period III	No	NA
	Reason: Withdrew Consent Date: (b) (6) Time: 1750 Last Treatment Received: Reference	Period II	No	NA

Incidence of Adverse Events in Individual Studies

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. BA19140131	
	Test (T) (2) N=54 (3) n (%)	Reference (R) (2) N=55 (3) n (%)
Musculoskeletal and connective tissue disorders		
Back pain	01 (01.85%)	-
Gastrointestinal disorders		
Vomiting	01 (01.85%)	-
General disorders and administration site conditions		
Pyrexia	01 (01.85%)	01 (01.82%)
Investigations		
White blood cell count increased	-	01 (01.82%)
Total	03 (05.56%)	02 (03.64%)

Protocol Deviations

Study No. BA19140131		
Type	**Subject #s (Test) (T)**	**Subject #s (Reference) (R)**
Blood draw time point deviations, Period I		(b) (6)
Missing Samples, Period I		
Blood draw time point deviations, Period II		

Missing Samples, Period II	(b) (6)
Blood draw time point deviations, Period III	
Missing Samples, Period III	
Blood draw time point deviations, Period IV	
Missing Samples, Period IV	
During Period I, subject (b) (6) has been dosed with 240 mL + 30 mL of extra water instead of 240 mL.	
During Period IV, subject (b) (6) has been dosed with 240 mL + 30 mL of extra water instead of 240 mL.	
In period IV, for subject (b) (6) housing deviation of 11 hours 23 min has been occurred.	
During Period I, concomitant medication (Diclofenac Diethylamine Topical Gel 5 g local application) was given to subject (b) (6) for resolution of Adverse Event of Back pain.	
During Period III, concomitant medication (Paracetamol 500 mg) was given to subject (b) (6) for resolution of Adverse Event of Pyrexia.	
During Period IV, concomitant medication (Paracetamol 650 mg) was given to subject (b) (6) for resolution of Adverse Event of Pyrexia.	
During Period I, for subject (b) (6) It was missed to tick on appropriate section of yellow light condition is ensured for subject (b) (6) at 6.500 hours and subject (b) (6) at 0.667 hours time points of blood collection.	
During Period I, for subject (b) (6) during check out vitals and physical examinations wellbeing assessment was performed and subject was asked about the wellbeing. However, it was missed to tick on wellbeing assessment 'well' column.	
During Period IV, vital sign (Sitting blood pressure, radial pulse rate) at 6.0 hours time point for subject (b) (6) (b) (6) were performed after scheduled time with deviation of 43 min, 41 min, 43 min, 43 min 43, min 44 min, 44 min and 45 min respectively.	

Comments on Dropouts/Adverse Events/Protocol Deviations:

- The two failed fasting sprinkle studies (Study # BA19140131 and BA19140426), and the pivotal fasting (BA19140130) and sprinkle fasting (B BA19140473) BE studies were conducted at the same analytical site and the clinical site.

- The numbers of adverse events in this failed fasting sprinkle BE study are comparable between test- and RLD-treated groups. However, the applicant did not provide severity of these AEs.

- There were 10 dropouts in this failed sprinkle fasting study.

Bioanalytical Method Validation

Results	
Bioanalytical method validation report location	Not Applicable
Analyte	Mesalamine
Internal standard (ISTD)	Mesalamine D3
Method description	Ultra-High Performance Liquid Chromatography Tandem Mass Spectrometric Method for the Estimation of Mesalamine in Human K3EDTA Plasma using Mesalamine D3 as an Internal Standard. [Solid phase extraction technique] (MV648/17)
Limit of quantitation (ng/mL)	1.54
Average recovery of drug (%)	62.79
Recovery of ISTD (%)	77.15
Standard Curve Concentration (ng/mL) (Nominal)	STDA: 1.54, STDA(DUP): 1.54, STDB: 4.41, STDC: 88.15, STDD: 220.38, STDE: 550.95, STDF: 1101.89, STDG 2203.79, STDH 4407.57, STDI: 5509.46 STDI(DUP): 5509.46
Standard curve concentrations (ng/mL) (Mean Value)	STDA: 1.553, STDA(DUP): 1.537, STDB: 4.300, STDC: 86.470, STDD: 220.807, STDE: 549.153, STDF: 1206.100, STDG: 2151.447, STDH: 4323.543, STDI: 5496.097, STDI(DUP) 5438.370
QC concentrations (ng/mL) (Nominal)	LOQQC – 1.55, LQC – 4.40, MQC –2202.01, HQC – 4404.02, D2QC-9370.26, D4QC-9370.26
QC concentrations (ng/mL) (Mean value)-Global statistics	LOQQC- 1.588, LQC- 4.239, MQC- 2116.483, HQC -4302.632, D2QC – 9270.080, D4QC – 9072.824
QC within batch accuracy range (%)	94.81 to 106.56
QC between batch accuracy range (%)	96.12 to 102.44
QC Intraday accuracy range (%)	95.70 to 103.28
QC within batch precision range (%)	0.52 to 17.20
QC between batch precision range (%)	2.71 to 10.49
QC Intraday precision range (%)	2.92 to 12.77
Bench-top stability in human plasma	8.25 hours, at room temperature, under low light
Stock solution stability of analyte (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
Stock solution stability of ISTD (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
In-injector stability (hours)	99.97 hours (10°C±1°C)
Freeze thaw stability (cycles)	Three cycles (frozen below -50°C and thawed at room temperature, under low light)
Dilution integrity*	Concentration diluted 2 and 4 times
Long Term Stability (days)	147 days in human plasma (stored below -50ºC)

Selectivity	Six lots of normal human plasma, two lots of Heamolyzed human plasma and two lots of lipemic human plasma with K3EDTA as an anticoagulant were evaluated and none showed significant interfering peaks at the retention times of Mesalamine and Mesalamine D3 (ISTD).

Summary of Standard Curve and QC Data for Sample Analyses

Bioequivalence Study No. BA19140131 Mesalamine									
Parameter									
Standard Curve Samples									
Nominal Concentration (ng/mL)	1.57	4.24	31.41	92.37	230.92	577.30	1443.26	3608.14	4510.18
Mean Concentration (ng/mL)	1.589	4.128	30.020	91.931	230.288	568.523	1477.139	3703.965	4649.189
Inter day Precision (%CV)	0.83	2.21	1.48	1.62	1.75	1.23	1.65	1.27	1.48
Inter day Accuracy (%Nominal)	101.24	97.37	95.58	99.52	99.73	98.48	102.35	102.66	103.08
Linearity (Range of r values)	0.9990-0.9999								
Linearity Range (ng/mL)	1.57-4510.18								
Sensitivity/ LOQ (ng/mL)	1.57								

Bioequivalence Study No. BA19140131 Mesalamine					
Parameter					
Quality Control Samples					
Nominal Concentration (ng/mL)	4.28	92.29	1442.03	3605.09	7686.75
Mean Concentration (ng/mL)	4.077	90.244	1462.351	3650.263	8269.453
Inter day Precision (% CV)	3.25	6.53	2.07	2.14	2.04
Inter day Accuracy (%Nominal)	95.25	97.78	101.41	101.25	107.58

SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title

SOP025099, Version No. 1.0 (Legacy document No.: OP005713, Version No. 6.0)	14 Dec 2018	Repeat Analysis

Reanalysis of Study Samples

Study No. BA19140131 Additional information in Volume(s), Page(s): N/AP								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays#**		**Actual number**		**% of total assays#**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code IR Repeats : Internal Standard Related	8	6	0.12	0.09	8	6	0.12	0.09
Code HR Repeats : Highest Calibration Standard Related	3	6	0.05	0.09	3	6	0.05	0.09
Code CR Repeats : Chromatography Related	1	0	0.02	0.00	1	0	0.02	0.00
Total	12	12	0.18	0.18	12	12	0.18	0.18

Comments on Study Assay Validation:

There is no pharmacokinetic repeat in the failed fasting sprinkle BE study.

Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route)[Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD) Mesalamine					Study Report Location
					C_{max} (ng/mL)	T_{max*} (hr)	AUC_{0-3} (ng.hr/mL)	AUC_{3-t} (ng.hr/mL)	AUC_{0-t} (ng.hr/mL)	
BA19140131	Single dose oral bioequivalence study of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) and 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules) in healthy adult human subjects under fasting condition with contents sprinkled over applesauce.	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover fully replicate bioequivalence study in healthy adult human subjects under fasting condition with contents sprinkled over applesauce Study Type: Pivotal Study	**Reference product (R):** Pentasa® (Mesalamine) Controlled release capsules 500 mg, 2 Capsules, Oral [Batch. /Lot No. 5783929] **Test product (T):** Mesalamine Extended Release Capsules USP 500 mg, 2 Capsules, Oral [Batch. /Lot No. 3967425]	A total of 56 healthy, adult, male human subjects were enrolled in the study. 47 subjects completed the study. Mean age: 29 ± 6 years (Completed subjects) Range: 19 – 44 Years (Completed Subjects)	Reference (R1) 2027.762 (±1271.7036/ 62.71) Reference (R2) 2138.301 (±1261.8355 /59.01) Test (T1) 1832.950 (±1228.3666 /67.02) Test (T2) 1644.484 (±964.1174 /58.63)	Reference (R1) 2.000 (0.667-6.000) Reference(R2) 1.667 (0.667-5.500) Test (T1) 1.834 (0.667-7.000) Test (T2) 2.000 (0.333-5.500)	Reference (R1) 2440.7536 (±1714.61893 /70.25) Reference (R2) 2513.8615 (±1617.72883 /64.35) Test (T1) 2093.5463 (±1412.61597 /67.47) Test (T2) 1843.4724 (±983.04498 /53.33)	Reference (R1) 2923.1201 (±1707.02758 /58.40) Reference (R2) 2955.6350 (±1406.99222 /47.60) Test (T1) 2130.5889 (±1324.62064 /62.17) Test (T2) 2088.6902 (±904.99400 /43.33)	Reference (R1) 5363.8737 (±2916.09918 /54.37) Reference (R2) 5469.4964 (±2544.73094 /46.53) Test (T1) 4224.1352 (±2388.64810 /56.55) Test (T2) 3932.1626 (±1552.03809 /39.47)	N/AP

Unscaled Average BE

Reference Scaled Average Bioequivalence Approach Used	☑Yes ☐ No
If No, then complete Table 3A only	
If Yes, then complete Tables 3A and 3B	

Mesalamine (No of subjects completed=47*) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – BA19140131						
Parameter	**Test (T)**	**N**	**Reference (R)**	**N**	**Ratio (%) (T/R)**	**90% CI (T/R)**
C_{max} (ng/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{0-t} (ng.h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{0-3} (ng h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{3-t} (ng.h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP

*Completed clinical phase of the study.

Statistical Summary of the Comparative Bioavailability Data

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2WR	sWR	Criteria Bound#	Method Used	Outcome
AUC_{0-t} (ng.h/mL)	74.51	N/AP	N/AP	0.12967	0.36009	0.05	RSAB	Non-Bioequivalent
AUC_{0-3} (ng h/mL)	79.64	N/AP	N/AP	0.39214	0.62621	-0.12	RSAB	Non-Bioequivalent
AUC_{3-t} (ng.h/mL)	71.23	N/AP	N/AP	0.15303	0.39119	0.06	RSAB	Non-Bioequivalent
C_{max} (ng/mL)	80.05	N/AP	N/AP	0.2861	0.5349	-0.07	RSAB	Bioequivalent

Assessor's Comments:

- The failed fasting sprinkle BE study was designed as a single-dose, full replicate crossover study comparing test product Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) to the corresponding reference product 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules). A total of 56 subjects were dosed, 47 subjects completed and 9 subjects were withdrawn. Forty seven (47) subjects were included in PK and statistical analysis.

- As reported by applicant in the tables above, only Cmax met the BE criteria while AUC_{0-3}, AUC_{3-t} and AUC_{0-t} all failed to meet the acceptance criteria of RSABE. The T/R ratios in this failed sprinkle fasting study were lower than 0.8 for AUC0-t, AUC0-3 and AUC3-t. The applicant did not provide the potential reason for the study failure. In the study report

for pivotal sprinkle fasting study[51], the applicant stated that "*Sample size estimation was based on available in-house study data on Mesalamine Extended release capsules. Considering a Test/Reference ratio approximately up to 90% and coefficient of variation of reference ~57%, 252 observations (126 Subjects) per treatment may yield a power of 80% to show bioequivalence under bioequivalence assumptions as per Reference Scaled Average Bioequivalence Approach. However, considering mesalamine drug having high pharmacokinetic variability and possible dropouts and/or withdrawals, a fully replicate design using Reference Scaled Average Bioequivalence Approach, 300 observations per treatment (150 subjects) were considered for this study*." As there are no study report or datasets submitted, this issue will be assessed when the applicant submits the requested information.

- The applicant will be asked to submit full study reports and datasets for further evaluation. The failed fasting sprinkle BE study is inadequate

[51] \\CDSESUB1\evsprod\anda214585\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-ba19140473\fast-body.pdf

4.1.5 Single-dose Sprinkled Fasting Bioequivalence Study (BA19140426, failed)

Study Information

Study Number	BA19140426
Study Title	Single dose oral bioequivalence study of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) and 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules) in healthy adult human subjects under fasting condition with contents sprinkled over applesauce.
Study Type	☑In Vivo BE □In Vitro BE □Permeability □Other
Submission Location: **o Study Report** **o Validation Report** **o Bioanalytical Report**	N/AP
Clinical Site (Name, Address, Phone #, Fax #)	Cliantha Research Limited Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201301, Uttar Pradesh, India. Tel# +91-120-6122100 FEI: 3013167427 DUNS: 871407072
Principal Clinical Investigator (Name, Email)	Dr. Sharad Chaturvedi, MBBS schaturvedi@cliantha.com
Analytical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited., Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India Tel: (91-124) 4768005, 4768199 Fax: N/AP
Principal Analytical Investigator (Name, Email)	Mr. Bala Krishna Panigrahy (Study Director) [Mail ID: BalaKrishna.Panigrahy@sunpharma.com]
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20° C to -80° C)**	59 Days The samples were stored at clinical site between -70 ± 10° C and analytical site below -50°C (Operational Range -50^0 C to - 80^0 C)
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	147 days in human plasma (Stored below -50°C) for Mesalamine
LTSS Data Location	N/AP

Product Information

Same as under fasting conditions.

Comments on the study Information:
The applicant conducted the failed fasting sprinkle studies (study No. BA19140131 and BA19140426) with test formulation (Batch # 3967425) and batch of RLD product (Lot # 5783929 and AK8368A. It could not be determined which RLD batch was used in this study based on information submitted). The test batch used in the failed fasting sprinkle BE studies was the same as that used in the passed pivotal fasting (#BA19140130) but different from that used in passed sprinkle fasting (BA19140473) study.

Demographic Profile of Subjects Completing the Bioequivalence Study

Study No. BA19140426			
		Treatment Groups	
		Test Product (T) N = 89	Reference Product (R) N = 89
Age (years)	Mean ± SD	31 (± 7)	31 (± 7)
	Range	18 - 44	18 - 44
Age Groups	< 18	00 (0%)	00 (0%)
	18 – 40	81(82.65%)	81(82.65%)
	41 – 64	08 (08.16%)	08 (08.16%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	89 (100.0%)	89 (100.0%)
	Female	00 (0.0%)	00 (0.0%)
Race	Asian	89 (100%)	89 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m^2)	Mean ± SD	22.5 (± 2.7)	22.5 (± 2.7)
	Range	18.6 – 28.6	18.6 – 28.6
Tobacco users/Smokers	Yes	00 (0.0%)	00 (0.0%)
	No	89(100.0%)	89(100.0%)
Other Factors		-	-

Dropout Information

Study No. BA19140426				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Reason: Withdraw Consent Date: (b) (6) Time: NA	NA	Yes	(b) (6)
	Reason: Own accord Date: (b) (6)	Period I	No	NA

(b) (6)	Time: 1126 Last Treatment Received: Test(T)			
	Reason: Own accord Date: (b) (6) Time: 1222 Last Treatment Received: Reference(R)	Period II	No	NA
	Reason: Medical Ground (Swelling) Date: (b) (6) Time: 1235 Last Treatment Received: Reference(R)	Period II	No	NA
	Reason: Protocol Violation (ABT Positive) Date: (b) (6) Time: 1210 Last Treatment Received: Reference(R)	Period II	No	NA
	Reason: Medical Ground (Furuncle) Date: (b) (6) Time: 1216 Last Treatment Received: Reference(R)	Period II	No	NA
	Reason: Protocol Violation (ABT Positive) Date: (b) (6) Time: 1207 Last Treatment Received: Test(T)	Period III	No	NA
	Reason: Own accord Date: (b) (6) Time: 1856 Last Treatment Received: Test(T)	Period I	No	NA
	Reason: Own accord Date (b) (6) Time: 1516 Last Treatment Received: Reference(R)	Period I	No	NA
	Reason Protocol Violation (UDS Positive) THC Date: (b) (6) 20 Time: 1501 Last Treatment Received: Reference (R)	Period I	No	NA
	Reason: Subject did not report Date: (b) (6) Time: 1850 Last Treatment Received: Reference (R)	Period II	No	NA
	Reason: Medical Ground (Swelling) Date: (b) (6) Time: 1230 Last Treatment Received: Test (T)	Period II	No	NA

Incidence of Adverse Events in Individual Studies

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups
	Fasted Bioequivalence Study Study No. BA19140426

	Test (T) (2) N=98 (3) n (%)	Reference (R) (2) N=98 (3) n (%)
Musculoskeletal and connective tissue disorders		
Back pain	01(1.02%)	-
Infections and infestations		
Furuncle	-	02 (2.04%)
General disorders and administration site conditions		
Swelling	-	01(1.02%)
Nervous system disorders		
Headache	01(1.02%)	-
Nervous system disorders		
Dizziness	01(1.02%)	-
Vascular disorders		
Thrombophlebitis	-	01(1.02%)
General disorders and administration site conditions		
Swelling	01(1.02%)	-
Nervous system disorders		
Dizziness	-	01(1.02%)
Investigations		
Blood glucose increased	01(1.02%)	
Total	05 (5.10 %)	05 (5.10 %)

Protocol Deviations

Study No. BA19140426		
Type	**Subject #s (Test) (T)**	**Subject #s (Reference) (R)** (b) (6)
Blood draw time point deviations, Period I		
Missing Samples, Period I		
Blood draw time point deviations, Period II		
Missing Samples, Period II		
Blood draw time point deviations, Period III		
Missing Samples, Period III		
Blood draw time point deviations, Period IV		
Missing Samples, Period IV		

Concomitant medicines (Thrombophob) have been given to the Sub (b) (6) for management of adverse event in P-III.	NA
During the IP administration process sub (b) (6) was unable to swallow the whole IP with 240 ml water as defined in the protocol. So as per Investigator discretion extra amount of water (30 ml) was given to the subject for proper administration of IP. After proper dose administration, Dosing compliance of the subject was verified by the study personal by mouth check in P-III.	NA
Accidently whole plasma of Subject (b) (6) at time point 2.667 hrs.(P-IV) was spilled out during the transfer of separated plasma from vacutainer to (b) (4) Vial by the concerned study personnel. So Aliquot I and II was not prepared due to sample spillage at time point 2.667.	NA

Comments on Dropouts/Adverse Events/Protocol Deviations:

- The numbers of adverse events in this failed fasting sprinkle BE study are comparable between test- and RLD-treated groups. However, the severity of AEs was not reported in the current submission.

- There were 12 dropouts in this failed fasting sprinkle study.

Bioanalytical Method Validation

Results	
Bioanalytical method validation report location	Not Applicable
Analyte	Mesalamine
Internal standard (ISTD)	Mesalamine D3
Method description	Ultra-High Performance Liquid Chromatography Tandem Mass Spectrometric Method for the Estimation of Mesalamine in Human K3EDTA Plasma using Mesalamine D3 as an Internal Standard. [Solid phase extraction technique] (MV648/17)
Limit of quantitation (ng/mL)	1.54
Average recovery of drug (%)	62.79
Recovery of ISTD (%)	77.15
Standard Curve Concentration (ng/mL) (Nominal)	STDA: 1.54, STDA(DUP): 1.54, STDB: 4.41, STDC: 88.15, STDD: 220.38, STDE: 550.95, STDF: 1101.89, STDG 2203.79, STDH 4407.57, STDI: 5509.46 STDI(DUP): 5509.46

Standard curve concentrations (ng/mL) (Mean Value)	STDA: 1.553, STDA(DUP): 1.537, STDB: 4.300, STDC: 86.470, STDD: 220.807, STDE: 549.153, STDF: 1206.100, STDG: 2151.447, STDH: 4323.543, STDI: 5496.097, STDI(DUP) 5438.370
QC concentrations (ng/mL) (Nominal)	LOQQC – 1.55, LQC – 4.40, MQC –2202.01, HQC – 4404.02, D2QC-9370.26, D4QC-9370.26
QC concentrations (ng/mL) (Mean value)-Global statistics	LOQQC- 1.588, LQC- 4.239, MQC- 2116.483, HQC -4302.632, D2QC – 9270.080, D4QC – 9072.824
QC within batch accuracy range (%)	94.81 to 106.56
QC between batch accuracy range (%)	96.12 to 102.44
QC Intraday accuracy range (%)	95.70 to 103.28
QC within batch precision range (%)	0.52 to 17.20
QC between batch precision range (%)	2.71 to 10.49
QC Intraday precision range (%)	2.92 to 12.77
Bench-top stability in human plasma	8.25 hours, at room temperature, under low light
Stock solution stability of analyte (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
Stock solution stability of ISTD (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
In-injector stability (hours)	99.97 hours (10°C±1°C)
Freeze thaw stability (cycles)	Three cycles (frozen below -50°C and thawed at room temperature, under low light)
Dilution integrity*	Concentration diluted 2 and 4 times
Long Term Stability (days)	147 days in human plasma (stored below -50ºC)
Selectivity	Six lots of normal human plasma, two lots of Heamolyzed human plasma and two lots of lipemic human plasma with K3EDTA as an anticoagulant were evaluated and none showed significant interfering peaks at the retention times of Mesalamine and Mesalamine D3 (ISTD).

Summary of Standard Curve and QC Data for Sample Analyses

Bioequivalence Study No. BA19140426 Mesalamine									
Parameter									
Standard Curve Samples									
Nominal Concentration (ng/mL)	1.54	4.50	45.04	225.20	450.40	900.81	1801.62	3603.24	4504.04
Mean Concentration (ng/mL)	1.541	4.500	44.617	222.947	449.915	898.514	1794.967	3617.329	4604.522
Inter day Precision (%CV)	0.67	1.83	1.35	1.87	1.62	1.25	1.18	1.47	1.66
Inter day Accuracy (%Nominal)	100.06	100.01	99.06	99.00	99.89	99.75	99.63	100.39	102.23
Linearity (Range of r values)	0.9983-1.0000								
Linearity Range (ng/mL)	1.54-4504.04								
Sensitivity/ LOQ (ng/mL)	1.54								

Bioequivalence Study No. BA19140426 Mesalamine				
Parameter				
Quality Control Samples				
Nominal Concentration (ng/mL)	4.51	45.08	1803.19	3567.15
Mean Concentration (ng/mL)	4.463	44.232	1785.378	3613.094
Inter day Precision (% CV)	3.92	3.48	2.54	2.74
Inter day Accuracy (%Nominal)	98.95	98.12	99.01	101.29

[13]If applicable, provide separate tables for the parent drug and metabolite.

SOP's Dealing with Bioanalytical Repeats of Study Samples

Please see Section 4.1.4.

Reanalysis of Study Samples

Study No. BA19140426 Additional information in Volume(s), Page(s): N/AP								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays[#]**		**Actual number**		**% of total assays[#]**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code IR Repeats: Internal Standard Related	1	1	0.01	0.01	1	1	0.01	0.01
Code CR Repeats: Chromatography Related	0	1	0.00	0.01	0	1	0.00	0.01
Total	1	2	0.01	0.02	1	2	0.01	0.02

[#]: % of total assay were calculated by dividing the number of samples reanalyzed with total number of samples analyzed

Comments on Study Assay Validation:

There is no pharmacokinetic repeat in the failed fasting sprinkle BE study.

Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route)[Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD) Mesalamine					Study Report Location
					C_{max} (ng/mL)	T_{max*} (hr)	AUC_{0-3} (ng.hr/mL)	AUC_{3-t} (ng.hr/mL)	AUC_{0-t} (ng.hr/mL)	
Study # BA19140426	**Primary Objective:** To evaluate the oral bioequivalence of Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules); manufactured by Sun Pharmaceutical Industries Limited, India with 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules); Manufactured for: Shire US Inc., USA, in healthy, adult, human subjects under fasting condition with contents sprinkled over applesauce. **Secondary Objective:** To monitor the safety of test product (T) and reference product (R) in healthy adult human subjects.	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover fully replicate bioequivalence study in healthy adult human subjects under fasting condition with contents sprinkled over applesauce.	Test product(T) : Mesalamine ER Capsules Strength:500 mg Capsule Dose: (2 x 500 mg) Rout: Oral [Batch #3967425] Reference product (R): PENTASA® (Mesalamine) controlled-release capsules strength :500 mg Capsule Dose: (2 x 500 mg) Rout: Oral [Lot # AK8368A]	No. of Subjects Completed (M)-:89 Healthy subjects mean age :31 (18-44)	Reference (R1) 1496.127 (± 714.8756/ 47.78) Reference (R2) 1391.165 (± 743.3800 / 53.44) Test (T1) 1178.101 (± 656.2374 / 55.70) Test (T2) 1242.425 (± 619.1608 / 49.83)	Reference (R1) 1.834 (0.667-6.500) Reference (R2) 2.667 (1.000 - 6.500) Test (T1) 1.667 (0.667 - 7.000) Test (T2) 2.000 (0.667 - 6.500)	Reference (R1) 1722.4665(± 1014.01823/ 58.87) Reference(R2) 1610.6344 (± 1195.30497 / 74.21) Test (T1) 1300.6138 (± 726.46201 / 55.86) Test (T2) 1370.0051 (± 816.93463 / 59.63)	Reference (R1) 2862.9483(± 1716.17922/ 59.94) Reference (R2) 2751.2350 (± 1357.70723 / 49.35) Test (T1) 2048.3993 (± 1124.37020 / 54.89) Test (T2) 2102.7171 (± 1198.80209 / 57.01)	Reference (R1) 4585.4148(± 2100.90816/ 45.82) Reference (R2) 4361.8694 (± 2016.79524 / 46.24) Test (T1) 3349.0131 (± 1451.69381 / 43.35) Test (T2) 3472.7223 (± 1512.46251 / 43.55)	N/AP

Unscaled Average BE

Reference Scaled Average Bioequivalence Approach Used	☑Yes ☐ No

If No, then complete Table 3A only						
If Yes, then complete Tables 3A and 3B						
Mesalamine (No of subjects completed=89*) Dose [2 × 500 mg(2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – BA19140426						
Parameter	**Test (T)**	**N**	**Reference (R)**	**N**	**Ratio (%) (T/R)**	**90% CI (T/R)**
C_{max} (ng/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{0-t} (ng h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{0-3} (ng.h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP
AUC_{3-t} (ng h/mL)	N/AP	N/AP	N/AP	N/AP	N/AP	N/AP

*Completed clinical phase of the study.

Statistical Summary of the Comparative Bioavailability Data

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2WR	sWR	Criteria Bound#	Method Used	Outcome
Including Interaction effect								
AUC_{0-t} (ng.h/mL)	76.56	N/AP	N/AP	0.10421	0.32282	0.02	RSAB	Non-Bioequivalent
AUC_{0-3} (ng h/mL)	82.57	N/AP	N/AP	0.19441	0.44092	-0.07	RSAB	Non-Bioequivalent
AUC_{3-t} (ng.h/mL)	73.36	N/AP	N/AP	0.13879	0.37255	0.03	RSAB	Non-Bioequivalent
C_{max} (ng/mL)	82.32	N/AP	N/AP	0.1760	0.4195	-0.05	RSAB	Non-Bioequivalent
Excluding Interaction effect								
AUC_{0-t} (ng.h/mL)	76.17	N/AP	N/AP	0.10421	0.32282	0.02	RSAB	Non-Bioequivalent
AUC_{0-3} (ng.h/mL)	82.18	N/AP	N/AP	0.19441	0.44092	-0.06	RSAB	Non-Bioequivalent
AUC_{3-t} (ng.h/mL)	73.00	N/AP	N/AP	0.13879	0.37255	0.04	RSAB	Non-Bioequivalent
C_{max} (ng/mL)	81.81	N/AP	N/AP	0.1760	0.4195	-0.05	RSAB	Non-Bioequivalent

Assessor's Comments:

- The failed fasting sprinkle BE study was designed as a single-dose, full replicate crossover study comparing test product Mesalamine Extended-Release Capsules 500 mg USP (2 x 500 mg capsules) to the corresponding reference product 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules). A total of 100 subjects were

dosed, 89 subjects completed and 11 subjects dropped out. Eighty-nine (89) subjects were included for PK and statistical analysis.

- As reported by the applicant in the tables above, no BE were demonstrated by the PK parameters. Based on the results, AUC_{0-3} and Cmax meet the acceptance criteria of RS ABE, but AUC0-t and AUC3-t did not meet the BE acceptance criteria. The T/R ratios in this failed fasting sprinkle study were relatively low (76.17%, 82.18%, 73.00% and 81.81% for AUC0-t, AUC0-3, AUC3-t and Cmax, respectively). The applicant implicated that the study power was insufficient in the study report for the pivotal fasting sprinkle study. However, as there are no study reports or dataset submitted, this issue will be assessed when the applicant submits more data.

- The applicant will be asked to submit full study reports and dataset for further evaluation. The failed sprinkle fasting BE study is inadequate.

4.1.6 Single-dose Pilot Fed Bioequivalence Study (MSM_1000C_0536_17, pilot)

Study Information

Study Number	MSM_1000C_0536_17			
Study Title	Single dose four-way crossover fully replicate study to compare bioavailability of Mesalamine extended release capsules USP 500 mg (two capsules of 500 mg each; total dose 1000 mg) in healthy adult human subjects under fed condition.			
Study Type	☐ In Vivo BE	☐ In Vitro BE	☐ Permeability	☑ Other – Bioavailability study
Submission Location:				
Study Report	N/AP			
Validation Report	N/AP			
Bioanalytical Report	N/AP			
Clinical Site (Name, Address, Phone #, Fax #)	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India Tel: (91-11) 2995-8529, 2995-6721 (Office) Fax: (91-11) 2605-9879			
Principal Clinical Investigator(s) (Name, Email)	Dr. Niraj Sharma E-mail: Niraj.Sharma1@sunpharma.com			
Analytical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited., Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India Tel: (91-124) 4768016 N/AP			
Principal Analytical Investigator (Name, Email)	Goru N.V.S Satyanarayana Goru.SatyaNarayana@sunpharma.com			
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)**	37 days			
(b) Temperature Range (eg, -20°C to -80°C)	The samples were stored at clinical and analytical sites below -50°C (Operational Range -50^0 C to - 85^0 C)			
Long-Term Storage Stability Coverage (no. days@ temp °C)	147 days in human plasma (Stored below -50°C) for Mesalamine			

LTSS Data Location	N/AP

Product Information

Product	Test	Reference
Treatment ID	**(T)**	**(R)**
Product Name	Mesalamine Extended Release Capsules USP 500 mg	Pentasa® (mesalamine) Controlled-Release Capsules 500 mg
Manufacturer	Sun Pharmaceutical Industries Limited, Sector – 18, Sarhaul, Gurugram	Manufactured For: Shire US Inc., 300 Shire Way, Lexington, MA 02421, USA, Product of Denmark
Distributed By	-	-
Batch/Lot No.	070-2018	5783929
Manufacture Date	Jul-18	N/AP
Expiration Date	Jun-19	03/2021
Strength	500 mg	500 mg
Dosage Form	Extended-Release Capsules	Controlled-Release Capsules
Bio-batch Size	(b) (4) Capsules	-
Production Batch Size	-	-
Potency	101.5 %w/w	102.0 % w/w
Content Uniformity (mean, %CV)	AV-1.8 (By Weight Variation)	-
Dose Administered	02 Capsules	02 Capsules
Route of Administration	Oral	Oral

Comments on the study Information:

The applicant conducted the pilot fed studies (study No. PKD_18_099 and MSM_1000C_0536_17) with test formulation (Batch # 070-2018) and batch of RLD product (Lot # 5783929). A different test batch was used in the pilot fed BE studies, but test formulation is the same as the bio-batches used in the pivotal BE studies, based on the formulation tables provided.

Quantitative composition of the Test Product (Batch no. 070-2018)

Ingredient	500 mg Capsule	
	Amount (mg)/capsule	Amount (%)/capsule
(b) (4)		

Demographic Profile of Subjects Completing the Bioequivalence Study

Study No. MSM_1000C_0536_17			
		Treatment Groups	
		Test Product N = 15	Reference Product N = 15
Age (years)	Mean ± SD	33.67 ± 8.09	33.67 ± 8.09
	Range	20 - 43	20 - 43
Age Groups	< 18	0 (0.00)%	0 (0.00)%
	18 – 40	11 (73.33%)	11 (73.33%)
	41 – 64	04 (26.67%)	04 (26.67%)
	65 – 75	0 (0.00)%	0 (0.00)%
	> 75	0 (0.00)%	0 (0.00)%
Sex	Male	15 (100 %)	15 (100 %)
	Female	0 (0.00)%	0 (0.00)%
Race	Asian	15 (100 %)	15 (100 %)
	Black	0 (0.00)%	0 (0.00)%
	Caucasian	0 (0.00)%	0 (0.00)%

	Hispanic	0 (0.00)%	0 (0.00)%
	Other	0 (0.00)%	0 (0.00)%
BMI (Kg/m^2)	**Mean ± SD**	22.04 ± 2.60	22.04 ± 2.60
	Range	17.68 – 26.53	17.68 – 26.53
Smokers	**Yes**	01 (6.67)%	01 (6.67)%
	No	14 (93.33%)	14 (93.33%)

Dropout Information

Study No. MSM_1000C_0536_17				
Subject No	**Reason for dropout/ Replacement[11]**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject withdrawn from the study in period I on (b) (6) due to failure to comply with the requirements of the study (unable to complete breakfast) and was not dosed with any of the investigational products.	I	No	NAP
	Subject withdrawn from the study in period I on (b) (6) due to adverse event of "Emesis" and was dosed only with reference product (R) in period I.	I	No	NAP
	Subject dropped-out from the study in period II on (b) (6) (not contactable) was dosed only with reference product (R) in period I.	II	No	NAP
	Subject withdrawn from the study in period II on (b) (6) due to Failure to comply with the requirements of the study (found positive for cannabinoids) and was dosed only with test product (T) in period I.	II	No	NAP
	Subject withdrawn from the study in period II on (b) (6) due to adverse event (Emesis) and was dosed with reference product (R) in period I and test product (T) in period II.	II	No	NAP
	Subject withdrawn from the study in period II on (b) (6) due to Failure to comply with the requirements of the study (found positive for cannabinoids) and was dosed only with test product (T) in period I.	II	No	NAP
	Subject dropped out from the study in period III on (b) (6) due to personal reasons and was dosed with reference product (R) in period I and test product (T) in period II.	III	No	NAP
	Subject dropped out from the study in period IV on (b) (6) due to personal reasons and was dosed with reference product (R) in period I and period III and test product (T) in period II.	IV	No	NAP
	Subject dropped out from the study in period IV on (b) (6) (Not contactable) and was dosed with test product (T) in period I and	IV	No	NAP

	period III and reference product (R) in period II.			

Incidence of Adverse Events in Individual Studies

Body system/Adverse Event	Reported Incidence by Treatment Groups[#]	
	Fed Bioavailability Study **Study No.** MSM_1000C_0536_17	
	Test T (N=37*)	**Reference R (N=37*)**
Gastrointestinal Disorder		
Emesis	01(2.70%)	01(2.70%)
Pain Abdomen	02 (5.41%)	01(2.70%)
Loose Stools	01(2.70%)	0 (0.00%)
Skin and subcutaneous tissue disorders		
Rashes	00 (0.00%)	01(2.70%)
Nervous system disorders		
Headache	02 (5.41%)	00 (0.00%)
Laboratory Abnormality		
Decreased Hemoglobin	00 (0.00%)	01(2.70%)
General Disorder and administration site condition		
Fever	01 (2.70%)	00 (0.00%)
Total	07 (18.92%)	04 (10.81%)

Protocol Deviations

Study No. MSM_1000C_0536_17		
Type	**Subjects # Test (T)**	**Subjects # Reference (R)**
Sample collection at time point 3.667 hours was delayed by + 03 minutes due to difficulty with veins in period IV	(b) (6)	

Impact: The above mentioned deviation did not have any impact on final study conclusion.

Other Protocol deviations:

1) As per section 11.1, Laboratory parameters of hepatic Profile (AST, ALT), biochemistry (BUN, Creatinine), urinalysis and hematology will be repeated at the end of the study at approximately 72.000 hours post dose of Period IV or at discretion of Principal Investigator. However, End of study safety assessment was repeated inadvertently for subject number (b) (6)

   Impact: No (The inadvertently repeated end of study safety assessment has no impact on the study)

2) As per section 11.1, Laboratory parameters of hepatic Profile (AST, ALT), biochemistry (BUN, Creatinine), urinalysis and hematology will be repeated at the end of the study at approximately 72.000 hours post dose of Period IV or at discretion of Principal Investigator (for the subjects who have been dosed at least once with the investigational products). However, end of study safety assessment was done for subject (b) (6) who was withdrawn prior to dosing in Period-I. The end of study safety sample was collected & assessment was done due to oversight of study personnel.

   Impact: This deviation has no impact on the outcome of the study

3) Laboratory parameters of hepatic Profile (AST, ALT), biochemistry (BUN, Creatinine), urinalysis and hematology will be repeated at the end of the study at approximately 72.000 hours post dose of Period IV, However, end of study safety sample was not done for subject (b) (6)

Impact: Not assessable-(The impact could not be assessed, as the subjects did not report for end of study assessments)

Comments on Dropouts/Adverse Events/Protocol Deviations:

- The numbers of adverse events in this pilot fed BE study are comparable between test- and RLD-treated groups.
- The applicant will be asked to provide severity information for AEs.
- There were 9 dropouts in this pilot fed study.

Bioanalytical Method Validation

Results	
Bio-analytical method validation report location	N/AP
Analyte	Mesalamine
Internal standard (ISTD)	Mesalamine D3
Method description	Ultra-High Performance Liquid Chromatography Tandem Mass Spectrometric Method for the Estimation of Mesalamine in Human K3EDTA Plasma using Mesalamine D3 as an Internal Standard [Solid phase extraction technique] (MV648/17)
Limit of quantitation (ng/mL)	1.54
Average recovery of drug (%)	62.79
Recovery of ISTD (%)	77.15
Standard Curve Concentration (ng/mL) (Nominal)	STDA: 1.54, STDA(DUP): 1.54, STDB: 4.41, STDC: 88.15, STDD: 220.38, STDE: 550.95, STDF: 1101.89, STDG 2203.79, STDH 4407.57, STDI: 5509.46 STDI(DUP): 5509.46
Standard curve concentrations (ng/mL) (Mean Value)	STDA: 1.553, STDA(DUP): 1.537, STDB: 4.300, STDC: 86.470, STDD: 220.807, STDE: 549.153, STDF: 1206.100, STDG: 2151.447, STDH: 4323.543 STDI: 5496.097, STDI(DUP) 5438.370
QC concentrations (ng/mL) (Nominal)	LOQQC – 1.55, LQC – 4.40, MQC –2202.01, HQC – 4404.02, D2QC-9370.26, D4QC-9370.26
QC concentrations (ng/mL) (Mean value)-Global statistics	LOQQC- 1.588, LQC- 4.239, MQC- 2116.483, HQC- 4302.632, D2QC – 9270.080, D4QC – 9072.824
QC within batch accuracy range (%)	94.81 to 106.56
QC between batch accuracy range (%)	96.12 to 102.44
QC Intraday accuracy range (%)	95.70 to 103.28
QC within batch precision range (%)	0.52 to 17.20

QC between batch precision range (%)	2.71 to 10.49
QC Intraday precision range (%)	2.92 to 12.77
Bench-top stability in human plasma	8.25 hours, at room temperature, under low light
Stock solution stability of analyte (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
Stock solution stability of ISTD (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
In-injector stability (hours)	99.97 hours (10°C±1°C)
Freeze thaw stability (cycles)	Three cycles (frozen below -50°C and thawed at room temperature, under low light)
Dilution integrity*	Concentration diluted 2 and 4 times
Long Term Stability (days)	147 days in human plasma (stored below -50ºC)
Selectivity	Six lots of normal human plasma, two lots of Heamolyzed human plasma and two lots of lipemic human plasma with K3EDTA as an anticoagulant were evaluated and none showed significant interfering peaks at the retention times of Mesalamine and Mesalamine D3 (ISTD).

Summary of Standard Curve and QC Data for Sample Analyses

Study No. MSM_1000C_0536_17 Mesalamine											
Parameter											
Standard Curve Samples											
Nominal Concentration (ng/mL)	1.56	1.56	4.37	15.08	41.90	116.38	323.27	646.54	1293.08	1616.35	1616.35
Mean Concentration (ng/mL)	1.560	1.579	4.275	14.575	40.144	117.453	320.638	650.878	1323.045	1663.566	1654.570
Inter day Precision (%CV)	1.75	1.82	2.59	1.28	1.51	1.70	2.19	1.30	1.47	0.68	2.25
Inter day Accuracy (%Nominal)	100.03	101.22	97.81	96.65	95.81	100.92	99.19	100.67	102.32	102.92	102.36
Linearity (Range of r values)	0.9990 – 0.9997										
Linearity Range (ng/mL)	1.56– 1616.35										
Sensitivity/ LOQ (ng/mL)	1.56										

Study No. MSM_1000C_0536_17 Mesalamine				
Parameter				
Quality Control Samples				
Nominal Concentration (ng/mL)	4.52	70.58	526.72	1254.10
Mean Concentration (ng/mL)	4.342	68.899	531.211	1301.723
Inter day Precision (% CV)	2.68	3.69	3.32	2.11
Inter day Accuracy (%Nominal)	96.06	97.62	100.85	103.80

SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
SOP No. OP005713, Version No. 5.0	23 Apr 2018	Repeat Analysis

SOP025099, Version No. 1.0 (Legacy document No.: OP005713, Version No. 6.0)	14 Dec 2018	Repeat Analysis

Reanalysis of Study Samples

Study No. MSM 1000C 0536 17 Additional information: N/AP								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Mesalamine							
	Actual number		**% of total assays#**		**Actual number**		**% of total assays#**	
	Test (T)	**Ref (R)**	**Test (T)**	**Ref (R)**	**Test (T)**	**Ref (R)**	**Test (T)**	**Ref (R)**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code IR Repeats: Internal Standard Related	9	5	0.36	0.20	9	5	0.36	0.20
Code PR Repeats: Processing Related	2	0	0.08	0.00	2	0	0.08	0.00
Total	11	5	0.44	0.20	11	5	0.44	0.20

Comments on Study Assay Validation:

There is no pharmacokinetic repeat in the failed pilot fed BE study.

Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route)[Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD) Mesalamine					Study Report Location
					C_{max} (ng/mL)	T_{max*} (hr)	AUC_{0-3} (ng hr/mL)	AUC_{3-t} (ng hr/mL)	AUC_{0-t} (ng.hr/mL)	
MSM_1000C_0536 – 17	Single dose four-way crossover fully replicate study to compare bioavailability of Mesalamine extended release capsules USP 500 mg (two capsules of 500 mg each; total dose 1000 mg) in healthy adult human subjects under fed condition.	An open label, balanced, randomized, two-treatment, two-sequence, four-period, single dose, crossover fully replicate bioavailability study in healthy adult human subjects under fed condition. Study Type: Pilot Study	**Reference product (R):** Pentasa® (mesalamine) Controlled Release Capsules 500 mg, 2 capsules, Oral [Batch. /Lot No. 5783929] **Test product (T):** Mesalamine Extended Release Capsules USP 500 mg, 2 Capsules, Oral [Batch. /Lot No. 070-2018]	A total of 24 healthy, adult, human male subjects were enrolled in the study. 15 male subjects completed the study. Mean age: 33.67 ± 8.09 years (Completed subjects) Range: 20 – 43 Years (Completed Subjects)	Reference (R1) 322.423 (± 332.7319/ 103.20) Reference (R2) 226.076 (± 200.0488/ 88.49) Test (T1) 212.256 (± 231.2965/ 108.97) Test (T2) 260.932 (± 289.6357 / 111.00)	Reference (R1) 2.667 (1.667 - 7.500) Reference (R2) 3.834 (1.000- 8.000) Test (T1) 3.333 (1.667 - 7.000) Test (T2) 3.334 (1.333- 30.000)	Reference (R1) 102.6296 (± 64.46214/ 62.81) Reference (R2) 156.8110 (±173.04585/ 110.35) Test (T1) 132.8470 (±169.73498 /127.77) Test (T2) 165.2168 (±234.92589/ 142.19)	Reference (R1) 586.5568 (±714.73661/ 121.85) Reference (R2) 547.6088 (± 483.20744/ 88.24) Test (T1) 352.0157 (± 255.07236 / 72.46) Test (T2) 407.3646 (± 325.15975/ 79.82)	Reference (R1) 689.1864 (±706.13020/102.46) Reference (R2) 704.4198 (± 558.95570/ 79.35) Test (T1) 484.8627 (± 369.98099/ 76.31) Test (T2) 572.5814 (± 454.41597 / 79.36)	N/AP

Statistical Summary of the Comparative Bioavailability Data

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2WR	sWR	Criteria Bound#	Method Used	Outcome
AUC_{0-t} (ng h/mL)	74.15	N/AP	N/AP	0.57901	0.76093	-0.03	RSAB	N/AP
AUC_{0-3} (ng h/mL)	74.46	N/AP	N/AP	0.63569	0.79730	-0.09	RSAB	N/AP
AUC_{3-t} (ng h/mL)	74.26	N/AP	N/AP	0.76717	0.87588	-0.14	RSAB	N/AP
C_{max} (ng/mL)	60.13	N/AP	N/AP	1.0619	1.0305	0.08	RSAB	N/AP

Assessor's Comments:

- The pilot fed BE study was designed as a single-dose, four-way full replicate crossover study comparing test product Mesalamine Extended Release Capsules, 500 mg USP (2 x 500 mg capsules) to the corresponding reference product 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules).

- The applicant stated that the results of the pilot fed study do not provide the conclusive evidence on the bioequivalence, owing to the less no. of volunteers, lower power of the study design and very high variability.

- The applicant submitted the 16 summary tables for the pilot fed study.

4.1.7 Single-dose Pilot Fed Bioequivalence Study (PKD_18_099, pilot)

Study Information

Study Number	PKD_18_099			
Study Title	A randomized, open label, balanced, two treatment, four period, two sequence, single dose, replicated, crossover, comparative bioavailability study of mesalamine extended release capsules 500 mg (2 x 500 mg dose) of sun pharmaceutical industries limited and pentasa® (mesalamine) controlled release capsule 500 mg (2 x 500 mg dose) of shire us inc., in 24 healthy adult subjects under fed condition.			
Study Type	☐ In Vivo BE	☐ In Vitro BE	☐ Permeability	☑ Other Bioavailability study
Submission Location:				
Study Report	N/AP			
Validation Report	N/AP			
Bioanalytical Report	N/AP			
Clinical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology Unit, Sun Pharmaceutical Industries Ltd., Near R. C. Patel Estate, Akota Road, Akota Vadodara- 390 020 (India) Phone Number: 91-265-2339103, 91-265-2330815 Fax: 91-265-2354897			
Principal Clinical Investigator(s) (Name, Email)	Dr. Sumit Devaliya MBBS, CIH Sumit.Devaliya@sunpharma.com			
Analytical Site (Name, Address, Phone #, Fax #)	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited., Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India Tel: (91-124) 4768016 Fax: N/AP			
Principal Analytical Investigator (Name, Email)	Mr. Goru N.V.S. Satya Narayana (Study Director) [Mail Id: Goru.SatyaNarayana@sunpharma.com]			
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)**	34days			
	The samples were stored at analytical site below -50°C (operational range -50°C to -85°C) and clinical sites below -50°C (operational range -50°C to -86°C)			

(b) Temperature Range (eg, -20°C to -80°C)	
Long-Term Storage Stability Coverage (no. days@ temp °C)	147 days (stored below -50°C)
LTSS Data Location	N/AP

Product Information

Please see Section 4.1.6 for details.

Standard FDA Meal Used?[15]	☒ Yes ☐ No

Comments on the study Information:

Based on the applicant's submission, the applicant conducted two pilot fed studies (study No. PKD_18_099 and MSM_1000C_0536_17) with the same test formulation (Batch # 070-2018) and batch of RLD product (Lot # 5783929).

Demographic Profile of Subjects Completing the Bioequivalence Study

		Study Number: PKD_18_099	
		Treatment Groups	
		Test Product N = 22	Reference Product N = 22
Age (Years)	**Mean ± SD**	31.3 ± 5.4	31.3 ± 5.4
	Range	23 – 42	23 – 42
Age Groups	**< 18**	0 (0.00%)	0 (0.00%)
	18-40	20 (90.91%)	20 (90.91%)
	41-64	2 (9.09%)	2 (9.09%)
	65-75	0 (0.00%)	0 (0.00%)
	>75	0 (0.00%)	0 (0.00%)
Sex	**Male**	22 (100.00%)	22 (100.00%)
	Female	0 (0.00%)	0 (0.00%)
Race	**Asian**	22 (100.00%)	22 (100.00%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	**Mean ± SD**	23.340 ± 2.633	23.340 ± 2.633
	Range	19.01 – 28.87	19.01 – 28.87
Other factors		–	–

Dropout Information

Study Number: PKD_18_099

Subject Number	Reason For Dropout/replacement			Period	Replaced?	Replaced With
	Cause	Date/Time	Treatment			
(b) (6)	Breath alcohol test positive at check-in	(b) (6)	NA	2	No	NA
	Subject withdrew from the study voluntarily		B	1	No	NA

Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups	
	Fed Comparative Bioavailability Study Number: PKD_18_099	
Med DRA System Organ Class Preferred Terms	Adverse Events	
	Test (A) N (%)	Reference (B) N (%)
Single treatment emergent adverse events		
Investigations		
Alanine aminotransferase increased	0 (0.00)	2 (50.00)
Aspartate aminotransferase increased	0 (0.00)	2 (50.00)
Total	**0 (0.00)**	**4 (100.00)**

Protocol Deviations

Study Number: PKD_18_089
No protocol deviation occurred during conduct of the study and reporting of results.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- The numbers of adverse events in this pilot fed BE study are comparable between test- and RLD-treated groups. There were no reports of deaths or serious AEs during the study.

- There were two dropouts in this pilot fed study.

Bioanalytical Method Validation

Results	
Bioanalytical method validation report location	N/AP
Analyte	Mesalamine
Internal standard (ISTD)	Mesalamine D3
Method description	Ultra-High Performance Liquid Chromatography Tandem Mass Spectrometric Method for the Estimation of Mesalamine in Human K_3EDTA Plasma using Mesalamine D3 as an Internal Standard. [Solid phase extraction technique] (MV648/17)
Limit of quantitation (ng/mL)	1.54
Average recovery of drug (%)	62.79
Recovery of ISTD (%)	77.15

Standard Curve Concentration (ng/mL) (Nominal)	STDA: 1.54, STDA(DUP): 1.54, STDB: 4.41, STDC: 88.15, STDD: 220.38, STDE: 550.95, STDF: 1101.89, STDG 2203.79, STDH 4407.57, STDI: 5509.46 STDI(DUP): 5509.46
Standard curve concentrations (ng/mL) (Mean Value)	STDA: 1.553, STDA(DUP): 1.537, STDB: 4.300, STDC: 86.470, STDD: 220.807, STDE: 549.153, STDF: 1206.100, STDG: 2151.447, STDH: 4323.543, STDI: 5496.097, STDI(DUP) 5438.370
QC concentrations (ng/mL) (Nominal)	LOQQC – 1.55, LQC – 4.40, MQC –2202.01, HQC – 4404.02, D2QC-9370.26, D4QC-9370.26
QC concentrations (ng/mL) (Mean value)-Global statistics	LOQQC- 1.588, LQC- 4.239, MQC- 2116.483, HQC-4302.632, D2QC – 9270.080, D4QC – 9072.824
QC within batch accuracy range (%)	94.81 to 106.56
QC between batch accuracy range (%)	96.12 to 102.44
QC Intraday accuracy range (%)	95.70 to 103.28
QC within batch precision range (%)	0.52 to 17.20
QC between batch precision range (%)	2.71 to 10.49
QC Intraday precision range (%)	2.92 to 12.77
Bench-top stability in human plasma	8.25 hours, at room temperature, under low light
Stock solution stability of analyte (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
Stock solution stability of ISTD (days)	67 days (stored in refrigerator between 1-10°C), Protected from light
In-injector stability (hours)	99.97 hours (10°C±1°C)
Freeze thaw stability (cycles)	Three cycles (frozen below -50°C and thawed at room temperature, under low light)
Dilution integrity*	Concentration diluted 2 and 4 times
Long Term Stability (days)	147 days in human plasma (stored below -50ºC)
Selectivity	Six lots of normal human plasma, two lots of Heamolyzed human plasma and two lots of lipemic human plasma with K3EDTA as an anticoagulant were evaluated and none showed significant interfering peaks at the retention times of Mesalamine and Mesalamine D3 (ISTD).

Summary of Standard Curve and QC Data for Sample Analyses

SOP's Dealing with Bioanalytical Repeats of Study Samples*

Bioequivalence Study No. PKD_18_099											
Parameter	**Mesalamine**										
Standard Curve Samples											
Nominal Concentration (ng/mL)	1.55	1.55	4.18	41.83	209.13	418.26	836.52	1673.04	4402.73	5503.41	5503.41
Mean Concentration (ng/mL)	1.555	1.566	4.024	40.742	204.401	413.590	840.497	1700.790	4517.437	5561.890	5623.081
Inter day Precision (%CV)	3.28	3.09	1.81	1.52	1.68	1.51	1.34	2.10	1.80	2.70	2.15
Inter day Accuracy (%Nominal)	100.34	101.04	96.26	97.40	97.74	98.88	100.48	101.66	102.61	101.06	102.17
Linearity (Range of r values)	0.9985 - 0.9999										
Linearity Range (ng/mL)	1.55– 5503.41										
Sensitivity/ LOQ (ng/mL)	1.55										

Bioequivalence Study No. PKD 18 099 Mesalamine				
Parameter				
Quality Control Samples				
Nominal Concentration (ng/mL)	4.19	209.57	1676.56	4412.01
Mean Concentration (ng/mL)	4.038	204.906	1701.316	4467.395
Inter day Precision (% CV)	5.77	3.36	2.88	5.04
Inter day Accuracy (%Nominal)	96.36	97.77	101.48	101.26

Reanalysis of Study Samples

Study No. PKD_18_099 Additional information: N/AP								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Mesalamine							
	Actual number		**% of total assays**		**Actual number**		**% of total assays[#]**	
	Ref (B)	**Test (A)**	**Ref (B)**	**Test (A)**	**Ref (B)**	**Test (A)**	**Ref (B)**	**Test (A)**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code IR Repeats: Internal Standard Related	3	2	0.10	0.07	3	2	0.10	0.07
Total	3	2	0.10	0.07	3	2	0.10	0.07

Comments on Study Assay Validation:

There is no pharmacokinetic repeat in the pilot fed study BE study.

Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route)[Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD) Mesalamine					Study Report Location
					C_{max} (ng/mL)	T_{max*} (hr)	AUC_{0-3} (ng.hr/mL)	AUC_{3-t} (ng hr/mL)	AUC_{0-t} (ng.hr/mL)	
PKD_18_099	Single dose four-way crossover fully replicate study to compare bioavailability of Mesalamine ER capsules USP 500 mg (two capsules of 500 mg each; total dose 1000 mg) in healthy adult human subjects under fed condition.	An open label, balanced, randomized, two treatment, two sequence, four period, single dose, replicated, crossover, comparative bioavailability study under fed condition. Study Type: Pilot Study	**Test (A):** Mesalamine / (2 x 500 mg) / Extended Release Capsule / Oral Batch Number: 070-2018 **Reference (B):** Pentasa® (Mesalamine) / (2 x 500 mg) / Controlled Release Capsule / Oral Lot Number: 5783929	22 healthy subjects (22/0) Mean age (Range): 31.3 (23 - 42) (Completed subjects)	Reference (B1) 321.444 (± 320.7929/ 99.80) Reference (B2) 354.44 (± 415.3876/ 117.19) Test (A1) 145.918 (± 172.0909/ 117.94) Test (A2) 211.826 (± 355.2543/ 167.71)	Reference (B1) 4.333 (1.333 - 7.000) Reference (B2) 3.667(1.667- 8.000) Test (A1) 4.000 (1.333- 8.000) Test (A2) 3.667 (2.333- 24.000)	Reference (B1) 131.0646 (± 184.31477 / 140.63) Reference (B2) 67.2550 (± 56.39194 / 83.85) Test (A1) 75.9178 (± 58.48000/ 77.03) Test (A2) 53.1538 (± 32.15899 / 60.50)	Reference (B1) 753.0515 (± 747.86036 / 99.31) Reference (B2) 647.2110 ± (718.84876 / 111.07) Test (A1) 333.3712 (± 226.42988 / 67.92) Test (A2) 400.3987 (± 462.27150/ 115.45)	Reference (B1) 884.116 (± 883.95357/ 99.98) Reference (B2) 714.465 (± 761.98965/ 106.65) Test (A1) 409.289 (± 260.87935 / 63.74) Test(A2) 453.5525 (± 474.63957 / 104.65)	N/AP

Statistical Summary of the Comparative Bioavailability Data

Parameter	A/B Ratio	Lower 90% CI	Upper 90% CI	s^2WR	sWR	Criteria Bound[#]	Method Used	Outcome
AUC_{0-3} (ng.h/mL)	83.74 %	N/AP	N/AP	0.33336	0.57737	-0.06	RSAB	N/AP
AUC_{3-t} (ng.h/mL)	73.00 %	N/AP	N/AP	0.56772	0.75347	-0.05	RSAB	N/AP
AUC_{0-t} (ng.h/mL)	74.21 %	N/AP	N/AP	0.47385	0.68837	-0.03	RSAB	N/AP
C_{max} (ng/mL)	68.24 %	N/AP	N/AP	0.8794	0.9378	-0.13	RSAB	N/AP

Assessor's Comments:

- The pilot fed BE study was designed as a single-dose, four-way full replicate crossover study comparing test product Mesalamine Extended Release Capsules 500 mg USP (2 x 500 mg capsules) to the corresponding reference product 'PENTASA®' (Mesalamine) Controlled-Release Capsules 500 mg (2 x 500 mg capsules).

- The applicant stated that the results of the pilot fed study do not provide the conclusive evidence on the bioequivalence, owing to the less no. of volunteers, lower power of the study design and very high variability.

- The applicant submitted the 16 summary tables for the pilot fed study.

4.2 Formulation Data

4.2.1 Test Formulation

Ingredient	Amount (mg) / Capsule	Amount (%) / Capsule
(b) (4)		

Following this page, 5 Pages Withheld in Full as (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
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 the drug product formulation:	The formulations of the test product Mesalamine Extended-Release Capsules, USP (b) (4) 500 mg are acceptable.

Comments on Formulation:

- The maximum daily intake (MDI) of all the inactive ingredients was calculated based on maximum daily dose (MDD) of 4000 mg per RLD labeling. All inactive ingredients of the test product fall within acceptable limits for FDA approved drugs with oral administration.

- The daily intake of elemental iron from the tablets based on the maximum daily dosage of the drug product is less than the required regulatory limit of 5 mg of elemental iron per day as per 21 CFR 73.1200(C).

- (b) (4)

- As per RLD labeling, safety and effectiveness for this drug product have not been established in pediatric patients.

- The formulations are acceptable.

4.3 Dissolution Testing

4.3.1 Dissolution Data

Table 5. Summary of In Vitro Dissolution Studies

Table 5 (a)-(1) Summary of In Vitro Dissolution Studies (Bio-Batch 3967425 vs 5783929) (Official media) (500 mg strength)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.05 M Phosphate buffer pH 7.50
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	% labeled amount of Mesalamine dissolved;1 hr: 5 – 25%, 2 hr: 30 – 50%, 4 hr: 60-90%, 8 hr: NLT 85%	
Dissolution Testing Site (Name, Address)	Test Product- Sun Pharmaceutical Industries Limited, A-41, Mohali,Punjab(India) RLD- Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)	

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	06/21/2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	9	19	40	74	97	100	101	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	6.1	2.7	3.1	2.4	1.7	1.7	1.9	
-	07/04/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	10	22	43	75	93	101	103	
					Range	(b) (4)							
					%CV	8.1	4.0	4.9	4.4	2.1	1.8	1.1	

Table 5 (a)-(2) Summary of In Vitro Dissolution Studies (3968987 vs 5783929)
(Official media) (500 mg strength)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.05 M Phosphate buffer pH 7.50
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	% labeled amount of Mesalamine dissolved;1 hr: 5 – 25%, 2 hr: 30 – 50%, 4 hr: 60-90%, 8 hr: NLT 85%	
Dissolution Testing Site (Name, Address)	Test Product- Sun Pharmaceutical Industries Limited, A-41, Mohali,Punjab(India) RLD- Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)	

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	06/19/2019	Mesalamine ER Capsules,500 mg Batch No: 3968987 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	10	23	45	80	97	99	99	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	5.7	1.7	1.7	1.0	0.5	0.8	0.9	
-	07/04/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	10	22	43	75	93	101	103	
					Range	(b) (4)							
					%CV	8.1	4.0	4.9	4.4	2.1	1.8	1.1	

Table 5 (a) (3) Summary of In Vitro Dissolution Studies (3965560 vs 5783929)
(Official media) (500 mg strength)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.05 M Phosphate buffer pH 7.50
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	% labeled amount of Mesalamine dissolved;1 hr: 5 – 25%, 2 hr: 30 – 50%, 4 hr: 60-90%, 8 hr: NLT 85%	
Dissolution Testing Site (Name, Address)	Test Product- Sun Pharmaceutical Industries Limited,A-41,Mohali,Punjab(India) RLD- Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)	

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	06/20/2019	Mesalamine ER Capsules, 500 mg Batch No: 3965560 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	7	17	36	69	94	100	101	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	4.1	3.0	1.4	1.3	1.4	1.4	1.6	
-	07/04/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	10	22	43	75	93	101	103	
					Range	(b) (4)							
					%CV	8.1	4.0	4.9	4.4	2.1	1.8	1.1	

Table 5 (a)- (4) Summary of In Vitro Dissolution Studies (AB78176 vs 5783929)
(Official media) (500 mg strength)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.05 M Phosphate buffer pH 7.50
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	% labeled amount of Mesalamine dissolved;1 hr: 5 – 25%, 2 hr: 30 – 50%, 4 hr: 60-90%, 8 hr: NLT 85%	
Dissolution Testing Site (Name, Address)	Test Product- Sun Pharmaceutical Industries Limited,A-41,Mohali,Punjab(India) RLD- Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)	

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	08/19/2020	Mesalamine ER Capsules, 500 mg Batch No: AB78176 Mfg. date: July,2020 Exp. Date: June, 2022	500 mg Extended Release Capsule	12	Mean	9	21	46	83	98	98	99	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	8.1	4.6	3.1	2.0	1.1	0.7	0.9	
-	07/04/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	10	22	43	75	93	101	103	
					Range	(b) (4)							
					%CV	8.1	4.0	4.9	4.4	2.1	1.8	1.1	

Table 5 (a)-(5) Summary of In Vitro Dissolution Studies (Bio-Batch 3967425 vs AK8368A) (Official media) (500 mg strength)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.05 M Phosphate buffer pH 7.50
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	% labeled amount of Mesalamine dissolved;1 hr: 5 – 25%, 2 hr: 30 – 50%, 4 hr: 60-90%, 8 hr: NLT 85%	
Dissolution Testing Site (Name, Address)	Test Product- Sun Pharmaceutical Industries Limited,A-41,Mohali,Punjab(India) RLD- Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)	

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	06/21/2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	9	19	40	74	97	100	101	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	6.1	2.7	3.1	2.4	1.7	1.7	1.9	
-	10/22/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: AK8368A Mfg. date: Not Applicable Exp. Date: October 2022	500 mg Controlled Release Capsule	12	Mean	8	19	39	70	88	97	101	
					Range	(b) (4)							
					%CV	4.8	4.2	3.3	2.0	0.9	1.0	1.1	

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Table 5 (b) (1) Summary of In Vitro Dissolution Studies (Multi-Media)
500 mg strength (Bio-Batch 3967425 vs 5783929) (0.1 N HCl)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/ YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	04/03/ 2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	15	35	65	99	102	102	101	**Module 2, Section 2.7**
					Range	[redacted] (b) (4)							
					%RSD	4.7	2.3	1.8	0.8	0.9	0.8	1.1	
-	06/18/ 2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	22	45	79	101	102	102	103	
					Range	[redacted] (b) (4)							
					%RSD	4.1	2.7	2.2	1.8	1.8	1.6	1.2	

Table 5 (b) (2) Summary of In Vitro Dissolution Studies (Multi-Media)
500 mg strength (Bio-Batch 3967425 vs 5783929) (pH 4.50 acetate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 4.50 acetate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date MM/DD/YYYY**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**										**Study Report Location**
						0.5 Hr.	**1 Hr**	**1.5 Hr**	**2 Hr**	**3 Hr**	**4 hr**	**5 Hr**	**6 hr**	**8 hr**	**12hr**	
-	06/28/2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	2	6	9	11	16	21	25	29	36	47	Module 2, Section 2.7
					Range	(b) (4)										
					%RSD	25.0	8.3	5.6	4.5	3.8	1.9	2.4	2.4	1.9	1.9	
-	06/21/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	3	6	9	12	18	23	28	33	43	57	
					Range	(b) (4)										
					%RSD	26.7	8.3	5.6	5.8	3.9	2.6	2.9	2.4	3.3	2.5	

Table 5 (b) (3) Summary of In Vitro Dissolution Studies (Multi-Media)
500 mg strength (Bio-Batch 3967425 vs 5783929) (pH 6.00 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.00 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD / YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**										**Study Report Location**
						0.5 Hr.	**1 Hr**	**1.5 Hr**	**2 Hr**	**3 Hr**	**4 hr**	**5 Hr**	**6 hr**	**8 hr**	**12hr**	
-	07/02/ 2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	2	5	9	12	18	23	28	31	39	50	Module 2, Section 2.7
					Range	(b) (4)										
					%RSD	20.0	10.0	3.3	5.0	2.8	4.3	2.5	2.6	3.6	3.6	
-	06/24/ 2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	3	7	10	14	21	27	34	39	49	64	
					Range	(b) (4)										
					%RSD	16.7	7.1	5.0	3.6	2.4	2.6	2.6	2.6	2.2	2.8	

Table 5 (b) (4) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg strength (Bio-Batch 3967425 vs 5783929) (pH 6.50 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.50 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	04/26/2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	4	10	19	36	50	61	82	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	12.5	3.0	2.6	1.4	2.2	3.0	2.3	
-	06/19/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	5	12	24	46	63	75	90	
					Range	(b) (4)							
					%RSD	6.0	5.8	4.2	3.5	2.4	3.1	2.3	

Table 5 (b) (5) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg strength (Bio-Batch 3967425 vs 5783929) (pH 6.80 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.80 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	Testing Date MM/DD/YYYY	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						30 min	1 Hr	2 Hr	4 Hr	6 hr	8 Hr	12hr	
-	04/05/2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	4	11	24	44	61	75	95	Module 2, Section 2.7
					Range							(b) (4)	
					%RSD	27.5	7.3	2.9	1.8	1.0	1.1	0.8	
-	06/20/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	6	14	29	54	73	86	96	
					Range							(b) (4)	
					%RSD	10.0	5.7	3.8	2.4	1.9	2.1	2.1	

Table 5 (b) (6) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg strength (Bio-Batch 3967425 vs 5783929) (pH 7.20 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 7.20 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	04/12/2019	Mesalamine ER Capsules, 500 mg Batch No: 3967425 Mfg. date: August, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	7	16	31	58	80	97	101	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	7.1	3.1	2.9	1.9	2.0	1.3	1.0	
-	04/11/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	8	18	37	67	86	97	103	
					Range	(b) (4)							
					%RSD	0.0	3.3	3.0	1.6	1.6	1.5	1.7	

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Table 5 (b) (13) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (AB78176 vs 5783929) (0.1 N HCl)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	01/21/2021	Mesalamine ER Capsules 500 mg Batch No: AB78176 Mfg. date: Not Applicable Exp. Date: Jun, 2022	500 mg Extended Release Capsule	12	Mean	21	44	78	95	96	97	96	**Module 2, Section 2.7**
					Range							(b) (4)	
					%RSD	2.4	1.4	1.4	2.3	2.1	2.1	2.3	
-	06/18/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	22	45	79	101	102	102	103	
					Range							(b) (4)	
					%RSD	4.1	2.7	2.2	1.8	1.8	1.6	1.2	

Table 5 (b) (14) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (AB78176 vs 5783929) (pH 4.50 acetate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 4.50 acetate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	08/27/2020	Mesalamine ER Capsules 500 mg Batch No: AB78176 Mfg. date: Not Applicable Exp. Date: Ju ne, 2022	500 mg Extended Release Capsule	12	Mean	3	7	14	25	33	40	51	Module 2, Section 2.7
					Range							(b) (4)	
					%RSD	10.0	0.0	0.0	2.0	1.5	1.0	0.8	
-	06/21/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	3	6	12	23	33	43	57	
					Range							(b) (4)	
					%RSD	26.7	8.3	5.8	2.6	2.4	3.3	2.5	

Table 5 (b) (15) Summary of In Vitro Dissolution Studies (Multi-Media)
for Test 500 mg vs RLD 500 mg (AB78176 vs 5783929) (pH 6.00 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.00 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	08/28/2020	Mesalamine ER Capsules 500 mg Batch No: AB78176 Mfg. date: Not Applicable Exp. Date: June, 2022	500 mg Extended Release Capsule	12	Mean	3	7	15	27	38	47	62	Module 2, Section 2.7
					Range	(b) (4)							
					%RSD	0.0	0.0	3.3	2.2	1.6	1.7	2.1	
-	06/24/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	3	7	14	27	39	49	64	
					Range	(b) (4)							
					%RSD	16.7	7.1	3.6	2.6	2.6	2.2	2.8	

Table 5 (b) (16) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (AB78176 vs 5783929) (pH 6.50 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.50 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	10/13/2020	Mesalamine ER Capsules 500 mg Batch No: AB78176 Mfg. date: Not Applicable Exp. Date: June, 2022	500 mg Extended Release Capsule	12	Mean	4	11	23	44	61	75	92	Module 2, Section 2.7
					Range							(b) (4)	
					%RSD	0.0	4.5	1.3	1.8	1.6	1.3	2.0	
-	06/19/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	5	12	24	46	63	75	90	
					Range							(b) (4)	
					%RSD	6.0	5.8	4.2	3.5	2.4	3.1	2.3	

Table 5 (b) (17) Summary of In Vitro Dissolution Studies (Multi-Media)
500 mg (AB78176 vs 5783929) (pH 6.80 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.80 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	10/12/2020	Mesalamine ER Capsules 500 mg Batch No: AB78176 Mfg. date: Not Applicable Exp. Date: June, 2022	500 mg Extended Release Capsule	12	Mean	6	14	29	55	76	91	98	Module 2, Section 2.7
					Range							(b) (4)	
					%RSD	8.3	2.9	1.7	1.5	1.3	1.3	1.3	
-	06/20/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	6	14	29	54	73	86	96	
					Range							(b) (4)	
					%RSD	10.0	5.7	3.8	2.4	1.9	2.1	2.1	

Table 5 (b) (18) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (AB78176 vs 5783929) (pH 7.20 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 7.20 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	01/22/2021	Mesalamine ER Capsules 500 mg Batch No: AB78176 Mfg. date: Not Applicable Exp. Date: June, 2022	500 mg Extended Release Capsule	12	Mean	8	19	40	74	94	96	96	**Module 2, Section 2.7**
					Range							(b) (4)	
					%RSD	6.3	2.6	2.0	1.6	1.0	0.7	1.0	
-	04/11/2019	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: 5783929 Mfg. date: Not Applicable Exp. Date: March 2021	500 mg Controlled Release Capsule	12	Mean	8	18	37	67	86	97	103	
					Range							(b) (4)	
					%RSD	0.0	3.3	3.0	1.6	1.6	1.5	1.7	

Table 5 (b) (19) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (3967425 vs AK8368A) (0.1 N HCl)

Dissolution Conditions	**Apparatus:**	USP Apparatus II
	Speed of Rotation:	100 rpm
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	04/03/2019	Mesalamine ER Capsules 500 mg Batch No: 3967425 Mfg. date: Aug, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	15	35	65	99	102	102	101	**Module 2, Section 2.7**
					Range							(b) (4)	
					%RSD	4.7	2.3	1.8	0.8	0.9	0.8	1.1	
-	05/15/2020	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: AK8368A Mfg. date: Not Applicable Exp. Date: Oct 2022	500 mg Controlled Release Capsule	12	Mean	20	41	74	98	101	102	102	
					Range							(b) (4)	
					%RSD	4.5	3.4	2.3	0.7	1.3	1.2	1.2	

Table 5 (b) (20) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (3967425 vs AK8368A) (pH 4.50 acetate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II
	Speed of Rotation:	100 rpm
	Medium:	pH 4.50 acetate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	Testing Date MM/DD/YYYY	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						30 min	1 Hr	2 Hr	4 Hr	6 hr	8 Hr	12hr	
-	06/28/2019	Mesalamine ER Capsules 500 mg Batch No: 3967425 Mfg. date: Aug, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	2	6	11	21	29	36	47	Module 2, Section 2.7
					Range	(b) (4)							
					%RSD	25.0	8.3	4.5	1.9	2.4	1.9	1.9	
-	05/12/2020	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: AK8368A Mfg. date: Not Applicable Exp. Date: Oct 2022	500 mg Controlled Release Capsule	12	Mean	3	6	11	22	31	39	53	
					Range	(b) (4)							
					%RSD	0.0	8.3	3.6	3.2	2.3	2.6	1.9	

Table 5 (b) (21) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (3967425 vs AK8368A) (pH 6.00 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II
	Speed of Rotation:	100 rpm
	Medium:	pH 6.00 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	07/02/2019	Mesalamine ER Capsules 500 mg Batch No: 3967425 Mfg. date: Aug, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	2	5	12	23	31	39	50	**Module 2, Section 2.7**
					Range							(b) (4)	
					%RSD	20.0	10.0	5.0	4.3	2.6	3.6	3.6	
-	05/12/2020	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: AK8368A Mfg. date: Not Applicable Exp. Date: Oct 2022	500 mg Controlled Release Capsule	12	Mean	4	7	14	28	39	48	64	
					Range							(b) (4)	
					%RSD	17.5	7.1	3.6	2.9	2.1	2.3	1.9	

Table 5 (b) (22) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (3967425 vs AK8368A) (pH 6.50 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II
	Speed of Rotation:	100 rpm
	Medium:	pH 6.50 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/ YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 min	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	04/26/2019	Mesalamine ER Capsules 500 mg Batch No: 3967425 Mfg. date: Aug, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	4	10	19	36	50	61	82	**Module 2, Section 2.7**
					Range	(b) (4)							
					%RSD	12.5	3.0	2.6	1.4	2.2	3.0	2.3	
-	05/14/2020	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: AK8368A Mfg. date: Not Applicable Exp. Date: Oct 2022	500 mg Controlled Release Capsule	12	Mean	6	12	23	44	61	75	90	
					Range	(b) (4)							
					%RSD	5.0	6.7	2.6	2.3	1.6	1.9	1.9	

Table 5 (b) (23) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (3967425 vs AK8368A) (pH 6.80 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II
	Speed of Rotation:	100 rpm
	Medium:	pH 6.80 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	**Testing Date** MM/DD/YYYY	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						30 minutes	**1 Hr**	**2 Hr**	**4 Hr**	**6 hr**	**8 Hr**	**12hr**	
-	04/05/2019	Mesalamine ER Capsules 500 mg Batch No: 3967425 Mfg. date: Aug, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	4	11	24	44	61	75	95	Module 2, Section 2.7
					Range							(b) (4)	
					%RSD	27.5	7.3	2.9	1.8	1.0	1.1	0.8	
-	05/13/2020	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: AK8368A Mfg. date: Not Applicable Exp. Date: Oct 2022	500 mg Controlled Release Capsule	12	Mean	6	13	28	52	71	84	96	
					Range							(b) (4)	
					%RSD	8.3	5.4	2.1	1.9	1.3	1.4	1.1	

Table 5 (b) (24) Summary of In Vitro Dissolution Studies (Multi-Media)
for 500 mg (3967425 vs AK8368A) (pH 7.20 phosphate buffer)

Dissolution Conditions	**Apparatus:**	USP Apparatus II
	Speed of Rotation:	100 rpm
	Medium:	pH 7.20 phosphate buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications		-
Dissolution Testing Site (Name, Address)		Sun Pharmaceutical Industries Limited/Research & Development Centre Sarhaul, Sector-18, Gurugram-122 015 Haryana, India (IND)

Study Ref No.	Testing Date MM/DD/YYYY	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						30 minutes	1 Hr	2 Hr	4 Hr	6 hr	8 Hr	12hr	
-	04/12/2019	Mesalamine ER Capsules 500 mg Batch No: 3967425 Mfg. date: Aug, 2018 Exp. Date: July, 2020	500 mg Extended Release Capsule	12	Mean	7	16	31	58	80	97	101	Module 2, Section 2.7
					Range	[redacted] (b) (4)							
					%RSD	7.1	3.1	2.9	1.9	2.0	1.3	1.0	
-	05/13/2020	Mesalamine CR Capsules (Pentasa Capsules) 500 mg Batch No: AK8368A Mfg. date: Not Applicable Exp. Date: Oct 2022	500 mg Controlled Release Capsule	12	Mean	10	20	39	69	89	96	101	
					Range	[redacted] (b) (4)							
					%RSD	5.0	2.5	1.5	1.4	0.6	0.9	0.9	

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

4.3.3 F2 Metric

F2 metric calculated?	☒ Yes (see table below) ☐ No
If no, reason why F2 not calculated	-

F2 Metric Test vs RLD (all strengths)

Strength(s)	RLD Batch #	Test Batch #	QC media (pH 7.5)	0.1 N HCl	pH 4.5	pH 6.0	pH 6.5	pH 6.8	pH 7.2
500 mg	5783929 (Bio-batch)	3967425 (Bio-batch)	77.15	51.36	64.87	56.30	52.31	55.78	64.08
		3968987	74.78						
		3965560	65.05						
		AB78176 (Bio-batch)	66.94						
	AK8368A (Bio-batch)	3967425 (Bio-batch)	67.05						
		3968987	57.88						
		3965560	73.77						
		AB78176 (Bio-batch)	54.58	75.27	82.53	91.02	91.02	71.57	72.84

(b) (4)

(b) (4)

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

Comment on In Vitro Comparative Dissolution Study for BE demonstration:

- The applicant submitted dissolution data in seven media (0.1N HCl, pH 4.5, pH 6.0, pH 6.5, pH 6.8, pH 7.2 and pH 7.5 buffers) as recommended in PSG. There is a USP recommended dissolution method Test 1 for this drug[68], as follows:

  Buffer: 0.05 M pH 7.5 phosphate buffer
  Apparatus 2: 100 rpm
  Times: 1, 2, 4, and 8 h
  Tolerances: 1 hr: 5-25%, 2 hrs: 30-50%, 4 hrs: 60-90% and 8 hrs: NLT 85%

- The applicant conducted the QC dissolution testing using USP method Test 1 as shown above. The QC dissolution testing is reviewed separately by OPQ for establishing the QC method and specifications for batch release[69], which is currently pending.

- (b) (4)

- As the pivotal BE studies were conducted using two sets of test and RLD products (i.e. Batches #3967425 (test) and #5783929 (RLD) for pivotal fasting and fed studies, Batches #AB78176 (test) and #AK8368A (RLD) for sprinkle fasting study), the applicant submitted dissolution data for these two sets of test/RLD in all 7 dissolution media. The dissolution profiles of these two test batches of bio-strength were considered comparable as indicated by the calculated f2 values >50 shown in the table below. However, it is noted that drug release of test bio-batch #3967425 is slower than the other test bio-batch and two RLD bio-batches.

Test (Bio-batch-1)	Test (Bio-batch-2)	QC Media (pH7.5)	0.1 N HCl	pH 4.5	pH 6.0	pH 6.5	pH 6.8	pH 7.2
3967425	AB78176	64.88	52.91	73.28	59.42	53.55	50.70	50.94

- As recommended in the PSG, for BE demonstration, based on the QC and multi-media dissolution testing data, the dissolution profiles are compared between the corresponding test and RLD products for both strengths in all media (f2 values >50).

[68] https://online.uspnf.com/uspnf/document/1_GUID-F44B5678-F9F2-4E44-BCA1-5C3DC5B0468D_3_en-US?source=Search%20Results&highlight=Mesalamine%20Extended-Release%20Capsules
[69] https://panorama.fda.gov/task/view?ID=6065bd6b003a4b41da97d0144b9970b1
[70] https://panorama.fda.gov/project/view?ID=5bc5fd6e001a78ca24bc20a1b040f08e

- However, the in vitro comparative dissolution study is still **inadequate** in perspective of bioequivalence of test and reference drug products pending submission of additional dissolution data at pH 4.5 and 6.0 as commented above.

Comments on In Vitro Dissolution Testing:

- (b) (4)

- There are several controlled correspondence documents which discussed dissolution testing for this product. In CC #081019[71], it stated that "*Rigorous dissolution testing is necessary because the in vivo dissolution of controlled release mesalamine capsules directly determines the rate and extent of delivery to the site of action, and dissolution testing is therefore necessary to demonstrate that test and reference products are targeting the same region of the gastrointestinal tract. Further, if in vitro dissolution is to serve as an appropriate surrogate for in vivo dissolution, it is critical that this dissolution testing be conducted, to the maximum extent feasible, using conditions that mimic those of the gastrointestinal tract. Thus, dissolution testing should be conducted over the range of pH values expected throughout the gastrointestinal tract, in order to demonstrate that the generic formulation releases mesalamine at the same rate as Pentasa under the range of conditions that occur in the gut*". In CC #120825[72], it stated that "*in vitro dissolution testing over a range of pH values reflecting conditions in the GI tract is necessary to show bioequivalence for the products*" as "*if a drug is intended to act locally rather than systemically, PK studies may be inadequate to demonstrate bioequivalence*" per CC#100151[73].

(b) (4)

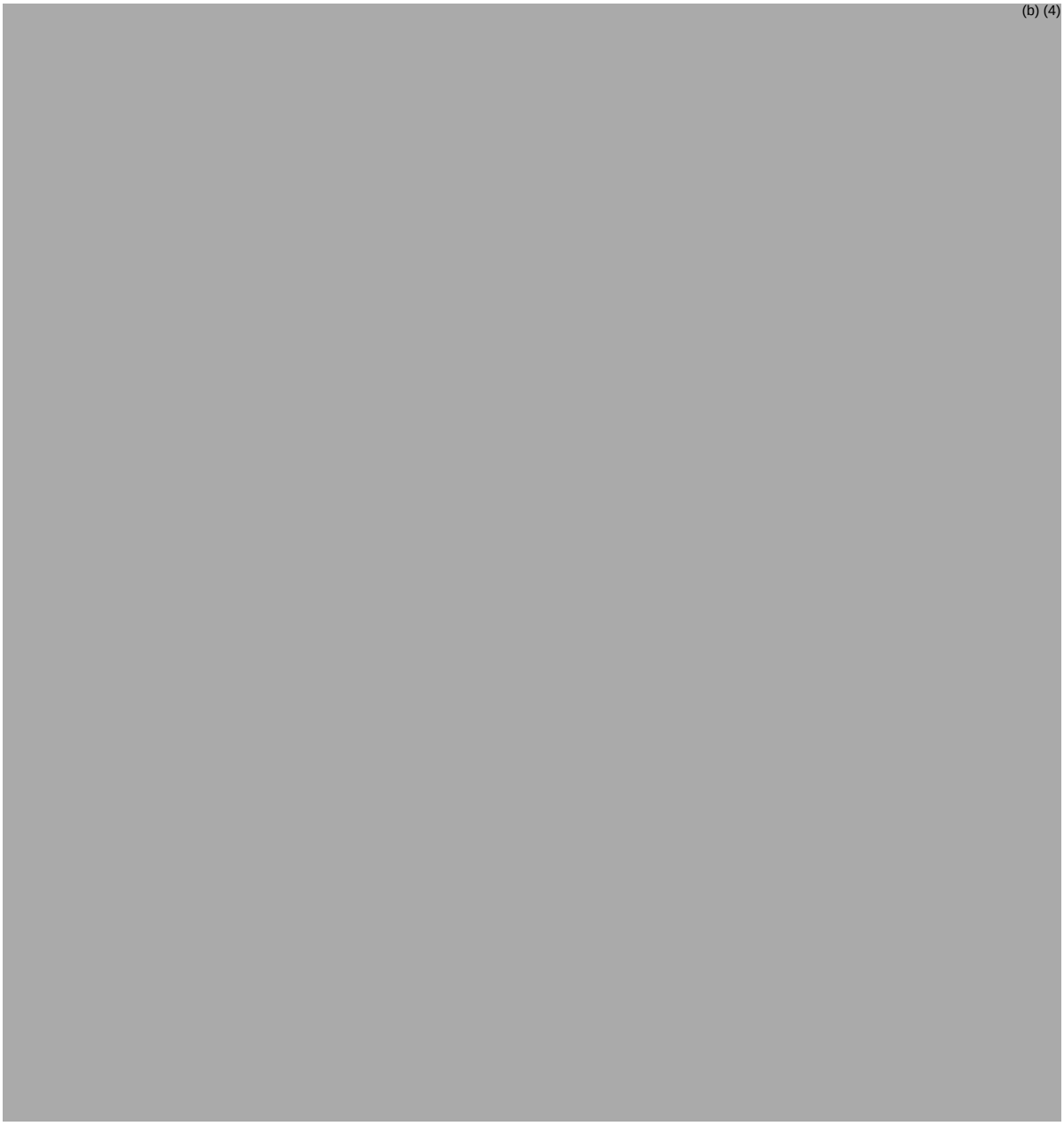
[71] https://ogd fda.gov/QDoc/RFS/Search
[72] https://ogd fda.gov/QDoc/RFS/Search
[73] https://ogd fda.gov/QDoc/RFS/Search

(b) (4)

- Per clinpharm review for NDA 020049, "*Based on the comparative dissolution profiles, the new Pentasa Extended Release Capsule, 500 mg is equivalent to the currently approved 250 mg Pentasa Extended Release Capsule*."[74] The dissolution testing was performed at pH 7.45 phosphate buffer (see below), which is similar to QC condition in the current ANDA.

(b) (4)

[74] DARRTS: NDA020049 Alfayoumi, Suliman 06/30/2004 Rev-Clinpharm-03 (General Review) https://darrts fda.gov/darrts/faces/ViewCommunication-task-flow/viewCommunication?_afrRedirect=565663039533903&_afrPage=3



- In vitro alcohol dose dumping testing is not recommended for this product and the applicant did not submit it.

- The applicant's in vitro dissolution testing is **inadequate**.

4.4 Attachments

4.4.1 SAS Output

Study	PKs	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	AUC0-3 AUC3-72	FastConcPK.xlsx	4wayreplicate-fast.sas	214585-ANALYSIS-Corrected.doc.rtf	
	AUC0-72 Cmax	FastConcPK.xlsx	A214585_4wayfullyreplicate(4PER2SEQ)_	214585-ANALYSIS.doc	214585-STAT OUTPUT.doc
Fed	AUC0-3 AUC3-72	FedConcPK.xlsx	4wayreplicate-fed.sas	214585-ANALYSIS.doc	
	AUC0-72 Cmax	FedConcPK.xlsx	A214585_4wayfullyreplicate(4PER2SEQ)_	214585-ANALYSIS.doc	214585-STAT OUTPUT.doc
Sprinkle	AUC0-3 AUC3-72	SprinkleConcPK.xlsx	HVRefScale4Per-Group Effect-ver1_Pval	214585-ANALYSIS-Corrected.doc.rtf	214585-STAT OUTPUT.doc
	AUC0-72 Cmax	SprinkleConcPK.xlsx	HVRefScale4Per-Group Effect-ver1_Pval	214585-ANALYSIS.doc	214585-STAT OUTPUT.doc

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	214585
APPLICANT:	Sun Pharmaceutical Industries Limited
DRUG PRODUCT:	Mesalamine Extended Release Capsules USP, (b) (4) 500 mg

The Division of Bioequivalence III (DBIII) has completed its review and your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Based on the dissolution data in your current submission, the release of mesalamine was incomplete for both test and reference listed drug (RLD) products in pH 4.5 and 6.0 media at the last time point of 12 hours. Please conduct new comparative dissolution testing for both strengths of test and RLD products at pH 4.5 and 6.0 conditions until at least 80% drug release is achieved (or a release plateau is reached).

2. You used two batches (Batch #3967425 and #AB78176) of test product in your pivotal bioequivalence (BE) studies. (b) (4)

3. In addition to three pivotal BE studies, you also conducted two failed fasting sprinkle BE studies (#BA19140131 and #BA19140426) using a four-way, fully replicate crossover design with 56 and 100 subjects dosed, respectively. The test batch (#3967425) used was the same as bio-batch in the pivotal fasting and fed BE studies. You indicated that the failure of these two fasting sprinkle BE studies might be due to the insufficient study power. Based on the BE summary tables submitted, it is noted that T/R ratios were lower than 0.80 for most of pharmacokinetic (PK) parameters. Please submit complete clinical, statistical and bioanalytical study reports (including the failed reasons) and concentration/PK datasets (in SAS transport format) for these two failed fasting sprinkle studies.

4. For your two pilot fed BE studies (#PKD_18_099 and #MSM_1000C_0536_17), please provide the details of all adverse events (AEs) observed during the study, including the severity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times.

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,

April C Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5. OUTCOME

COMPLETED ASSIGNMENT FOR 214585 ID: 45948

Reviewer:	Mao, Jason (Jinzhe)	**Date Completed:**
Verifier:	,	**Date Verified:**
Division:	Division of Bioequivalence	
Description:	ANDA214585-Mesalamine Extended Release Capsules USP, [redacted] (b) (4) 500 mg-Sun	

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
45948	8/6/2021	BIO	ANDA Original [1]	1	1
45948	8/6/2021	Parallel	Fasting Study [1]	1	1
45948	8/6/2021	Parallel	Fed Study [1]	1	1
45948	8/6/2021	Parallel	Sprinkle Study [1]	1	1
45948	8/6/2021	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
45948	8/6/2021	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
45948	8/6/2021	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
45948	8/6/2021	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
45948	8/6/2021	Parallel	Pre-Screening [0.25]	0.25	0.25

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	214585		
Drug Product Name	Mesalamine Extended-Release Capsules, USP		
Strength(s)	500 mg		
Applicant Name	Sun Pharmaceutical Industries Limited		
Applicant Address	Sun House, Plot No. 201 B/1 Western Express Highway, Goregaon (E) Mumbai, Maharashtra, India 400 063		
US Contact Name and US Mailing Address	Praveen Devakadaksham Sun Pharmaceutical Industries, Inc. 2 Independence Way Princeton, NJ 08540 Email: Praveen.devakadaksham@sunpharma.com		
US Contact Telephone Number	(b) (6)		
US Contact Fax Number	(609) 720-8503		
Original Submission Date(s)	03/31/2021 (Original submission)		
Submission Date(s) of Amendment(s) Under Review	10/20/2021 (Sequence0007, Response to DRL-BE and IRL-BE; (b) (4)		
Primary Reviewer	Jason Mao, Ph.D.		
Secondary Reviewer	Yi Zhang, Ph.D.		
Tertiary Reviewer	Wendy Cai, Ph.D.		
Study Number(s)	BA19140130	MSM_1000C_0652_18	BA19140473
Study Type(s)	Fasting	Fed	Sprinkle-Fasting
Strength(s)	2 x 500 mg	2 x 500 mg	2 x 500 mg
Clinical Site	Cliantha Research Limited	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited	Cliantha Research Limited
Clinical Site Address	Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India.	Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India	Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India

Analytical Site	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited			
Analytical Site Address	Plot No. GP-5, Sector-18, HSIDC Old Delhi-Gurugram Road, Gurugram 122 015, Haryana, India.			
Study Number(s)	PKD_18_099	MSM_1000C_0536_17	BA19140426	BA19140131
Study Type(s)	Fed (pilot)	Fed (pilot)	Fasting sprinkle (failed)	Fasting sprinkle (failed)
Strength(s)	2 x 500 mg	2 x 500 mg	2 x 500 mg	2 x 500 mg
Clinical Site	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited		Cliantha Research Limited	
Clinical Site Address	Near R. C. Patel Estate, Akota Road, Akota Vadodara- 390 020 (India)	Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India	Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India	
Analytical Site	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited			
Analytical Site Address	Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India			
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**		**Post October 1, 2014 ANDAs** ☐ **Pending** ☐ **Pending For Cause Inspection** ☒ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☒ **N/A**			
QC Dissolution	☐ **Pending** ☒ **Adequate**[1] ☐ **Inadequate**			
Formulation	☒ **Adequate** ☐ **Inadequate**			
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**			
Deficiency Classification	☐ **Major** ☐ **Minor** ☒ **N/A (Review is adequate)**			

[1] https://panorama.fda.gov/task/view?ID=6065bd6b003a4b41da97d0144b9970b1

Major Deficiency Theme	**N/A**		
Justification for Major Designation	**N/A**		
Overall Review Result	**☒ Adequate ☐ Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	**☒ Recommended/Latest Revision Date:** ***Recommended Sept 2012; Revised Jul 2014, Oct 2017*** **RLD/RS Number: NDA 020049** **☐ N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	**☐ YES ☒ NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
2	**Fasting**	**500 mg**	**☒ Adequate ☐ Inadequate**
2	**Fed**	**500 mg**	**☒ Adequate ☐ Inadequate**
2	**Sprinkle-Fasting**	**500 mg**	**☒ Adequate ☐ Inadequate**
2, 7	**In vitro Comparative Dissolution**	**500 mg**	**☒ Adequate ☐ Inadequate**

Review of an Amendment

I. Executive Summary

This is an assessment of a study amendment dated 10/20/2021 (Supporting Document #07/Seq0007) for Sun Pharmaceutical Industries Limited's Mesalamine Extended-Release (ER) Capsules, USP, (b) (4) 500 mg, in response to the bioequivalence (BE) Division Review Letter (DRL) dated 09/21/2021[2] and Information Request (IR) dated 10/14/2021[3].

In the original submission (dated 03/21/2021), the applicant submitted the results of three in vivo BE studies (i.e., fasting, fed and fasting sprinkle studies) comparing a test product, Sun Pharmaceutical Industries Limited's Mesalamine ER Capsules, 500 mg, to the corresponding reference listed drug (RLD) product, Shire Development Inc.'s Pentasa® (mesalamine) ER Capsules, 500 mg (NDA 020049). (b) (4) [redacted] In addition, as two bio-batches of test products were used in pivotal BE studies (i.e., Batch #3967425 for fasting and fed studies, and Batch #AB78176 for fasting sprinkle study), the applicant was asked to provide clarification with respects to any difference(s) between these two bio-batches through a BE IR dated 10/14/2021[5].

(b) (4) [redacted] Based on the complete study reports/datasets submitted, further analysis of study power and T/R ratios of PK parameters (absolute values, numbers of subjects with T/R ration < 0.8, between 0.8 and 1.2 and >1.2, and trends in change between test and RLD products) for the failed fasting sprinkle studies as compared to the pivotal fasting sprinkle study suggested that the failure may result from the low T/R ratio of PK parameters and the potentially insufficient study power. The increased T/R ratios in the pivotal fasting sprinkle study resulted from more increases in PK parameter values for the test product. No study integrity issue was discovered with DABERS analysis of the data for

[2] https://panorama.fda.gov/task/view?ID=6149e6f3000360adf584948e3a59670e
[3] https://panorama fda.gov/task/view?ID=6168749c0086d31fbf67b8dd359a79b2
[4] https://panorama fda.gov/task/view?ID=6065bd6b003a47b8c3095dfa09e292c9
[5] https://panorama fda.gov/task/view?ID=6168749c0086d31fbf67b8dd359a79b2

passing pivotal studies. In addition, in response to the BE IR, the applicant stated that there was no difference between two test bio-batches (b) (4) Therefore, the response to deficiencies related to in vivo BE studies and in vitro comparative dissolution study are now considered acceptable for the 500 mg strength.

As a result, the Division of Bioequivalence III (DBIII) deems the test product, Sun Pharmaceutical Industries Limited's Mesalamine Extended-Release (ER) Capsules, 500 mg, to be bioequivalent to the corresponding strength of the reference product, Shire Development Inc.'s Pentasa® (mesalamine) ER Capsules, 500 mg.

Office of Study Integrity and Surveillance (OSIS) Inspection "Complete":
Per the original BE assessment, the overall OSIS inspection status for the clinical and analytical sites for the current ANDA remain complete.

The BE portion of application is **adequate** with no deficiency.

II. **Table of Contents**

III. **Background Information**

- In the original submission (dated 03/21/2021), the applicant submitted the results of three pivotal in vivo BE studies (i.e., fasting, fed and fasting sprinkle studies) comparing a test product, Sun Pharmaceutical Industries Limited's Mesalamine ER Capsules, 500 mg, to the corresponding reference product, Shire Development Inc.'s Pentasa® (mesalamine) ER Capsules, 500 mg (b) (4) (b) (4) The RLD product is Shire Development Inc.'s Pentasa® (mesalamine) ER Capsules, 250 mg and 500 mg (NDA 020049; approved on May 10, 1993 for the 250 mg strength and July 8, 2004 for 500 mg strength, respectively). Each of the BE studies was designed as a single-dose, two-treatment, two-sequence, four-period, fully-replicated crossover study in healthy male subjects and considered adequate per original BE review.

- In addition, the applicant conducted two failed fasting sprinkled (Study # BA19140131, with 47 subjects completed, and Study # BA19140426, with 89 subjects completed) and two pilot fed BE studies (Study # PKD_18_099, with 22 subjects completed and Study # MSM_1000C_0536_17, with 15 subjects completed) in healthy male subjects. The formulation of the test product used in the failed fasting sprinkled and pilot fed studies is the same as that of test product used in the above three pivotal fasting, fed and sprinkled fasting studies.

- Per the original BE review, the application was considered inadequate with the following deficiencies:

    1. Incomplete release of mesalamine was observed for both test and RLD products in pH 4.5 and 6.0 media at the last time point of 12 hours.

    2. (b) (4)

    3. Incomplete submission of study data for the two failed fasting sprinkle BE studies (#BA19140131 and #BA19140426) and the two pilot fed BE studies (#PKD_18_099 and #MSM_1000C_0536_17).

- The above deficiencies were communicated to the applicant via a DRL (email dated 09/21/2021)[6].

- On 10/05/2021[7], the applicant submitted two questions through email regarding to DRL deficiency #2 prior to MRCM meeting. The applicant (1) intended to justify the non-

[6] https://panorama.fda.gov/task/view?ID=6149e6f3000360adf584948e3a59670e
[7] V:\DIVISION\BIO\BIO3\Email Communications\ANDA 214585-Mesalamine ER Capsules

comparable dissolution profiles in multi-pH media using the acceptable window (b) (4) (b) (4) of QC specifications for the dissolution testing, and (2) (b) (4) (b) (4).

- On 10/06/2021[8], a MRCM was held to provide review status updates by the midpoint of the first cycle review. For the two MCRM questions submitted by the applicant, for question#1, DBIII agreed to provide a written response incorporated into the meeting minutes if possible. For question#2, DBIII informed the applicant there was no issue from BE standpoint if they only seek for approval of the 500 mg strength of test product as long as all the BE criteria are met after reviewing their DRL response.

- As a commitment, DBIII drafted written responses to the aforementioned MRCM questions (document available in GDRP)[9]. However, as further communicated with the applicant by RPM, (b) (4) (b) (4)

- On 10/14/2021[11], a written response with information request (IR) was sent to the applicant via email.

- On 10/20/2021, the applicant submitted the current amendment in response to the above deficiency comments in the DRL dated 09/21/2021 and IR letter dated 10/14/2021.

IV. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DB History

The PK/PD information and relevant DB history have not been changed since the original BE review below was conducted.

For details, please refer to the following previous BE reviews[12]:
GDRP, ANDA 214585, Bioequivalence Discipline Review, A214585N000DB-Review01-03322021.docx uploaded on 09/20/2021.

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[8] https://panorama.fda.gov/task/view?ID=6065bd6b003a4a19936e0849334fd784
[9] A214585N000DB-Response01-MRCM10062021.docx;
https://panorama.fda.gov/task/view?ID=6065bd6b003a47b8c3095dfa09e292c9
[10] V:\DIVISION\BIO\BIO3\Email Communications\ANDA 214585-Mesalamine ER Capsules
[11] https://panorama.fda.gov/task/view?ID=6168749c0086d31fbf67b8dd359a79b2
[12] https://panorama.fda.gov/task/view?ID=6065bd6b003a47b8c3095dfa09e292c9

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	-
Waiver requests	No	-
BCS Waivers	No	-
Clinical Endpoints	No	-
Other Studies (in vitro)	No	-
Equilibrium Binding	No	-
Kinetic Binding	No	-
Amendments	Yes	1

C. Review of Amendment Submissions

The applicant's response to the DRL deficiencies and the assessor's evaluation of the responses are provided in this section of the review.

Deficiency #1: *Based on the dissolution data in your current submission, the release of mesalamine was incomplete for both test and reference listed drug (RLD) products in pH 4.5 and 6.0 media at the last time point of 12 hours. Please conduct new comparative dissolution testing for both strengths of test and RLD products at pH 4.5 and 6.0 conditions until at least 80% drug release is achieved (or a release plateau is reached).*

Applicant's Response to Deficiency #1: SPIL has conducted new comparative dissolution testing for 500 mg strength of test and RLD products at pH 4.5 and 6.0 conditions until at least 80% drug release is achieved or a release plateau is reached. Details have been included in Addendum-5 to Product Development Report provided in Module 3, Section 3.2.P.2, which was extracted as shown below:

Time (hrs)	**pH 4.50 acetate buffer, 900 ml, 100 rpm, USP-II, Paddle**					
	Ref: AK1614B - 500 mg (Pentasa® (mesalamine) Controlled-Release Capsules			**Test: AB78176 - 500 mg (Mesalamine ER Capsules USP)**		
	Expiry June 2022			**Expiry June 2022**		
	Mean (n=12)	%RSD	Range	Mean (n=12)	%RSD	Range
0.5	2	25.0	(b) (4)	2	0.0	(b) (4)
1	5	8.0		5	0.0	
2	10	5.0		11	4.5	
4	21	2.9		20	2.0	
6	31	1.6		29	1.7	
8	39	1.0		35	1.1	
12	54	1.5		46	1.1	
16	66	1.1		55	1.3	
20	75	1.1		62	1.1	

24	84	0.8	(b) (4)	69	1.0	(b) (4)
30	91	0.9		77	0.6	
36	96	0.7		81	0.9	
40	99	0.8		83	1.0	

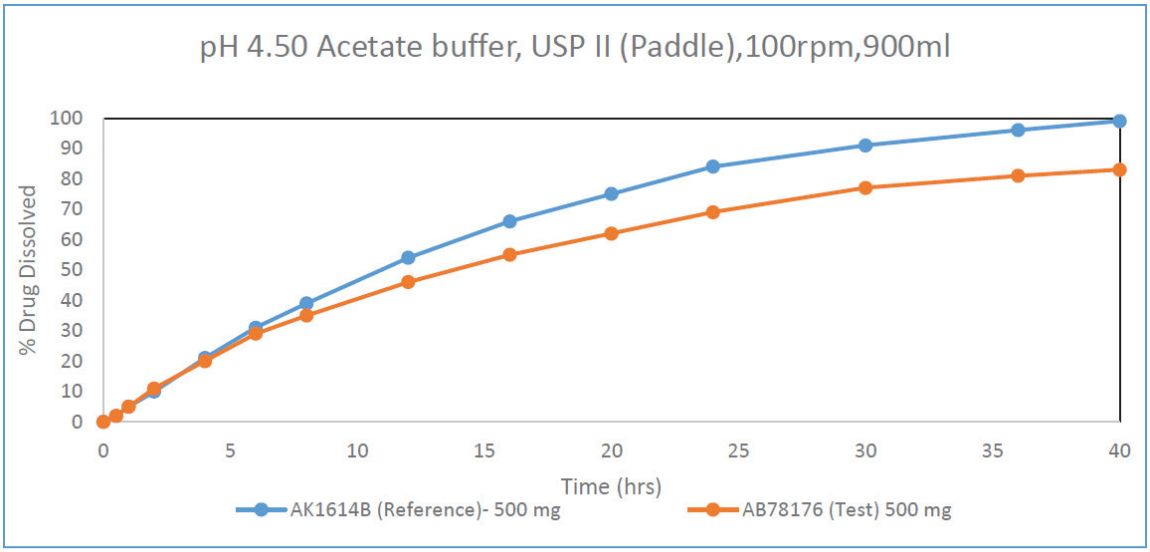


Figure 1: Comparative dissolution profile of test and RLD in pH 4.50 acetate buffer

Time (hrs)	pH 6.00 phosphate buffer, 900 ml, 100 rpm, USP-II, Paddle					
	Ref: AK1614B - 500 mg (Pentasa® (mesalamine) Controlled-Release Capsules			Test: AB78176 - 500 mg (Mesalamine ER Capsules USP)		
	Expiry June 2022			Expiry June 2022		
	Mean (n=12)	%RSD	Range	Mean (n=12)	%RSD	Range
0.5	2	25.0	(b) (4)	2	25.0	(b) (4)
1	6	8.3		6	8.3	
2	12	3.3		12	5.0	
4	23	1.7		22	2.3	
6	33	1.2		31	1.6	
8	42	1.4		39	1.5	
12	56	1.3		52	1.2	
16	66	1.4		62	1.6	
20	74	1.1		71	1.4	
24	79	1.1		75	0.8	
30	83	0.8		79	0.9	
36	84	1.2		79	1.3	
40	83	1.1		79	1.1	

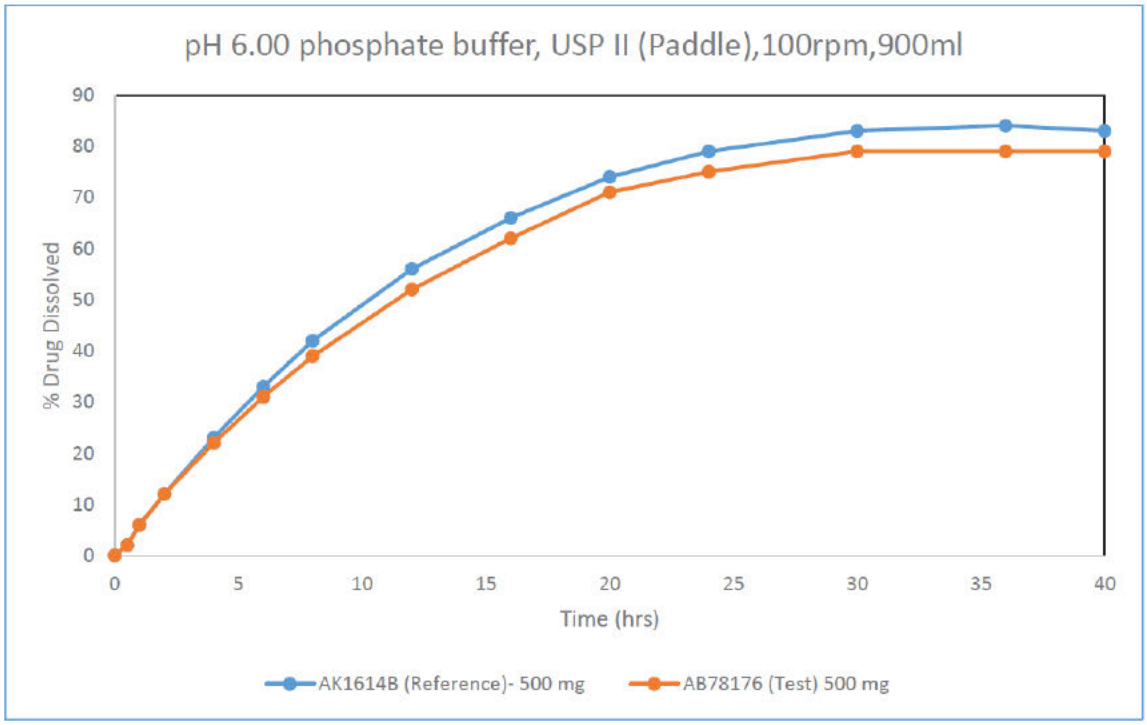


Figure 2 : Comparative dissolution profile of test and RLD in pH 6.00 phosphate buffer

Assessor's Comments on Applicant's Response to Deficiency #1:

- The applicant conducted new comparative dissolution testing for (b) (4) strengths of test (Lot #AB78176) and RLD (Lot #AK1614B) products at pH 4.5 and 6.0 until at least 80% drug release was achieved or release plateau was reached around 30-40 hours. The test lot used for the new dissolution testing was the same lot used in pivotal fasting sprinkle BE study. Both test and RLD lots were within expiration dates (06/2022 for Lot #AB78176 and 10/2022 for Lot #AK1614B). The dissolution profiles were comparable between test and RLD. The calculated f2 values of test vs RLD were 50.08 and 74.12 at pH 4.5 and 6.0, respectively (see table below for summary based on the current dissolution data). Therefore, the in vitro comparative dissolution testing results are now considered acceptable in all seven media (including pH 4.5 and pH 6.0) as recommended in current PSG to support BE for the 500 mg strength of test product.

F2 Metric Test vs RLD for 500 mg strength (by assessor)

Strength(s)	RLD Batch #	Test Batch #	QC media (pH 7.5)	0.1 N HCl	pH 4.5	pH 6.0	pH 6.5	pH 6.8	pH 7.2
500 mg	5783929 (Bio-batch)	3967425 (Bio-batch)	77.15	51.36	NA*	NA*	52.31	55.78	64.08
		3968987	74.78						
		3965560	65.05						
		AB78176 (Bio-batch)	66.94						
	AK8368A (Bio-batch)	3967425 (Bio-batch)	67.05						
		3968987	57.88						

		3965560	73.77						
		AB78176 (Bio-batch)	54.58	75.27	NA*	NA*	91.02	71.57	72.84
	AK1614B				50.08	74.12			

Assessor's Note: No f2 was calculated due to incomplete release, and new dissolution data submitted in current amendment.

- [redacted] (b) (4)

- The applicant's response to the Deficiency #1 is adequate.

Deficiency #2: *You used two batches (Batch #3967425 and #AB78176) of test product in your pivotal bioequivalence (BE) studies.* [redacted] (b) (4)

Applicant's Response to Deficiency #2: [redacted] (b) (4)

Assessor's Comments on Applicant's Response to Deficiency #2:

- [redacted] (b) (4)

- The applicant's response to Deficiency #2 is considered acceptable.

Deficiency #3: *In addition to three pivotal BE studies, you also conducted two failed fasting sprinkle BE studies (#BA19140131 and #BA19140426) using a four-way, fully replicate crossover design with 56 and 100 subjects dosed, respectively. The test batch (#3967425) used was the same as bio-batch in the pivotal fasting and fed BE studies. You indicated that the failure of these two fasting sprinkle BE studies might be due to the insufficient study power. Based on the BE summary tables submitted, it is noted that T/R ratios were lower than 0.80 for most of pharmacokinetic (PK) parameters. Please submit complete clinical, statistical and bioanalytical study reports (including the failed reasons) and concentration/PK datasets (in SAS transport format) for these two failed fasting sprinkle studies.*

Applicant's Response to Deficiency #3: The complete clinical, statistical and bioanalytical study reports and concentration/PK datasets (in SAS transport format) for these two failed fasting sprinkle studies (#BA19140131 and #BA19140426) have been provided in module 5. The Rationale for Repeat Bioequivalence Study under Fasting Apple

Sauce Condition was included in the document "mesalaminerationaleapplesauce" provided in module 2, section 2.7 (eCTD sequence 0002).

Assessor's Comments on Applicant's Response to Deficiency #3:

- The assessor checked and verified that the applicant submitted complete clinical, statistical and bioanalytical study reports (including the failed reasons, i.e., high pharmacokinetic variability) and concentration/PK datasets (in SAS transport format) for these two failed fasting sprinkle studies (#BA19140131 and #BA19140426) in the current amendment submission.

(b) (4)

[redacted]

- There was no serious adverse (AE) event reported in both studies. A total of five AEs were reported by five subjects in #BA19140131 and ten AEs by ten subjects in #BA19140426. All AEs were mild to moderate in severity.

- There is no PK repeat in the failed fasting sprinkle BE studies. As verified by assessor, the bioanalytical data submitted by the applicant including the repeat analysis are acceptable.

- The assessor conducted SAS analysis with the datasets submitted by the applicant in its response. The results are discussed as below.

    - For study #BA19140131, the assessor performed the statistical analysis using HVScale4Period.SAS program (18 March 2009) to obtain the results of the PK parameters, pAUC0-3, pAUC3-72, AUC0-t and Cmax as shown below.

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Mesalamine (No of subjects completed=52) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – BA19140131					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
$LAUC_{0-3}$ (hr. ng/mL)	1566.59	1954.29	0.80	68.57	93.71
$LAUC_{3-72}$ (hr. ng/mL)	1826.15	2501.82	0.73	66.86	79.68
$LAUC_{0-72}$ (hr. ng/mL)	3618.99	4783.99	0.76	69.78	82.01
LCMAX (ng/mL)	1428.44	1743.51	0.82	72.68	92.35

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
$LAUC_{0-3}$ (hr. ng/mL)	0.7964	68.57	93.71	0.3921354	0.6262072	-0.12843	Scaled/PE	FAIL
$LAUC_{3-72}$ (hr. ng/mL)	0.71	66.86	79.68	0.1530321	0.3911931	0.0699758	Scaled/PE	FAIL
$LAUC_{0-72}$ (hr. ng/mL)	0.75	69.78	82.01	0.1296672	0.3600933	0.046188	Scaled/PE	FAIL
LCMAX (ng/mL)	0.80	72.68	92.35	0.2860945	0.534878	-0.085086	Scaled/PE	PASS

The results of statistical analysis show that the within-subject variability of the reference product (sWR) for AUC0-3, AUC3-72, AUC0-72 and Cmax pharmacokinetic (PK) parameters are all greater than 0.294. Therefore, the reference scaled average BE criteria were applied to evaluate AUC0-3, AUC3-t, AUC0-72 and Cmax for mesalamine in the fasting sprinkle BE study. Only Cmax meets the BE criteria, while AUC0-3, AUC3-t and AUC0-t all failed to meet the acceptance criteria of RSABE.

The applicant proposed that "the pool of 47 subjects may not be sufficient to prove bioequivalence"[13], which is in line with the analysis result the observed intrasubject variability (RMSE from SAS analysis = 0.69294) and T/R ratio (T/R =1.2) conducted by Dr. Dev Patel as shown below.

[13] \\CDSESUB1\evsprod\anda214585\0002\m2\27-clin-sum\mesalaminerationaleapplesauce.pdf

```
> sampleN.RSABE(targetpower=0.8, theta0=1.2, CV=0.692924,design="2x2x4")

++++++++ Reference scaled ABE crit. +++++++++
           Sample size estimation
---------------------------------------------
Study design: 2x2x4 (4 period full replicate)
log-transformed data (multiplicative model)
1e+05 studies for each step simulated.

alpha  = 0.05, target power = 0.8
CVw(T) = 0.692924; CVw(R) = 0.692924
True ratio = 1.2
ABE limits / PE constraints = 0.8 ... 1.25
FDA regulatory settings
- CVswitch            = 0.3
- regulatory constant = 0.8925742
- pe constraint applied


Sample size search
 n     power
168   0.79937
170   0.80069
```

POWER WITH SAMPLE SIZE OF 47

```
> power.RSABE(CV=0.692924, theta0=1.2, n=47, design="2x2x4")
Unbalanced design. n(i)=24/23 assumed.
[1] 0.66987
```

Based on the preliminary analysis, despite the low T/R ratio, even the true ratio value was set as 1.2, a minimum of 170 subjects would be required to meet the sufficient power for the study. Therefore, it is likely that the study power was not sufficient in the sprinkle fasting study. The applicant conducted another sprinkle fasting study (#BA19140426) by increasing subject numbers.

- In study #BA19140426, a total of 100 subjects were dosed in two groups and 89 subjects completed the study. First, the assessor performed PK analysis with a SAS code (HVScale4Period-group effect.SAS) to test group effect. Significant treatment*group effect was found ($p<0.1$) for the PK parameters Cmax ($p=0.0024$), AUC0-3 ($p=0.0292$), AUC3-72 ($p=0.0768$), and AUCT ($p=0.0082$). Therefore, the SAS analysis was conducted with data combined (trt*grp=1) or as two separate groups as shown below:

SUMMARY OF STATISTICAL ANALYSIS for All Subjects Combined - UNSCALED DATA

Mesalamine (No of subjects completed=94) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – BA19140426					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
$LAUC_{0-3}$ (hr. ng/mL)	1135.38	1370.01	0.83	76.88	89.34
$LAUC_{3-72}$ (hr. ng/mL)	1774.95	2401.06	0.74	69.25	78.91
$LAUC_{0-72}$ (hr. ng/mL)	3074.28	3988.18	0.77	73.04	81.35
LCMAX (ng/mL)	1054.45	1266.37	0.83	77.46	89.50

SUMMARY OF STATISTICAL ANALYSIS for All Subjects Combined - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
$LAUC_{0-3}$ (hr. ng/mL)	0.83	76.88	89.34	0.1938977	0.4403381	-0.070651	Scaled/PE	PASS
$LAUC_{3-72}$ (hr. ng/mL)	0.73	69.25	78.91	0.1390779	0.3729316	0.0366972	Scaled/PE	FAIL
$LAUC_{0-72}$ (hr. ng/mL)	0.77	73.04	81.35	0.1031588	0.3211835	0.0253476	Scaled/PE	FAIL
LCMAX (ng/mL)	0.82	77.46	89.50	0.1767738	0.4204447	-0.058969	Scaled/PE	PASS

SUMMARY OF STATISTICAL ANALYSIS for Group 1 Subjects - UNSCALED DATA

Mesalamine (No of subjects completed=47) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – BA19140426					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
$LAUC_{0-3}$ (hr. ng/mL)	1026.09	1368.71	0.75	67.03	83.84
$LAUC_{3-72}$ (hr. ng/mL)	1832.81	2659.55	0.69	62.43	76.07
$LAUC_{0-72}$ (hr. ng/mL)	2989.62	4230.55	0.71	65.30	76.47
LCMAX (ng/mL)	949.10	1305.05	0.73	65.21	81.11

SUMMARY OF STATISTICAL ANALYSIS for Group 1 Subjects - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
$LAUC_{0-3}$ (hr. ng/mL)	0.74	67.03	83.84	0.2118396	0.4602603	0.0153616	Scaled/PE	FAIL
$LAUC_{3-72}$ (hr. ng/mL)	0.68	62.43	76.07	0.1423324	0.3772697	0.1325658	Scaled/PE	FAIL
$LAUC_{0-72}$ (hr. ng/mL)	0.69	65.30	76.47	0.1045139	0.3232861	0.1170312	Scaled/PE	FAIL
LCMAX (ng/mL)	0.70	65.21	81.11	0.1866663	0.432049	0.0712672	Scaled/PE	FAIL

SUMMARY OF STATISTICAL ANALYSIS for Group 2 Subjects - UNSCALED DATA

Mesalamine (No of subjects completed=47) Dose [1 × 1000 mg (2 Capsules of 500 mg)] Least Squares Geometric Means and Ratio of Means and 90% Confidence Intervals Fasting Bioequivalence Study – BA19140426					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
$LAUC_{0-3}$ (hr. ng/mL)	1256.37	1371.32	0.92	82.55	101.68
$LAUC_{3-72}$ (hr. ng/mL)	1718.96	2167.20	0.79	72.50	86.77
$LAUC_{0-72}$ (hr. ng/mL)	3159.44	3757.99	0.84	77.92	90.71
LCMAX (ng/mL)	1171.49	1228.11	0.95	86.50	105.19

SUMMARY OF STATISTICAL ANALYSIS for Group 2 Subjects - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
$LAUC_{0-3}$ (hr. ng/mL)	0.92	82.55	101.68	0.176373	0.4199679	-0.087508	Scaled/PE	PASS
$LAUC_{3-72}$ (hr. ng/mL)	0.79	72.50	86.77	0.1358992	0.3686451	0.0027078	Scaled/PE	FAIL
$LAUC_{0-72}$ (hr. ng/mL)	0.84	77.92	90.71	0.1018353	0.3191164	-0.013657	Scaled/PE	PASS
LCMAX (ng/mL)	0.96	86.50	105.19	0.1671113	0.4087925	-0.0931	Scaled/PE	PASS

The result of statistical analysis shows that the within-subject variability values of the reference product (sWR) for AUC0-3, AUC3-72, AUC0-t and Cmax PK parameters in subjects combined and both groups are all greater than 0.294. Therefore, Reference-Scaled Average BE approach was used to determine BE. The outcome of the statistical analysis for AUC3-72 and AUC0-t in subjects combined and AUC0-3, AUC3-72, AUC0-t and Cmax PK parameters in group 1 and AUC3-72 in group 2 using reference scaled average BE approach failed to meet the reference scaled average BE criteria since test/reference ratios fell outside of the acceptance range of 0.80-1.25, and the 95% upper confidence bounds were all positive. Only AUC0-3 and Cmax in subjects combined and AUC0-3, AUC0-t and Cmax PK parameters in group 2 met the reference scaled average BE criteria. Thus, the study was failed.

- It has been noted that the T/R ratios for PK parameters in both failed fasting sprinkle studies were relatively low, while the T/R ratios in the pivotal fasting sprinkle study were within acceptable range of 0.8-1.2 as shown below.

T/R Ratio	#BA19140131 (Failed)	#BA19140426 (Failed)			#BA19140473 (Pivotal)
		Whole	Group #1	Group #2	
AUC_{0-72}	0.75	0.77	0.69	0.84	1.01
AUC_{0-3}	0.8	0.83	0.74	0.92	1.13
AUC_{3-72}	0.71	0.73	0.68	0.79	1.05
C_{max}	0.8	0.82	0.7	0.96	1.1

- The distribution of T/R ratio was analyzed for the three fasting sprinkle studies as shown below. It could be observed that the T/R ratio was increased globally for the passed pivotal fasting sprinkle study.

PK	Number of Subjects with T/R ratio			Total # of Subjects	% of Subjects with T/R ratio		
	<0.8	>0.8 but <1.2	>1.2		<0.8	>0.8 but <1.2	>1.2
	BA19140131 (Failed)						
AUC_{0-3}	23	17	12	52	44.23	32.69	23.08
AUC_{3-72}	31	15	6	52	59.62	28.85	11.54
AUC_{0-72}	30	18	4	52	57.69	34.62	7.69
Cmax	21	23	8	52	40.38	44.23	15.38

	BA19140426 (Failed)						
AUC_{0-3}	43	33	18	94	45.74	35.11	19.15
AUC_{3-72}	53	36	5	94	56.38	38.30	5.32
AUC_{0-72}	54	33	7	94	57.45	35.11	7.45
Cmax	48	25	21	94	51.06	26.60	22.34
	BA19140473 (Passed)						
AUC_{0-3}	30	49	62	141	21.28	34.75	43.97
AUC_{3-72}	36	67	38	141	25.53	47.52	26.95
AUC_{0-72}	23	72	46	141	16.31	51.06	32.62
Cmax	28	61	52	141	19.86	43.26	36.88

- Further data analysis was performed on the applicant's passed pivotal and failed fasting sprinkle studies to determine the source of low T/R for PK parameters. Overall, as compared to the failed studies (especially the 2nd failed study #BA19140426 with larger subject numbers), the AUC and Cmax values in the pivotal study increased for both test product and RLD, with more increase for the test product.

  In the passed pivotal fasting sprinkle study, the test product had 24-47% increase in AUC and 16% increase in Cmax compared to the 1st failed fasting sprinkle study and 49-83% increase in AUC and 67% increase in Cmax compared to the 2nd failed fasting sprinkle study. The reference product in the passed pivotal fasting sprinkle study had a small change in AUC (5% increase to 12% decrease) and Cmax (12% decrease) compared to the 1st failed fasting sprinkle study and 10-30% increase in AUC and 27% increase in Cmax compared to the 2nd failed fasting sprinkle study.

PK Parameters	Test			RLD		
	#BA19140131 (Failed)	#BA19140426 (Failed)	#BA19140473 (Pivotal)	#BA19140131 (Failed)	#BA19140426 (Failed)	#BA19140473 (Pivotal)
AUC_{0-3}	1970.96	1334.56	2442.66	2475.85	1668.08	2167.58
AUC_{3-72}	2110.05	2074.97	3096.34	2938.73	2808.62	3092.98
AUC_{0-72}	4081.01	3409.52	5539.00	5414.57	4476.70	5260.56
C_{max}	1740.57	1209.56	2024.76	2080.82	1445.08	1840.11

- These results indicated that the increased T/R ratios in the passed pivotal fasting sprinkle study are due to more increase of PK parameter values for the test product.

(b) (4)

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

- Based on the above stick plots, no significant difference was observed in number of subjects with extremely increased/decreased values between test and RLD treatment across the studies.

- To assess whether any study integrity issue in the pivotal studies, Dr. Dev Patel conducted DABERS analysis for the three pivotal studies (i.e., fasting, fed and fasting sprinkle BE studies)[14]. Although four pairs of common profiles (b) (6) (b) (6)) were detected by DABERS in the pivotal fasting study, these profiles are not considered as superimposable or very similar by visually inspecting. Similarly, one pair of common profiles (b) (6) were detected in the pivotal fed study but not considered as similar or superimposable. Also, no similar profiles were detected in the pivotal sprinkle fasting study. In addition, there are no unusual PK trends found in all three pivotal studies. Therefore, the DABERS analysis suggested that integrity concern for the pivotal studies was minimal.

- (b) (4) . Therefore, these two bio-batches were considered acceptable.

- The applicant's response to Deficiency #3 is considered adequate.

Deficiency #4: *For your two pilot fed BE studies (#PKD_18_099 and #MSM_1000C_0536_17), please provide the details of all adverse events (AEs) observed during the study, including the severity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times.*

[14] V:\DIVISION\BIO\DABERS Evaluation\Jason 214585
[15] V:\DIVISION\BIO\BIO3\Email Communications\ANDA 214585-Mesalamine ER Capsules
[16] https://panorama.fda.gov/task/view?ID=6065bd6b003a4ab8f0724ba5e7f2ff1d

Applicant's Response to Deficiency #4: Adverse event tables detailing all adverse events (AEs) observed during the study, including the severity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times for pilot fed BE studies (MSM_1000C_0536_17 and PKD_18_099) have been provided as Annexure-01 and Annexure-02 to this response, respectively.

Assessor's Comments on Applicant's Response to Deficiency #4:

- The assessor checked and verified that the applicant submitted adverse event (AE) tables detailing all AEs for the two pilot fed studies (i.e. # MSM_1000C_0536_17 and PKD_18_099) in the current amendment submission.

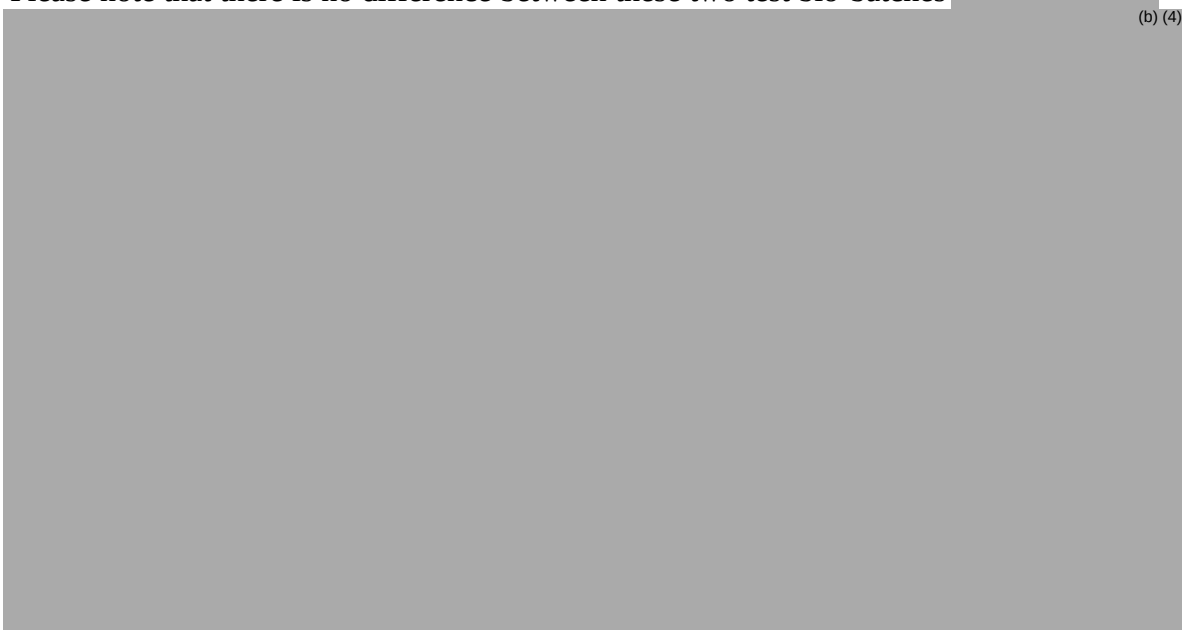
- There was no serious adverse event reported in both studies. A total of 12 AEs were reported by 10 subjects in #MSM_1000C_0536_17 and 4 AEs by 2 subjects in #PKD_18_099. All AEs were mild to moderate in severity.

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

BE IR issued on 10/14/2021: *Based on your submitted information, since two different bio-batches of test product were used in your pivotal fasting and fed BE studies (Bio-Batch #3967425) and your pivotal sprinkle study (Bio-Batch #AB78176), please provide your clarification with respects to any difference(s) between these two test bio-batches (including those in the manufacturing process and the in-process control if applicable). You may provide the requested information along with your responses to the discipline review letter (DRL) deficiencies.*

Applicant's Response to the BE IR: Two different bio-batches of test product were used in SPIL's pivotal fasting and fed BE studies (Bio-Batch #3967425; henceforth called batch #425) and pivotal sprinkle study (Bio-Batch #AB78176; henceforth called batch #176). Please note that there is no difference between these two test bio-batches (b) (4)

(b) (4)



(b) (4)

Kindly refer Module 3, sections 3.2.P.3.3 and 3.2.P.3.4 (eCTD sequence 0005). As can be seen, the observations for batch #425 and #176 are identical.

(b) (4)

Assessor's Comments on Applicant's IR Response:

- The applicant reaffirmed that there is no difference between these two test bio-batches (i.e., Bio-Batch #3967425; henceforth called batch #425 used in SPIL's pivotal fasting and fed BE studies and Bio-Batch #AB78176; henceforth called batch #176 in pivotal fasting sprinkle study), (b) (4)

(b) (4)

.

- Per drug product review by OPQ, (b) (4) [17] In addition, OPQ confirmed that they "*do not find the significant deviations from the predeterminated acceptance ranges*" and "*there was no impact to drug product quality with this minor change*" for these two bio-batches[18]. Both bio-batches #3967425 and #AB78176 have been considered adequate from quality perspective.

- Therefore, the applicant's response to Deficiency in IR is adequate.

D. Additional Attachment

NA

[17] https://panorama.fda.gov/task/view?ID=6065bd6b003a4ab8f0724ba5e7f2ff1d Pages 16 and 30 of 34.
[18] V:\DIVISION\BIO\BIO3\Email Communications\ANDA 214585-Mesalamine ER Capsules

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	214585
APPLICANT:	Sun Pharmaceutical Industries Limited
DRUG PRODUCT:	Mesalamine Extended-Release Capsules USP, 500 mg

The Division of Bioequivalence III (DBIII) 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 after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Generic Drugs
Center for Drug Evaluation and Research

E. Outcome Page

Completed Assignment for 214585 ID: 46707

Reviewer: Mao, Jason (Jinzhe) **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: ANDA214585-Mesalamine Extended Release Capsules USP, (b) (4) 500 mg-Sun-DRL Response

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
46707	11/9/2021	BIO	ANDA Amendment [1]	1	1
46707	11/9/2021	Parallel	Minor Amendment (Original or Supplement) [1]	1	1
				Total:	2

Deficiency #2 in the Division of Bioequivalence III (DBIII)'s Discipline Review Letter (DRL) issued on 09/22/2021:

You used two batches (Batch #3967425 and #AB78176) of test product in your pivotal bioequivalence (BE) studies. [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

[redacted]

Therefore, your intention of using QC specifications for finished product to justify the observed differences in drug release (f2 <50) between the two test product strengths is not acceptable from BE perspectives. Please address deficiency #2 in the BE discipline review letter (DRL) dated 09/22/2021.

In addition, since two different bio-batches of test product were used in your pivotal fasting and fed BE studies (Bio-Batch #3967425) and your pivotal fasting sprinkle study (Bio-Batch #AB78176), please clarify in your DRL response with respects to any difference(s) between these two test bio-batches (including those in the manufacturing process if applicable).

(b) (4)

[redacted]

(b) (4)

DBIII's Response to Question B:

(b) (4)

. For the question if it is needed to update labelling section, we will defer the question to the Labelling team. You may submit a separate request to the Division of Labelling Review.

DIVISION OF BIOEQUIVALENCE

Information Request (IR)

ANDA No.	214585		
Drug Product Name	Mesalamine Extended-Release Capsules, USP		
Strength(s)	(b) (4) 500 mg		
Applicant Name	Sun Pharmaceutical Industries Limited		
Applicant Address	Sun House, Plot No. 201 B/1 Western Express Highway, Goregaon (E) Mumbai, Maharashtra, India 400 063		
US Contact Name and US Mailing Address	Praveen Devakadaksham Sun Pharmaceutical Industries, Inc. 2 Independence Way Princeton, NJ 08540 Email: Praveen.devakadaksham@sunpharma.com		
US Contact Telephone Number	(b) (6)		
US Contact Fax Number	(609) 720-8503		
Original Submission Date(s)	03/31/2021		
Submission Date(s) of Amendment(s) Under Review	N/A		
Primary Reviewer	Jason Mao, Ph.D.		
Secondary Reviewer	Yi Zhang, Ph.D.		
Tertiary Reviewer	Wendy Cai, Ph.D.		
Study Number(s)	BA19140130	MSM_1000C_0652_18	BA19140473
Study Type(s)	Fasting	Fed	Sprinkle-Fasting
Strength(s)	2 x 500 mg	2 x 500 mg	2 x 500 mg
Clinical Site	Cliantha Research Limited	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited	Cliantha Research Limited
Clinical Site Address	Property No 2A, Block A Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India.	Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India	Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India
Analytical Site	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited		

Analytical Site Address	Plot No. GP-5, Sector-18, HSIDC Old Delhi-Gurugram Road, Gurugram 122 015, Haryana, India.			
Study Number(s)	PKD_18_099	MSM_1000C_0536_17	BA19140426	BA19140131
Study Type(s)	Fed (pilot)	Fed (pilot)	Fasting sprinkle (failed)	Fasting sprinkle (failed)
Strength(s)	2 x 500 mg	2 x 500 mg	2 x 500 mg	2 x 500 mg
Clinical Site	Clinical Services Clinical Pharmacology Unit Sun Pharmaceutical Industries Limited		Cliantha Research Limited	
Clinical Site Address	Near R. C. Patel Estate, Akota Road, Akota Vadodara- 390 020 (India)	Hakeem Abdul Hameed Centenary Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062, India	Property No 2A, Block A, Sector 63, Gautambudh Nagar, Noida - 201 301, Uttar Pradesh, India	
Analytical Site	Clinical Pharmacology & Pharmacokinetics Sun Pharmaceutical Industries Limited			
Analytical Site Address	Plot No. GP-5, Sector 18, Udyog Vihar Industrial Area, HSIDC Old Delhi – Gurugram Road Gurugram 122 015, Haryana, India			
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**		**Post October 1, 2014 ANDAs** ☐ **Pending** ☐ **Pending For Cause Inspection** ☒ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**			
QC Dissolution	☒ **Pending**[1] ☐ **Adequate** ☐ **Inadequate**			
Formulation	☒ **Adequate** ☐ **Inadequate**			
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**			
Deficiency Classification	☐ **Major** ☒ **Minor/IRL** ☐ **N/A**			
Major Deficiency Theme	**N/A**			
Justification for Major Designation	**N/A**			

1 [redacted] (b) (4)

Overall Review Result	☐ **Adequate** ☒ **Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	☒ **Recommended/Latest Revision Date:** ***Recommended Sept 2012; Revised Jul 2014, Oct 2017*** **RLD/RS Number: NDA 020049** ☐ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
2	**Fasting**	**500 mg**	☒ **Adequate** ☐ **Inadequate**
2	**Fed**	**500 mg**	☒ **Adequate** ☐ **Inadequate**
2	**Sprinkle-Fasting**	**500 mg**	☒ **Adequate** ☐ **Inadequate**
2	**In vitro Comparative Dissolution**	(b) (4) **500 mg**	☐ **Adequate** ☒ **Inadequate**
(b) (4)			

The deficiency presented below represent *INFORMATION REQUEST* identified during the full ANDA review and the current ANDA review cycle will remain open. The following comment should be communicated to the the applicant via a Division of Bioequivalence III (DBIII)'s Information Request letter (IRL).

1. Based on your submitted information, since two different bio-batches of test product were used in your pivotal fasting and fed BE studies (Bio-Batch #3967425) and your pivotal sprinkle study (Bio-Batch #AB78176), please provide your clarification with respects to any difference(s) between these two test bio-batches (including those in the manufacturing process and the in-process control if applicable). You may provide the requested information along with your responses to the discipline review letter (DRL) deficiencies.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214585Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL AP or TA (NEW STRENGTH)**

RPM and TL: Gwen Murphy and Kevin Denny

ANDA #: 214585 Applicant: Sun Pharma Industries Limited
Established Product Name: Mesalamine Extended Release Capsules USP, 500 mg

Basis of Submission (BOS)/RLD (Application#/Proprietary Name/Applicant): N#20049, Pentasa Extended-Release Capsules, Takeda Pharmas USA

If BOS discontinued: [insert hyperlink to FRN] ☐ Safety/effectiveness FRN pending

Select, as applicable:

☒ RX ☐ OTC

☐ History of tentative or split approval action

☐ Shared Bio Studies (list ANDA number(s)) ☐ Shared Labeling (list ANDA number(s) _____)

☐ Memo uploaded for PAL item or OGDP confirmation

Priority: ☐ First Generic Approval (i.e., no other generics approved) ☐ Drug Shortage ☐ PEPFAR ☒ CGT

☐ Other priority _____

Misc: ☐ REMS ☐ Combination product ☐ Suitability Petition ☐ 180-day language ☐ MOU ☐ PEPFAR

☒ ***RPM Has Verified the Following:*** **Date: 5/10/2022**

1. ANDA number, NDA/RLD, Drug product and strength(s) are correct on all discipline/subdiscipline reviews
2. All submissions have been reviewed: Relevant disciplines are adequate and finalized/archived in the appropriate system of record
3. Most recent BE guidance is included in the review or a memo has been uploaded
4. No RLD updates or changes to exclusivity/patents impact endorsed labeling
5. All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d). (Not applicable to supplements)
6. OSIS Clinical Endpoint and Bioequivalence Site Inspections acceptable or not applicable
7. No blocking legal or regulatory issue (refer to Policy Alert Tracker)
8. OGD Communications has been notified if Priority Approval (First generic, Drug Shortage, PEPFAR, CGT, other OGD Communications priorities)
9. OMIR is Approve with no new facility alerts and a DP and API manufacturer listed in Submission Facility Status View
10. No open issues or tasks in Platform
11. No pending consults
12. Filing review completed for NSA or reformulation
13. PNR review is current
14. Correct language, format and content in action letter (e.g., relevant contact from 356h form)
15. Endorsements are within 29 days

Discipline Completion Dates:

Bioequivalence **12/13/2021** Labeling **12/14/2021** Clinical **NA**	Integrated Quality Assessment: **5/10/2022** If there is no IQA, provide the applicable date(s): • Chemistry _____ • Microbiology NA • Biopharmaceutics/Dissolution 12/17/2021 DMF No(s). 29575 Date(s) Acceptable 5/20/2021

Additional Notes (if applicable)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 5/10/2022
Name: IM

Patent/Exclusivity Certification:

☐ **No Relevant Patents** ☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** ☐ **section viii**

Reminders:
- Check the policy alert list for any pending exclusivity determinations
- Verify in the Orange Book there are no unexpired ODE's that cover the active moiety
- Confirm the ANDA is not blocked by other ANDA's eligibility for 180-day CGT exclusivity
- Confirm S/E determination completed for RLDs in the discontinued section of the OB

RLD = **Pentasa** NDA# **20049** ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#: **5/10/2022**

Type of Letter:
☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL AP or TA (NEW STRENGTH)

Forfeiture Information
- Confirm whether the first applicant remains eligible for 180-day exclusivity (i.e., that a forfeiture event under section 505(j)(5)(D) has not occurred) and document the determination

Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐
If yes, the date forfeiture memo was completed
Date _____ ANDA # _____

Competitive Generic Therapy 75 Day Special Forfeiture Rule:
First Applicant: ANDA # _____
Date of Approval: _____
75 Day Date: _____

180 Day Exclusivity Information
Is applicant eligible for H-W 180 day exclusivity Yes ☐ No ☐
☐ Sole
☐ Shared
Is applicant eligible for CGT 180 day exclusivity Yes ☒ No ☐
☒ Sole
☐ Shared
Is applicant blocked by a triggered CGT 180 day exclusivity
Yes ☐ No ☐
If no, the date and time checked for notification of commercial marketing: Date _____ Time: _____

Comments:
BOS = Pentasa (NDA 20049) Application submission 3/31/2021 with a PI certification. Acknowledgment letter signed 5/20/2021.

(b) (4) .

There are no unexpired patents or exclusivities listed on the OB to the NDA. Sun requested the ANDA receive CGT designation in the 1/4/2021 submission and the request was granted 3/5/2021. There are no unexpired patents or exclusivities listed in the OB to the NDA. There is a pending exclusivity for Lialda that should not impact Pentasa.

Sun's ANDA is eligible for Full Approval with CGT 180-day exclusivity.

180 Day/CGT Exclusivity Status/Landscape: CGT granted to this ANDA
If known, impact on pending exclusivity determinations: N/A
If Tentative Approval, if known, anticipated full approval date: N/A

2. Final Decision

Date: 5/11/2022
Name: CAP

☒ Verified the following:

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

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

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****

(b) (4)

Following this page, 2 Pages Withheld in Full as (b)(4)

Endorsement Signatures (To be provided by endorsees in the event of Platform unavailability):

- Division of Legal and Regulatory Support Endorsement
  - Sign & Date_____
- Paragraph IV Evaluation
  - Sign & Date_____
- REMS Endorsement
  - Sign & Date_____
- Quality Endorsement
  - Sign & Date_____
- Bioequivalence Endorsement
  - Sign & Date_____
- Clinical-Bioequivalence Endorsement
  - Sign & Date_____
- Labeling Endorsement
  - Sign & Date_____
- RPM Team Leader Endorsement
  - Sign & Date_____
- ORO IO Endorsement
  - Sign & Date_____

REFERENCES / ASSOCIATED DOCUMENTS

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

REVISION HISTORY

Author	Role	Version	Change Date	Summary of Changes
Heather Strandberg	Author	1.0	2014-10-01	New Form
Kevin Denny	Reviser	2.0	2017-10-03	Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 Remove content adequately captured in the platform Update information captured in the Division of Legal and Regulatory Support Endorsement section Other minor administrative corrections to format and content
Kevin Denny	Reviser	3.0	2018-01-14	Update Final Decision section
Joe Shin	Reviser	4.0	2019-03-04	Changes made: 1) "No Relevant Patents" checkbox added to patent types; 2) Basis of Submission was updated to include (NDA#/Proprietary Name/Applicant); 3) Removed "(CR)" from the second checkbox in the RPM Evaluation section; 4) Added "Shared BE studies..." and "Shared Labeling..." bullets to the review date section; 5) Added a not applicable checkbox for the MMA question; 6) Sentence revised to include not applicable cases in the OSIS question
John Ibrahim/QM Team	Reviser/QM	5.0	2021-08-18	• Update page 1 (revisted ANDA information section, RPM checklist, and discipline completion dates) • QM Team updated Header, document #, & title to conform to OGD Controlled Documents Program naming conventions & formatting standards • QM Team updated Footer to conform to ISO 8601 – International Time & Date Standards

ANDA 214585

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Praveen Devakadaksham:

This is in reference to your amendment received on March 31, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Mesalamine Extended Release Capsules USP, 500 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is May 14, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

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

Gwendolyn Murphy

Digitally signed by Gwendolyn Murphy
Date: 2/16/2022 02:35:13PM
GUID: 542af06d01243746ca2493dc5935bd01

ANDA 214585

INFORMATION REQUEST

Sun Pharmaceuticals Industries Inc
U.S. Agent for Sun Pharma Industries Ltd
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Extended-Release Capsules, 500 mg.

We also refer to the submissions dated, October 27, 2021 and November 3, 2021.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Biopharmaceutics

1. We acknowledge that the FDA recommended dissolution acceptance criteria for your product, mesalamine extended release capsules, differ from the USP. Please initiate a revision to an official monograph for mesalamine extended release capsules to the USP under the USP Pending Monograph Process. Until your product is in alignment with the test or test method in the USP monograph, include the following statement in the Labeling, “FDA approved dissolution test specifications differ from USP”.

We request a prompt written response, no later than **December 16, 2021** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

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 Maya Johnson-Nimo, MHSA, Regulatory Business Process Manager, at Maya.Johnson-Nimo@fda.hhs.gov or (301) 796 - 5885.

Sincerely,

{See appended electronic signature page}

Maya Johnson-Nimo, MHSA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Maya Johnson-Nimo

Digitally signed by Maya Johnson-Nimo
Date: 12/13/2021 12:14:26PM
GUID: 530cd02c000e6e390ae2463534584d78

ANDA 214585

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Praveen Devakadaksham:

This is in reference to your amendment received on November 3, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Mesalamine Extended Release Capsules USP, (b) (4) 500 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is February 2, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

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

Gwendolyn Murphy

Digitally signed by Gwendolyn Murphy
Date: 11/04/2021 12:02:42PM
GUID: 542af06d01243746ca2493dc5935bd01

ANDA 214585

MID-REVIEW-CYCLE MEETING
MEETING MINUTES

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham
Director, Regulatory Affairs & Business Continuity

Dear Praveen Devakadaksham:

This is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Extended-Release Capsules USP, (b) (4) 500 mg.

We also refer to the mid-review-cycle meeting between the applicant and the FDA on October 6, 2021. The purpose of the mid-review-cycle meeting was to discuss deficiencies identified by the midpoint of the first cycle review of your qualifying generic drug product, as noted in the agenda dated September 29, 2021.

A copy of the official minutes of the mid-review-cycle meeting is enclosed for your information. Please notify the Agency in writing via the Electronic Submissions Gateway of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Mid-review-cycle meeting
Meeting Date and Time: October 6, 2021; 10:15 a.m. EST

Application Number: 214585
Product Name: Mesalamine Extended Release Capsules USP, (b) (4) 500 mg
Applicant Name: Sun Pharmaceutical Industries Limited

Meeting Recorder: Gwendolyn Murphy

FDA ATTENDEES

Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management
Kevin Denny, Team Lead, Division of Project Management
Maya Johnson-Nimo, Lead Regulatory Health Project Manager, OPQ
Issa Nesheiwat, Project Manager, Office of Bioequivalence
Jinzhe (Jason) Mao, Reviewer, Office of Bioequivalence
Wendy Cai, Lead Pharmacologist, Office of Bioequivalence
Yi Zhang, Lead Pharmacologist, Office of Bioequivalence
Julie Call, Project Manager, Division of Labeling Review
Esther Kim, Reviewer, Division of Labeling Review
Markham Luke, Office of Research Standards
Sue Chih Lee, Office of Research Standards

APPLICANT ATTENDEES

Dr. Pradeep Sanghvi, Executive Vice President- Research & Development
Mr. Rajeev Mathur, Head – Global Generic Regulatory & Business Continuity
Mr. Praveen Devakadaksham, Director, Regulatory Affairs & Business Continuity
Ms. Nayna Daptardar, Associate Vice President, Regulatory & Business Continuity
Ms. Navneet Kaur, Deputy General Manager, Regulatory & Business Continuity
Ms. Shubhika Kwatra, Manager, Regulatory & Business Continuity
Dr. Romi Singh, Head- Formulation Research & Development- Orals
Dr. Sumit Madan, Associate Vice President, Formulation Research & Development- Orals
Mr. Anuj K Fanda, Senior Manager, Formulation Research & Development- Orals
Dr. Arshad Khuroo, Head - Bioavailability and Bioequivalence, Pharmacokinetics
Dr. Sudershan Kumar, Senior Manager, Pharmacokinetics
Mr. Prashant Kane, Senior Vice President, R&D, Project Management Office, Manufacturing Science & Technology transfer Group, Site Head (SPIL Tandalja)

Ms. Meenakshi Mathur, Senior General Manager, Project Management
Dr. P. Rita Santhakumar, Head - Analytical Development
Dr. Ashutosh Sharma, Senior General Manager, Analytical Development

A. BACKGROUND

The purpose of the mid-review-cycle meeting was to provide review status updates and discuss Agency-selected deficiencies identified by the midpoint of the first cycle review of your qualifying generic drug product, as noted in the agenda dated September 29, 2021.

B. DISCIPLINE STATUS UPDATES AND DISCUSSION ITEMS

1. **Pharmaceutical Quality** (Maya Johnson-Nimo)

   a. **Drug Substance** (Maya Johnson-Nimo)

      i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on September 28, 2021, and FDA has no further questions at this time.

      ii. **Discussion:** N/A

   b. **Drug Product** (Maya Johnson-Nimo)

      i. **Status:** Deficiencies, clarifications, or requests for further information regarding the ANDA were identified in either an IR or DRL that was sent to the applicant on September 28, 2021, and FDA has no further questions at this time.

      ii. **Discussion:** N/A

   c. **Process** (Maya Johnson-Nimo)

      i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on September 28, 2021, and FDA has no further questions at this time.

      ii. **Discussion:** N/A

   d. **Biopharmaceutics** (Maya Johnson-Nimo)

      i. **Status:** The discipline review is currently adequate.

      ii. **Discussion:** N/A

2. **Bioequivalence** (Issa Nesheiwat and Yi Zhang)

   i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on September 21, 2021, and FDA has no further questions at this time.

   ii. **Discussion:** The applicant referred to two questions submitted via email prior to the meeting. Yi Zhang stated that Question #2 was answered via email and he reiterated that the Office of Bioequivalence has no issue with the applicant seeking approval of only the 500 mg strength of test product as long as all the BE criteria are met after reviewing applicant's DRL response. Regarding the second part of Question #2, whether or not it is necessary to update the labeling section in this case, Yi deferred to Julie Call in the Division of Labeling Review. With regard to applicant's Question #1, Yi informed the applicant that additional time would be needed to review and respond to this query. OB agreed to do their best to provide a written response with the meeting minutes.

3. **Labeling** (Julie Call)

   i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on July 26, 2021, and FDA has no further questions at this time.

   ii. **Discussion:** (b) (4)

C. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

D. ACTION ITEMS

Action Item/Description	Owner	Due Date
Sun Pharmaceutical Industries Limited submitted two questions via email prior to the meeting, the second of which has already been answered via email and that response was reiterated during the	FDA	November 5, 2021

meeting. The Office of Bioequivalence had agreed to provide a written response to Question #1 to be incorporated into the meeting minutes, which are due to the applicant by November 5, 2021. However, after the meeting concluded, the applicant (b) (4)		

E. ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Gwendolyn Murphy

Digitally signed by Gwendolyn Murphy
Date: 10/18/2021 04:11:33PM
GUID: 542af06d01243746ca2493dc5935bd01

ANDA 214585

INFORMATION REQUEST

Sun Pharmaceutical Industries Inc
U.S. Agent for Sun Pharma Industries Ltd
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Capsules, Extended Release, (b) (4) 500mg.

We are reviewing the Labeling section of your submission.

We request the following additional information/clarification:

Based on your submitted information, since two different bio-batches of test product were used in your pivotal fasting and fed BE studies (Bio-Batch #3967425) and your pivotal sprinkle study (Bio-Batch #AB78176), please provide your clarification with respects to any difference(s) between these two test bio-batches (including those in the manufacturing process and the in-process control if applicable). You may provide the requested information along with your responses to the discipline review letter (DRL) deficiencies.

We request a complete written response no later than November 3, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

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

INFORMATION REQUEST
LABELING

If you do not submit a complete written response by November 3, 2021, the listed information requests may be incorporated in a discipline review letter or complete response letter.

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

Sincerely,

{See appended electronic signature page}

Issa Nesheiwat
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Issa Nesheiwat

Digitally signed by Issa Nesheiwat
Date: 10/14/2021 02:27:46PM
GUID: 54ff24450008419018f1461952bfefaf

ANDA 214585

MID-REVIEW-CYCLE MEETING
MEETING AGENDA

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham
Director, Regulatory Affairs & Business Continuity

Dear Praveen Devakadaksham:

This is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Extended-Release Capsules USP, (b) (4) 500mg.

We also refer to the mid-review-cycle meeting to be held between the applicant and the FDA on October 6, 2021. The purpose of the meeting is to provide review status updates and discuss Agency-selected deficiencies identified by the midpoint of the first cycle review of your qualifying generic drug product. A copy of the agenda for the meeting is enclosed for your information.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Agenda

MEETING AGENDA

Meeting Type: Mid-review-cycle meeting
Meeting Date and Time: October 6, 2021; 10:15 a.m. EST

Application Number: 214585
Product Name: Mesalamine Extended-Release Capsules USP, (b) (4) 500mg
Applicant Name: Sun Pharmaceutical Industries Limited

Meeting Recorder: Gwendolyn Murphy

Phone Arrangements: CALL IN NUMBER 1-669-254-5252
Toll Free: 1-833-568-8864
Meeting Number 161-524-2114
Passcode (if needed) 462311

FDA ATTENDEES

Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management
Kevin Denny, Team Lead, Division of Project Management
Maya Johnson-Nimo, Lead Regulatory Health Project Manager, OPQ
Issa Nesheiwat, Project Manager, Office of Bioequivalence
Jinzhe (Jason) Mao, Reviewer, Office of Bioequivalence
Kimberly Witzmann, Office of Bioequivalence
Wendy Cai, Lead Pharmacologist, Office of Bioequivalence
April Braddy, Supervisory Pharmacologist, Office of Bioequivalence
Julie Call, Project Manager, Division of Labeling Review
Esther Kim, Reviewer, Division of Labeling Review
Ellen Koo, Team Lead, Division of Labeling Review
Kris Andre, Office of Research Standards
Markham Luke, Office of Research Standards
Darby Kozak, Office of Research Standards
Liang Zhao, Office of Research Standards
Myongjin Kim, Office of Research Standards

APPLICANT ATTENDEES

Praveen Devakadaksham, Director, Regulatory Affairs & Business Continuity, Sun Pharmaceutical Industries, Inc.

To Be Determined

A. BACKGROUND

The purpose of the mid-review-cycle meeting is to provide review status updates and discuss Agency-selected deficiencies identified by the midpoint of the first cycle review of your qualifying generic drug product.

B. DISCIPLINE STATUS UPDATES AND DISCUSSION ITEMS AND REPRESENTATIVES FOR AGENDA

1. **Pharmaceutical Quality** (Maya Johnson-Nimo)

    a. **Drug Substance** (Maya Johnson-Nimo)

        i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on September 28, 2021, and FDA has no further questions at this time.

    b. **Drug Product** (Maya Johnson-Nimo)

        i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on September 28, 2021, and FDA has no further questions at this time.

    c. **Process** (Maya Johnson-Nimo)

        i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on September 28, 2021, and FDA has no further questions at this time.

    d. **Biopharmaceutics** (Maya Johnson-Nimo)

        i. **Status:** The discipline review is currently adequate.

2. **Bioequivalence** (Issa Nesheiwat and Jinzhe (Jason) Mao)

        i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on September 21, 2021, and FDA has no further questions at this time.

3. **Labeling** (Julie Call and Esther Kim)

        i. **Status:** Deficiencies in the ANDA were identified in either an information request (IR) or discipline review letter (DRL) that was sent to the applicant on July 26, 2021, and FDA has no further questions at this time. Applicant response is under review.

C. ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the agenda.

APPEARS THIS
WAY ON ORIGINAL

Gwendolyn Murphy

Digitally signed by Gwendolyn Murphy
Date: 9/29/2021 06:39:39PM
GUID: 542af06d01243746ca2493dc5935bd01

ANDA 214585

DISCIPLINE REVIEW LETTER
QUALITY

Sun Pharmaceutical Industries Inc
U.S. Agent for Sun Pharma Industries Ltd
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Capsules, Extended Release, (b) (4) 500mg.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

(b) (4)

B. Drug Product

(b) (4)

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

(b) (4)

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than **October 27, 2021**. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. 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
QUALITY

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 Generic Drug User Fee Amendments of 2017 (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 or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Maya Johnson-Nimo, MHSA, Regulatory Business Process Manager, at Maya.Johnson-Nimo@fda.hhs.gov or (301) 796 - 5885.

Sincerely,

{See appended electronic signature page}

Maya Johnson-Nimo, MHSA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Maya Johnson-Nimo

Digitally signed by Maya Johnson-Nimo
Date: 9/28/2021 08:02:28PM
GUID: 530cd02c000e6e390ae2463534584d78

ANDA 214585

DISCIPLINE REVIEW LETTER

Sun Pharmaceutical Industries, Inc.
2 Independence Way
Princeton, NJ 08540

Dear Sir or Madam:

This letter is in reference to your amendment received on March 31, 2021 submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Extended-Release Capsules, USP, (b) (4) 500 mg.

The following possible deficiencies have been identified by BIOEQUIVALENCE:

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.

1. Based on the dissolution data in your current submission, the release of mesalamine was incomplete for both test and reference listed drug (RLD) products in pH 4.5 and 6.0 media at the last time point of 12 hours. Please conduct new comparative dissolution testing for both strengths of test and RLD products at pH 4.5 and 6.0 conditions until at least 80% drug release is achieved (or a release plateau is reached).

2. You used two batches (Batch #3967425 and #AB78176) of test product in your pivotal bioequivalence (BE) studies. (b) (4)

3. In addition to three pivotal BE studies, you also conducted two failed fasting sprinkle BE studies (#BA19140131 and #BA19140426) using a four-way, fully replicate crossover design with 56 and 100 subjects dosed, respectively. The test batch (#3967425) used was the same as bio-batch in the pivotal fasting and fed BE studies. You indicated that the failure of these two fasting sprinkle BE studies might be due to the insufficient study power.

Based on the BE summary tables submitted, it is noted that T/R ratios were lower than 0.80 for most of pharmacokinetic (PK) parameters. Please submit complete clinical, statistical and bioanalytical study reports (including the failed reasons) and concentration/PK datasets (in SAS transport format) for these two failed fasting sprinkle studies.

4. For your two pilot fed BE studies (#PKD_18_099 and #MSM_1000C_0536_17), please provide the details of all adverse events (AEs) observed during the study, including the severity of the AEs (i.e., mild, moderate, severe, serious etc.), onset and resolution times.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than October 22, 2021 . If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. 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
BIOEQUIVALENCE:

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 Generic Drug User Fee Amendments of 2017 (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 or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Issa Nesheiwat PharmD., M.S. RAC, BIOEQUIVALENCE Project Manager at Issa.Nesheiwat@fda.hhs.gov.

Sincerely,

Issa Nesheiwat PharmD. M.S. RAC
Project Manager
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Issa Nesheiwat

Digitally signed by Issa Nesheiwat
Date: 9/21/2021 10:36:24AM
GUID: 54ff24450008419018f1461952bfefaf

ANDA 214585

DISCIPLINE REVIEW LETTER
LABELING

Sun Pharmaceutical Industries, Inc.
U.S. Agent for: Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham
U.S. Agent

Dear Mr. Devakadaksham:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Extended Release Capsules USP, (b) (4) 500 mg.

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

The following possible deficiencies have been identified by Labeling:

Labeling deficiencies based on your submissions received March 31, 2021, June 7, 2021, and July 1, 2021:

PRESCRIBING INFORMATION

a. GENERAL: Ensure references to the drug substance and drug product are consistent throughout the Prescribing Information. Ensure to use the established name, Mesalamine Extended-Release Capsules, (i.e., dosage form included) when referring to the drug product.
b. DESCRIPTION: (b) (4)."
c. HOW SUPPLIED, second and fourth paragraphs: Add the strength to follow "Mesalamine extended-release capsules USP".

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

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated

and explained. We also advise that you only address the deficiencies noted in this communication.

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

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

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than August 9, 2021. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. 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

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 Generic Drug User Fee Amendments of 2017 (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 or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD, PMP
Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Julie Call

Digitally signed by Julie Call
Date: 7/26/2021 10:52:53AM
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ANDA 214585

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Sir:

This is in reference to your amendment received on June 7, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Mesalamine Extended-Release Capsules USP, (b) (4) 500 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is January 30, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

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

Gwendolyn Murphy

Digitally signed by Gwendolyn Murphy
Date: 6/08/2021 12:05:28PM
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ANDA 214585

INFORMATION REQUEST

Sun Pharmaceutical Industries Inc
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Extended Release Capsules, USP, (b) (4) 500mg.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Product

1. (b) (4)

2.

Following this page, 2 Pages Withheld in Full as (b)(4)

3. (b) (4)

4.

5.

C. Biopharmaceutics

1. Based on the submitted in vitro dissolution data, the proposed dissolution acceptance criteria are permissive for your mesalamine extended-release capsules and NOT acceptable. The following data-driven dissolution acceptance criteria are recommended for all strengths: (b) (4) (b) (4)" for your proposed drug product at release and on stability. Implement these dissolution acceptance criteria for all strengths of your drug product at release and on stability and update the specifications of the drug product with the revised criteria for the dissolution test, accordingly.

   In addition, please be advised, that all proposed exhibit batches are expected to meet the revised dissolution acceptance criteria in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

We request a prompt written response, no later than **July 1, 2021** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

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 Maya Johnson-Nimo, MHSA, Regulatory Business Process Manager, at Maya.Johnson-Nimo@fda.hhs.gov or (301) 796 - 5885.

Sincerely,

{See appended electronic signature page}

Maya Johnson-Nimo, MHSA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Maya Johnson-Nimo

Digitally signed by Maya Johnson-Nimo
Date: 6/04/2021 02:27:58PM
GUID: 530cd02c000e6e390ae2463534584d78

ANDA 214585

MID-REVIEW-CYCLE MEETING NOTIFICATION

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on March 31, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Extended-release Capsules USP, (b) (4) 500 mg.

In accordance with Guidance for Industry, Competitive Generic Therapies (February 2019), FDA may offer a mid-review-cycle meeting to an applicant of an ANDA for a drug designated as a CGT during the first review cycle.

The teleconference is scheduled as follows:

Date:	October 6, 2021
Time:	10:15 a.m. - 10:45 a.m. EST
Phone Arrangements:	CALL IN NUMBER 1-669-254-5252 Toll Free: 1-833-568-8864 Meeting Number 161-524-2114 Passcode (if needed) 462311

Agenda items will be issued to the applicant no later than seven calendar days prior to the mid-review-cycle meeting.

Discussions points and action items will be summarized at the conclusion of the teleconference and reflected in FDA's meeting minutes.

If you need to reschedule or choose to decline the mid-review-cycle meeting, please notify the Agency in writing via the Electronic Submissions Gateway. If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Gwendolyn Murphy

Digitally signed by Gwendolyn Murphy
Date: 5/25/2021 12:43:40PM
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ANDA 214585

ACKNOWLEDGEMENT
ANDA RECEIPT

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
2 Independence Way
Princeton, NJ 08540
Attention: Praveen Devakadaksham

Dear Praveen Devakadaksham:

This is in reference to your abbreviated new drug application (ANDA) 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 ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Mesalamine Extended-release Capsules USP, (b) (4) 500 mg

DATE OF APPLICATION: March 31, 2021

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: March 31, 2021

Reference is made to the information request dated May 14, 2021 and to any amendments thereafter.

This original ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). The GDUFA goal date for review of this standard original ANDA is January 30, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including the Agency's recommendations reflected in relevant product specific guidances.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at gwendolyn.murphy@fda.hhs.gov[1] or (240) 402 - 9624. We also recommend that you sign up for Generic Drug e-mail updates,[2] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Bijal Patel, Pharm.D., BCPS
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

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

2 See FDA's Subscription Management Center at https://www.fda.gov/about-fda/contact-fda/get-email-updates

Bijal Patel

Digitally signed by Bijal Patel
Date: 5/20/2021 01:53:50PM
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