CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 203286

Name: Mesalamine Delayed-Release Tablets USP, 800 mg

Sponsor: Zydus Pharmaceuticals, Inc.

Approval Date: July 21, 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203286

ANDA APPROVAL

Zydus Pharmaceuticals (USA) Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President and Head of Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 13, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mesalamine Delayed-Release Tablets USP, 800 mg.

Reference is also made to the complete response letter issued by this office on February 3, 2017, and to your amendments received on April 6, 2017.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Mesalamine Delayed-Release Tablets USP, 800 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Asacol HD Delayed-Release Tablets, 800 mg, of Allergan Pharmaceuticals International Limited (Allergan). Your dissolution testing should be incorporated into the stability and quality control program using the USP dissolution method and specification for your application.

The RLD upon which you have based your ANDA, Allergan's Asacol HD Delayed-Release Tablets, 800 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,893,662 (the '662 patent)	November 15, 2021
8,580,302 (the '302 patent)	November 15, 2021
9,089,492 (the '492 patent)	November 15, 2021

Your ANDA contains paragraph IV certifications to the patents[1] under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Mesalamine Delayed-Release Tablets USP, 800 mg, under this ANDA. You have notified the Agency that Zydus Pharmaceuticals (USA) Inc. (Zydus) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated within the statutory 45-day period against Zydus for infringement of the '662 patent in the United States District Court for the District of Delaware [Warner Chilcott Company, LLC v. Zydus Pharmaceuticals (USA) Inc., and Cadila Healthcare Limited, (d/b/a Zydus Cadila), Civil Action No. 1:11-cv-01105-UNA]. You have also notified the Agency that this case was dismissed.

With respect to 180-day generic drug exclusivity, we note that Zydus was the first ANDA applicant for Mesalamine Delayed-Release Tablets USP, 800 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, Zydus may have been eligible for 180 days of generic drug exclusivity for Mesalamine Delayed-Release Tablets USP, 800 mg. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that Zydus failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination of Zydus's eligibility for 180-day exclusivity. You have notified the Agency that Zydus commenced commercial marketing of an authorized generic of the RLD, Allergan's Asacol HD Delayed-Release Tablets, 800 mg, on August 1, 2016. Therefore, any 180-day exclusivity that Zydus may have been eligible for has been triggered and expired.

Under section 506A of 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. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

[1] The Agency notes that the '302 and '492 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

PROMOTIONAL MATERIALS

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

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

CONTENT OF LABELING

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

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

Sincerely yours,

{See appended electronic signature page}

For Priya Shah, PharmD
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Heidi Lee

Digitally signed by Heidi Lee
Date: 7/21/2017 05:39:18PM
GUID: 52795fe90009070673e7de063d080d1f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203286

COMPLETE RESPONSE

Zydus Pharmaceuticals (USA), Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: G. Srinivas
Head – Regulatory Affairs

Dear Sir:

This letter 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), for Mesalamine Delayed-Release Tablets USP, 800 mg.

We acknowledge receipt of your amendments dated June 10, June 21, and August 9, 2016. The June 21, 2016, submission constituted a complete response to our April 29, 2016 action 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.

PRODUCT QUALITY

(b) (4)

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

5. (b) (4)

DISSOLUTION

We acknowledge that you will conduct the dissolution testing of your test product using the current USP Dissolution Method for Mesalamine Delayed-Release Tablets.

LABELING

1. CONTAINER LABEL – The following comments are based on the Asacol® HD container label, approved on May 5, 2016.

   a. (b) (4)

   b. Revise the administration direction to read as follows:

      Swallow Mesalamine Delayed-Release Tablets whole. Do not cut, break, or chew the tablets.

   c. Include the text "Dispense in original container" as does the Asacol® HD tablets label.

2. CARTON – 100 (10 x 10) Unit-dose Tablets

   See comments under CONTAINER, whichever applicable.

3. PRESCRIBING INFORMATION

   HOW SUPPLIED/STORAGE AND HANDLING

   Revise the dispensing statement to read as follows:

   Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle.

4. STRUCTURED PRODUCT LABELING (SPL)
   See comments under CONTAINER and PRESCRIBING INFORMATION.

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

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

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

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

http://www.accessdata.fda.gov/scripts/cder/daf

FACILITY INSPECTIONS/EVALUATIONS

During a recent inspection of the Cadila Healthcare Limited (FEI 3002984011) manufacturing facility for this ANDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this ANDA may be approved. Please list communications submitted to, or held with, the agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

BIOEQUIVALENCE, DISSOLUTION,

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

OTHER

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

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

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY/LABELING

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

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

ANNUAL FACILITY FEES

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

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

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

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

If you have any questions, call Edward Taylor, Regulatory Project Manager, Division of Project Management, at (240) 402-6094.

Sincerely yours,

{See appended electronic signature page}

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

Aaron Sigler

Digitally signed by Aaron Sigler
Date: 2/03/2017 02:57:59PM
GUID: 508da6fa0002827f1a9f2526d1b2cc69

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203286

COMPLETE RESPONSE

Zydus Pharmaceuticals (USA), Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: G. Srinivas
Head – Regulatory Affairs

Dear Sir:

This letter 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), for Mesalamine Delayed-release Tablets USP, 800 mg.

We acknowledge receipt of your amendments dated October 19, 2015; and March 1, 2016. The October 19, 2015, submission constituted a complete response to our August 13, 2015, action 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.

PRODUCT QUALITY

(b) (4)

DISSOLUTION

We acknowledge that you will conduct the dissolution testing of your test product using current USP Dissolution Method for Mesalamine Delayed-release Tablets.

FACILITY INSPECTIONS/EVALUATIONS

During a recent inspection of the Cadila Healthcare Limited (FEI 3002984011) manufacturing facility for this ANDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this ANDA may be approved.

BIOEQUIVALENCE, DISSOLUTION, LABELING

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

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

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

OTHER

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

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

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY

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

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

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

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

ANNUAL FACILITY FEES

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

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

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

If you have any questions, call Edward Taylor, Regulatory Project Manager, Division of Project Management, at (240) 402-6094.

Sincerely yours,

Denise P. Toyer -S

Digitally signed by Denise P. Toyer -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300112898, cn=Denise P. Toyer -S
Date: 2016.04.29 15:15:09 -04'00'

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 203286

COMPLETE RESPONSE

Zydus Pharmaceuticals (USA), Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: G. Srinivas
Head – Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 12, 2011, received July 13, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed-release Tablets USP, 800 mg.

We acknowledge receipt of your amendments dated February 24 and June 23, 2015. The February 24, 2015, submission constituted a complete response to our February 24, 2014, action 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.

PRODUCT QUALITY

1. (b) (4)

2.

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

BIOEQUIVALENCE

At pH 6.8, there is a significant difference in the dissolution profile for the test product between the original (July 12, 2011) and amendment (February 24, 2015) submissions. Please provide an explanation for this difference. In addition, please submit 12 units dissolution data of the test and reference products in buffers with pH around 6.8 (e.g. pH (b) (4) 6.8, (b) (4) using the following dissolution method on your test product:

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of:

(b) (4)
(2) pH 6.8 Phosphate buffer at 50 rpm
(b) (4)

Volume: 900 mL
Temperature: 37ºC
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison.

Please submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable. Besides the dissolution summary table in the eCTD format, please submit the individual unit dissolution data and mean values in excel or sas transport format.

DISSOLUTION

We acknowledge that you will conduct the dissolution testing of your test product using current USP Dissolution Method for Mesalamine Delayed-Release Tablets.

LABELING

The Division of Labeling Review has no further questions/comments at this time based on your labeling submission dated June 23, 2015.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

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

FACILITY INSPECTIONS

During a recent inspection of the Cadila Healthcare Limited manufacturing facility for this ANDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this ANDA may be approved.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY/BIOEQUIVALENCE

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

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

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

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

If you have any questions, call Edward Taylor, Regulatory Project Manager, at (240) 402-6094.

Sincerely yours,

Denise P. Toyer -A

Digitally signed by Denise P. Toyer -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300112898, cn=Denise P. Toyer -A
Date: 2015.08.13 17:12:28 -04'00'

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

COMPLETE RESPONSE

ANDA 203286

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

TO: Zydus Pharmaceuticals (USA) Inc. TEL: 609-730-1900

ATTN: G. Srinivas FAX: 609-730-1999

FROM: Heidi Lee FDA CONTACT PHONE: 240-276-9717

Dear Sir:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 203286

COMPLETE RESPONSE

Zydus Pharmaceuticals (USA) Inc.
Attention: G. Srinivas
Sr. Director – Regulatory Affairs
73 Route 31 North
Pennington, NJ 08534

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 12, 2011, received July 13, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed-release Tablets USP, 800 mg.

We acknowledge receipt of your amendment dated March 13, 2012.

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.

PRODUCT QUALITY

1) (b) (4)

2)

3)

4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

23) (b) (4)

24)

25)

(b) (4)

BIOEQUIVALENCE

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

The Division of Bioequivalence II (DB II) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. We cannot locate the individual data for comparative dissolution testing in 0.1 N HCl followed by pH 4.5 Acetate buffer.

2. Due to the high variability of your submitted dissolution data conducted in multimedia, an f2 test using mean profiles of test vs. reference listed drug ("RLD") is not sufficient as per the CDER Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms ("Dissolution Guidance"). Therefore, we calculated the f2 metric (an f2 confidence interval) using a bootstrapping method for the dissolution profile comparison. For general information on this approach, please refer to Shah et al. In Vitro Dissolution Profile

Comparison-Statistics and Analysis of the Similarity Factor, f2. Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896.

For the test products, the mean values (f2) in pH 6.8 and pH 7.5 phosphate buffer are lower than 50 and the lower bound of 90% confidence interval ("CI") for the f2 test comparing test vs. RLD in pH 6.8, pH 7.2, and pH 7.5 phosphate buffer is lower than those comparing the RLD against itself under the same conditions. These values suggest that the dissolution profiles of the test product are significantly different from those of the corresponding reference under these conditions. Your dissolution data in pH 6.8, 7.2 and 7.5 are not acceptable.

3. To address why the test product is different from the RLD product, please repeat comparative dissolution testing on your **fresh test product** using a **larger sample** of tablets to provide a better estimate of the mean difference, or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculation.

   The dissolution testing should be conducted on at least 24 tablets (more if necessary) of the test product and at least two lots of unexpired RLD product (using 12 tablets per lot) using the following method as specified in the FDA Guidance on Mesalamine (800 mg):

   Apparatus: USP Apparatus II (paddle)
   Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
   Evaluation Stage:
   Each of
   (1) pH 4.5 Acetate buffer at 50 rpm
   (2) pH 6.8 Phosphate buffer at 50 rpm
   (3) pH 7.2 Phosphate buffer at 50 rpm
   (4) pH 7.5 Phosphate buffer at 50 rpm

   Volume: 900 mL
   Temperature: 37ºC
   Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison

   Please submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable.

   The DB II will perform an f2 test on your submitted dissolution data. If the variability of the dissolution data is such that mean data cannot be used for the f2 test, as per the Dissolution Guidance, we will use the above-referenced bootstrapping approach.

   For the bootstrapping method, sampling with replacement is used for creating 10,000 replicates of test and reference products. The means of the test and reference units at each time point for each replicate are obtained and used for f2 calculation. The 90% confidence intervals of the f2 values are calculated using the percentile approach as described in the Shah et al. reference. Similar procedure can be followed for comparing reference vs. reference products.

Please note only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

LABELING

Labeling Deficiencies determined on April 21, 2013 based on your submission dated July 12, 2011:

1. CONTAINER (b) (4) 180s, (b) (4)

   a. (b) (4)

   b.

2. BLISTER – 10s

   If space permits, include the phrase "Made in India".

3. INSERT

   a. GENERAL

      i. Please refer to 21 CFR 201.56(d) regarding PLR format for the final printed labeling. Please ensure that the highlight sections and the entire insert can easily be read and that the point type not be smaller than 6.

      ii. Please replace "Asacol-HD" with either "mesalamine delayed-release tablets" (b) (4) " depending on the context throughout the text.

      iii. (b) (4)

   b. DESCRIPTION

      (b) (4)

   c. 8 USE IN SPECIFIC POPULATIONS – 8.1 Pregnancy: (b) (4)

Revise this subsection heading to read "Pregnancy: [redacted] (b) (4) We refer you to CFR 201.57(9)(A)(3).

Submit your revised labeling electronically in final print format.

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.

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

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

FACILITY INSPECTIONS

We have not yet completed inspection(s)/compliance evaluation of your manufacturing facility(s) named or referenced in this ANDA. We must perform a complete evaluation of the information associated with the inspection before determining that the site(s) are satisfactory and this ANDA may be approved.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY / BIOEQUIVALENCE / LABELING

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

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

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

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

If you have any questions, contact Heidi Lee, Regulatory Project Manager, at heidi.lee@fda.hhs.gov or (240) 276-9717.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

02/24/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

LABELING


No Varnished Area (Do Not Print)
(18 x 50.5 mm)
NDC 68382-435-28
Mesalamine
Delayed-release
Tablets, USP
800 mg
435
Do not substitute one Mesalamine Delayed-release Tablets 800 mg with two Mesalamine Delayed-release 400 mg oral products
180 TABLETS
Rx only
zydus pharmaceuticals
Each delayed-release tablet contains 800 mg of mesalamine USP.
Usual Dosage: For the treatment of moderately active ulcerative colitis, the recommended dose of mesalamine delayed-release tablets in adults is two 800 mg tablets to be taken three times daily with or without food for a total daily dose of 4.8 gm for a duration of 6 weeks.
See package insert for complete prescribing information.
Swallow Mesalamine Delayed-Release Tablets whole. Do not cut, break, or chew the tablets.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Protect from moisture.
Dispense in a tightly closed container.
Dispense in original container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 02/17
Manufactured by: Cadila Healthcare Ltd. Ahmedabad India
Distributed by: Zydus Pharmaceuticals USA Inc. Pennington NJ 08534
50.5 mm
97 mm

(b) (4)

Mesalamine
Delayed-release
Tablets, USP

800 mg

NDC 68382-435-77

Mesalamine
Delayed-release
Tablets, USP

800 mg

Lot:

Exp:

NDC 68382-435-77

Mesalamine Delayed-release

Tablets, USP

800 mg

435

Do not substitute one Mesalamine Delayed-release Tablets 800 mg with two Mesalamine Delayed-release 400 mg oral products

This unit-dose package is not child-resistant.

100 Tablets
(10 X 10 Unit-Dose)

Rx only

zydus pharmaceuticals

Mesalamine
Delayed-release
Tablets, USP

800 mg

Each delayed-release tablet contains 800 mg of mesalamine, USP.

Usual Dosage: For the treatment of moderately active ulcerative colitis, the recommended dose of mesalamine delayed-release tablets in adults is two 800 mg tablets to be taken three times daily with or without food, for a total daily dose of 4.8 gm, for a duration of 6 weeks.

See package insert for complete prescribing information.

Swallow Mesalamine Delayed-Release Tablets whole. Do not cut, break, or chew the tablets.

Store at 20° to 25°C (68° to 77°F)
[See USP Controlled Room Temperature].
Protect from moisture.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

Rev.: 02/17

Mesalamine
Delayed-release
Tablets, USP

800 mg

NDC 68382-435-77

(b) (4)


N 3 68382 43530 9
Mesalamine
Delayed-release
Tablet, USP 800 mg
Made in INDIA
Distributed by: Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534
Lot: Exp:
Rev. 02/17

(b) (4)

UPC-E Barcode: 119711

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MESALAMINE DELAYED-RELEASE TABLETS safely and effectively. See full prescribing information for MESALAMINE DELAYED-RELEASE TABLETS.

MESALAMINE delayed-release tablets, for oral use
Initial U.S. Approval: 1987

----------INDICATIONS AND USAGE----------

Mesalamine delayed-release tablets are aminosalicylate indicated for the treatment of moderately active ulcerative colitis in adults. (1)

Limitation of Use: Safety and effectiveness of mesalamine delayed-release tablets beyond 6 weeks have not been established (1)

--------DOSAGE AND ADMINISTRATION-------

Important Administration Instructions (2.1):

- Do not substitute one mesalamine delayed-release tablet, 800 mg for two mesalamine delayed-release 400 mg oral products. (2.1)
- Evaluate renal function prior to initiation of mesalamine delayed-release tablets, 800 mg. (2.1, 5.1)
- Take on an empty stomach, at least 1 hour before and 2 hours after a meal.
- Swallow whole; do not cut, break or chew the tablets.

Treatment of Moderately Active Ulcerative Colitis (2.2):

- Recommended dosage is 1600 mg (two 800 mg tablets) three times daily for 6 weeks.

--------DOSAGE FORMS AND STRENGTHS----

- Delayed-release tablets: 800 mg (3)

----------CONTRAINDICATIONS----------

- Known or suspected hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of mesalamine delayed-release tablets (4, 5.3)

----------WARNINGS AND PRECAUTIONS-----

- ***Renal Impairment***: Evaluate the risks and benefits in patients with known renal impairment or taking nephrotoxic drugs; monitor renal function (5.1, 7.1, 8.6, 13.2)
- ***Mesalamine-induced Acute Intolerance Syndrome:*** Symptoms may be difficult to distinguish from an ulcerative colitis exacerbation; monitor for worsening symptoms; discontinue if acute intolerance syndrome suspected (5.2)
- ***Hypersensitivity Reactions, including Myocarditis and Pericarditis:*** Evaluate patients immediately and discontinue if a hypersensitivity reaction is suspected (5.3)
- ***Hepatic Failure***: Evaluate the risks and benefits in patients with known liver impairment (5.4)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (≥ 2%) are headache, nausea, nasopharyngitis, abdominal pain, and worsening of ulcerative colitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals USA Inc. at 1-877-993-8779, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- ***Nephrotoxic Agents including NSAIDs***: Increased risk of nephrotoxicity; monitor for changes in renal function and mesalamine related adverse reactions. (7.1)
- ***Azathioprine or 6-Mercaptopurine***: Increased risk of blood disorders; monitor complete blood cell counts and platelet counts (7.2)

----------USE IN SPECIFIC POPULATIONS----

Geriatric Patients: Increased risk of blood dyscrasias; monitor complete blood cell counts and platelet counts (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Mesalamine delayed-release tablets are indicated for the treatment of moderately active ulcerative colitis in adults.

Limitations of Use:

Safety and effectiveness of mesalamine delayed-release tablets beyond 6 weeks have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Do not substitute one mesalamine delayed-release tablet 800 mg for two mesalamine delayed-release 400 mg oral products *[see Clinical Pharmacology (12.3)]*.
- Evaluate renal function prior to initiation of mesalamine delayed-release tablets.
- Take mesalamine delayed-release tablets on an empty stomach, at least 1 hour before and 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.
- Swallow mesalamine delayed-release tablets whole. Do not cut, break or chew the tablets.
- Intact, partially intact, and/or tablet shells have been reported in the stool; Instruct patients to contact their physician if this occurs repeatedly.
- Protect mesalamine delayed-release tablets from moisture. Close the container tightly and leave desiccant pouches in the bottle along with the tablets.

2.2 Dosage Information

For the treatment of moderately active ulcerative colitis, the recommended dosage of mesalamine delayed-release tablets in adults is 1600 mg (two 800 mg tablets) three times daily (total daily dosage of 4.8 grams) for a duration of 6 weeks.

3 DOSAGE FORMS AND STRENGTHS

Mesalamine delayed-release tablets are available as reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets imprinted with “435” on one side and plain on other side.

4 CONTRAINDICATIONS

Mesalamine delayed-release tablets are contraindicated in patients with known or suspected hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of mesalamine delayed-release tablets *[see Warnings and Precautions (5.3), Adverse Reactions (6.2), and Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients taking products such as mesalamine delayed-release tablets that contain or are converted to mesalamine *[see Adverse Reactions (6.2)]*.

Evaluate renal function prior to initiation of mesalamine delayed-release tablets and periodically while on therapy. Evaluate the risks and benefits of using mesalamine delayed-release tablets in patients with known renal impairment or history of renal disease or taking concomitant nephrotoxic drugs *[see Drug Interactions (7.1), Use in Specific Populations (8.6) and Nonclinical Toxicology (13.2)]*.

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Exacerbation of the symptoms of colitis has been reported in 2.3% of mesalamine-treated patients in controlled clinical trials. This acute reaction, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, has been reported after the initiation of mesalamine delayed-release tablets as well as other mesalamine products. Symptoms usually abate when mesalamine delayed-release tablets are discontinued.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some patients may have a similar reaction to mesalamine delayed-release tablets 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 delayed-release tablets if an alternative etiology for the signs or symptoms cannot be established.

5.4 Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Caution should be exercised when administering mesalamine delayed-release tablets to patients with liver impairment.

6 ADVERSE REACTIONS

The most serious adverse reactions seen in mesalamine delayed-release tablets clinical trials or with other products that contain mesalamine or are metabolized to mesalamine were:

- Renal Impairment *[see Warnings and Precautions (5.1)]*
- Mesalamine-Induced Acute Intolerance Syndrome *[see Warnings and Precautions*
- *(5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Hepatic Failure *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Mesalamine has been evaluated in 896 patients with ulcerative colitis in controlled studies. Three six-week, active-controlled studies were conducted comparing mesalamine 4.8 grams per day with mesalamine-delayed release tablets 2.4 grams per day in patients with mildly to moderately active ulcerative colitis. In these studies, 727 patients were dosed with the mesalamine delayed-release tablet, 800 mg and 732 patients were dosed with mesalamine delayed-release tablets, 400 mg.

The most common reactions reported in the mesalamine group were headache (4.7%), nausea (2.8%), nasopharyngitis (2.5%), abdominal pain (2.3%), diarrhea (1.7%), and dyspepsia (1.7%); Table 1 enumerates adverse reactions that occurred in the three studies. The most common reactions in patients with moderately active ulcerative colitis (602 patients dosed with mesalamine delayed-release tablet, 800 mg and 618 patients dosed with the mesalamine delayed-release tablet, 400 mg) were the same as all treated patients.

Discontinuations due to adverse reactions occurred in 3.9% of patients in the mesalamine delayed-release tablet, 800 mg group and in 4.2% of patients in the mesalamine delayed-release tablet, 400 mg comparator group. The most common cause for discontinuation was gastrointestinal symptoms associated with ulcerative colitis.

Serious adverse reactions occurred in 0.8% of patients in the mesalamine delayed-release tablet, 800 mg group and in 1.8% of patients in the mesalamine delayed-release tablet, 400 mg comparator group. The majority involved the gastrointestinal system.

Table 1
Adverse Reactions Occurring in ≥ 1% of All Treated Patients
(Three studies combined)

Adverse Reaction	**Mesalamine delayed-release 2.4 grams per day (400 mg Tablet) (N = 732)**	**Mesalamine delayed-release 4.8 grams per day (800 mg Tablet) (N = 727)**
Headache	4.9 %	4.7 %
Nausea	2.9 %	2.8 %
Nasopharyngitis	1.4 %	2.5 %
Abdominal pain	2.3 %	2.3 %
Diarrhea	1.9 %	1.7 %
Dyspepsia	0.8 %	1.7 %
Vomiting	1.6 %	1.4 %
Flatulence	0.7 %	1.2 %
Influenza	1.2 %	1.0 %

Adverse Reaction	Mesalamine delayed-release 2.4 grams per day (400 mg Tablet) (N = 732)	Mesalamine delayed-release 4.8 grams per day (800 mg Tablet) (N = 727)
Pyrexia	1.2 %	0.7 %
Cough	1.4 %	0.3 %

N = number of patients within specified treatment group
Percent = percentage of patients in category and treatment group

6.2 Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving the mesalamine delayed-release tablet 800 mg, the adverse events listed below have been reported in postmarketing experience with other mesalamine-containing products or products that are metabolized to mesalamine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole

Facial edema, edema, peripheral edema, asthenia, chills, infection, malaise, pain, neck pain, chest pain, back pain, abdominal enlargement, lupus-like syndrome, drug fever (rare).

Cardiovascular

Pericarditis (rare) and myocarditis (rare) [*see Warnings and Precautions (5.3)*], pericardial effusion, vasodilation, migraine.

Gastrointestinal

Dry mouth, stomatitis, oral ulcers, anorexia, increased appetite, eructation, pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer (rare), constipation, hemorrhoids, rectal hemorrhage, bloody diarrhea, tenesmus, stool abnormality.

Hepatic

There have been rare reports of hepatotoxicity, including jaundice, cholestatic jaundice, hepatitis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. Asymptomatic elevations of liver enzymes which usually resolve during continued use or with discontinuation of the drug have also been reported. One case of Kawasaki-like syndrome, that included changes in liver enzymes, was also reported *[see Warnings and Precautions (5.4)]*.

Hematologic

Agranulocytosis (rare), aplastic anemia (rare), anemia, thrombocytopenia, leukopenia, eosinophilia, lymphadenopathy.

Musculoskeletal

Gout, rheumatoid arthritis, arthritis, arthralgia, joint disorder, myalgia, hypertonia.

Neurological/Psychiatric
Anxiety, depression, somnolence, insomnia, nervousness, confusion, emotional lability, dizziness, vertigo, tremor, paresthesia, hyperesthesia, peripheral neuropathy (rare), Guillain-Barré syndrome (rare), and transverse myelitis (rare).

Respiratory/Pulmonary
Sinusitis, rhinitis, pharyngitis, asthma exacerbation, pleuritis, bronchitis, eosinophilic pneumonia, interstitial pneumonitis.

Skin
Alopecia, psoriasis (rare), pyoderma gangrenosum (rare), erythema nodosum, acne, dry skin, sweating, pruritus, urticaria, rash.

Special Senses
Ear pain, tinnitus, ear congestion, ear disorder, conjunctivitis, eye pain, blurred vision, vision abnormality, taste perversion.

Renal/Urogenital
Renal failure (rare), interstitial nephritis, minimal change nephropathy *[see Warnings and Precautions (5.1)]*, dysuria, urinary frequency and urgency, hematuria, epididymitis, decreased libido, dysmenorrhea, menorrhagia.

Laboratory Abnormalities
Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated GGT, elevated LDH, elevated bilirubin, elevated serum creatinine and BUN.

7 DRUG INTERACTIONS

7.1 Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs
The concurrent use of mesalamine with known nephrotoxic agents, including nonsteroidal 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 *[see Warnings and Precautions (5.1)]*.

7.2 Azathioprine or 6-Mercaptopurine
The concurrent use of mesalamine with azathioprine or 6-mercaptopurine may increase the risk for blood disorders. If concomitant use of mesalamine delayed-release tablet 800 mg and azathioprine or 6- mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on mesalamine use in pregnant women are insufficient to inform a drug-associated risk. No fetal harm was observed in animal reproduction studies of mesalamine in rats and rabbits at oral doses approximately 0.97 times (rat) and 1.95 times (rabbit) the recommended human dose [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Reproduction studies with mesalamine were performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg/day. There was no evidence of harm to the fetus. These mesalamine doses were about 0.97 times (rat) and 1.95 times (rabbit) the recommended human dose of 4.8 grams per day, based on body surface area.

8.2 Lactation

Risk Summary

Mesalamine and its N-acetyl metabolite are present in human milk in undetectable to small amounts [*see Data*]. There are limited reports of diarrhea in breastfed infants. There is no information on the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mesalamine and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.

Clinical Considerations

Monitor breastfed infants for diarrhea.

Data

Human Data

In published lactation studies, maternal mesalamine doses from various oral and rectal formulations and products ranged from 500 mg to 3 g daily. The concentration of mesalamine in milk ranged from non-detectable to 0.11 mg/L. The concentration of the Nacetyl-5-aminosalicylic acid metabolite ranged from 5 to 18.1 mg/L. Based on these concentrations, estimated infant daily dosages for an exclusively breastfed infant are 0 to 0.017 mg/kg/day of mesalamine and 0.75 to 2.72 mg/kg/day of N-acetyl-5-aminosalicylic acid.

8.4 Pediatric Use

Safety and effectiveness of mesalamine in pediatric patients have not been established. See the prescribing information for other approved mesalamine products for the safety and effectiveness of these products in pediatric patients.

8.5 Geriatric Use

Clinical studies of mesalamine delayed-release tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Reports from uncontrolled clinical studies and postmarketing experience for another oral formulation of mesalamine suggest a higher incidence of blood dyscrasias (agranulocytosis, neutropenia, pancytopenia) in patients who were 65 years or older compared to younger patients. Monitor complete blood cell counts and platelet counts in elderly patients during therapy with mesalamine delayed-release tablets.

In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing mesalamine delayed-release tablets *[see Use in Specific Populations (8.6)]*.

8.6 Renal Impairment

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 mesalamine delayed-release tablets therapy. Monitor patients with known renal impairment or history of renal disease or taking nephrotoxic drugs for decreased renal function and mesalamine-related adverse reactions [*see Warnings and Precautions (5.1), Drug Interactions (7.1) and Adverse Reactions (6.2)*].

10 OVERDOSAGE

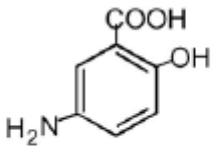
There is no specific antidote for mesalamine overdose and treatment for suspected acute severe toxicity with mesalamine should be symptomatic and supportive. This may include prevention of further gastrointestinal tract absorption, correction of fluid electrolyte imbalance, and maintenance of adequate renal function. Mesalamine delayed-release tablet is a pH dependent delayed-release product and this factor should be considered when treating a suspected overdose.

Single oral doses of 5000 mg/kg mesalamine suspension in mice (approximately 4.2 times the recommended human dose of mesalamine based on body surface area), 4595 mg/kg in rats (approximately 7.8 times the recommended human dose of mesalamine based on body surface area) and 3000 mg/kg in cynomolgus monkeys (approximately 10 times the recommended human dose of mesalamine based on body surface area) were lethal.

11 DESCRIPTION

Each mesalamine delayed-release tablet for oral administration contains 800 mg of mesalamine USP, an aminosalicylate. Mesalamine, USP is light tan to pink colored, needle-shaped crystals. Color may darken on exposure to air. It is odorless or may have a slight characteristic odor, slightly soluble in water; very slightly soluble in methanol, in dehydrated alcohol, and in acetone; practically insoluble in n-butyl alcohol, in chloroform, in ether, in ethyl acetate, in n-hexane, in methylene chloride, and in n-propyl alcohol and soluble in dilute hydrochloric acid and in dilute alkali hydroxides. Mesalamine delayed-release tablets 800 mg have single layered coating consisting of an

acrylic based resin Eudragit S (methacrylic acid copolymer B, NF), which dissolves at pH 7 or greater, releasing mesalamine for topical anti-inflammatory action in the colon. Mesalamine (also referred to as 5-aminosalicylic acid or 5-ASA) has the chemical name 5-amino-2-hydroxybenzoic acid and its structural formula is:



Molecular Weight: 153.1
Molecular Formula: $C_7H_7NO_3$

Each mesalamine delayed-release tablet contains 800 mg of mesalamine. In addition, each tablet contains the following inactive ingredients: acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mesalamine is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, that is, prostanoids, and through the lipoxygenase pathways, that is, leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

12.3 Pharmacokinetics

Absorption

Plasma concentrations of mesalamine (5-aminosalicylic acid; 5-ASA) and its metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA) are highly variable following administration of mesalamine delayed-release tablets. Following single dose oral administration of mesalamine delayed-release tablet 800 mg in healthy subjects (N = 139) under fasted conditions, the mean C_{max}, $AUC_{8\text{-}48h}$ and $AUC_{0\text{-}tldc}$ values were 208 ng/mL, 2296 ng.h/mL, and 2533 ng.h/mL, respectively. The median [range] T_{max} for mesalamine following administration of mesalamine delayed-release tablet 800 mg was approximately 24 hours [4 to 72 hours], reflecting the delayed-release characteristics of the formulation.

Based on cumulative urinary recovery of mesalamine and N-Ac-5-ASA from single dose studies in healthy subjects, approximately 20% of the orally administered mesalamine in mesalamine delayed-release tablets is systemically absorbed.

Food Effect: A high calorie (800 to 1000 calories), high fat (approximately 50 % of total caloric content) meal increased mesalamine C_{max} by 2.4-fold and mesalamine systemic exposure (AUC_{8-48} and AUC_{0-tldc}) by 2.8-fold; the median lag-time increased by 8 hours and median t_{max} by 6 hours (from 24 to 30 hours) *[see Dosage and Administration (2.1)]*.

Comparative exposure between one mesalamine delayed-release tablet 800 mg and two mesalamine delayed-release 400 mg oral products is unknown *[see Dosage and Administration (2.1)]*.

Elimination
Metabolism
The absorbed mesalamine is acetylated in the gut mucosal wall and by the liver to N-Ac-5-ASA.

Excretion
Absorbed mesalamine is excreted mainly by the kidneys as N-acetyl-5-aminosalicylic acid. Unabsorbed mesalamine is excreted in feces.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dietary mesalamine was not carcinogenic in rats at doses as high as 480 mg/kg/day, or in mice at 2000 mg/kg/day. These doses are approximately 0.97 and 2.0 times the 4.8 grams per day mesalamine delayed-release tablets dose (based on body surface area). Mesalamine was not genotoxic in the Ames test, the Chinese hamster ovary cell chromosomal aberration assay, and the mouse micronucleus test. Mesalamine, at oral doses up to 480 mg/kg/day (about 0.97 times the recommended human treatment dose based on body surface area), was found to have no effect on fertility or reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

In animal studies (rats, mice, dogs), the kidney was the principal organ for toxicity. (In the following, comparisons of animal dosing to recommended human dosing are based on body surface area and a 4.8 grams per day dose for a 60 kg person).

Mesalamine causes renal papillary necrosis in rats at single doses of approximately 750 mg/kg to 1000 mg/kg (1.5 to 2.0 times the recommended human dose). Doses of 170 and 360 mg/kg/day (about 0.3 and 0.73 times the recommended human dose) given to rats for six months produced papillary necrosis, papillary edema, tubular degeneration, tubular mineralization, and urothelial hyperplasia.

In mice, oral doses of 4000 mg/kg/day (approximately 4.1 times the recommended human dose) for three months produced tubular nephrosis, multifocal/diffuse tubulo-interstitial inflammation, and multifocal/diffuse papillary necrosis.

In dogs, single doses of 6000 mg (approximately 6.25 times the recommended human dose) of delayed-release mesalamine tablets resulted in renal papillary necrosis but were not fatal. Renal changes have occurred in dogs given chronic administration of mesalamine at doses of 80 mg/kg/day (0.5 times the recommended human dose).

14 CLINICAL STUDIES

14.1 Moderately Active Ulcerative Colitis

The efficacy of mesalamine delayed-release tablets at 4.8 grams per day was studied in a six-week, randomized, double-blind, active-controlled study in 772 patients with moderately active ulcerative colitis (UC). Moderately active UC was defined as a Physician's Global Assessment (PGA) score of 2; the PGA is a four-point scale (0 to 3) that encompasses the clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy findings.

Patients were randomized 1:1 to the mesalamine delayed-release tablets 4.8 grams per day group (two mesalamine delayed-release tablets three times a day) or the mesalamine delayed-release 2.4 grams per day group (two mesalamine delayed-release 400 mg tablets three times a day).

Patients characteristically had a history of previous use of oral 5-ASAs (86%), steroids (41%), and rectal therapies (49%), and demonstrated clinical symptoms of three or more stools over normal per day (87%) and obvious blood in the stool most or all of the time (70%). The study population was primarily Caucasian (97%), had a mean age of 43 years (8% aged 65 years or older), and included slightly more males (56%) than females (44%).

The primary endpoint was treatment success defined as improvement from baseline to Week 6 based on the PGA. Treatment success rates were similar in the two groups: 70% in the mesalamine group and 66% in the mesalamine delayed-release 400 mg tablets group (difference: 5%; 95% CI: [-1.9%, 11.2%]).

A second controlled study supported the efficacy of mesalamine at 4.8 grams per day. Treatment success was 72% in patients with moderately active UC treated with mesalamine.

16 HOW SUPPLIED/STORAGE AND HANDLING

Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows:

NDC 68382-435-28 in bottles of 180 tablets
NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose)

Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle.

17 PATIENT COUNSELING INFORMATION

Administration *[see Dosage and Administration (2.1)]*

- Inform patients that if they are switching from a previous oral mesalamine therapy to mesalamine delayed-release tablets to discontinue their previous oral mesalamine therapy and follow the dosing instructions for mesalamine delayed-release tablets. One mesalamine delayed-release tablet 800 mg is not substitutable for two mesalamine delayed-release 400 mg oral products.
- Inform patients to take mesalamine delayed-release tablets on an empty stomach, at least 1 hour before and 2 hours after a meal.
- Instruct patients to swallow the mesalamine delayed-release tablets whole, taking care not to break, cut, or chew the tablets, because the coating is an important part of the delayed-release formulation.
- Inform patients that intact, partially intact, and/or tablet shells have been reported in the stool. Instruct patients to contact their physician if this occurs repeatedly.
- Instruct patients to protect mesalamine delayed-release tablets from moisture. Instruct patients to close the container tightly and to leave desiccant pouches in the bottle along with the tablets.

Renal Impairment

- Inform patients that mesalamine delayed-release tablets may decrease their renal function, especially if they have known renal impairment or are taking nephrotoxic drugs, and periodic monitoring of renal function will be performed while they are on therapy. Advise patients to complete all blood tests ordered by their physician *[see Warnings and Precautions (5.1)]*.

Mesalamine-Induced Acute Intolerance Syndrome

- Instruct patients to report to their physician if they experience new or worsening symptoms of cramping, abdominal pain, bloody diarrhea, and sometimes fever, headache, and rash *[see Warnings and Precautions (5.2)]*.

Hypersensitivity Reactions

- Inform patients of the signs and symptoms of hypersensitivity reactions, and advise them seek immediate medical care should signs and symptoms occur *[see Warnings and Precautions (5.3)]*.

Hepatic Failure

- Inform patients with known liver disease of the signs and symptoms of worsening liver function and advise them to report to their physician if they experience such signs or symptoms *[see Warnings and Precautions (5.4)]*.

Blood Disorders

- Inform elderly patients and those taking azathioprine or 6-mercaptopurine of the risk for blood disorders and the need for periodic monitoring of complete blood cell

counts and platelet counts while on therapy. Advise patients to complete all blood tests ordered by their physician *[see Drug Interactions (7.2), Use in Specific Populations (8.5)]*.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Manufactured by:
Cadila Healthcare Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals USA Inc.
Pennington, NJ 08534

Rev.: 02/17

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

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	05/15/2017
ANDA Number(s)	203286
Review Number	5
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
Established Name & Strength(s)	Mesalamine Delayed-Release Tablets USP, 800 mg
Proposed Proprietary Name	None
Submission Received Date	04/06/2017
Labeling Reviewer	Esther Park
Labeling Team Leader	Ellen Hwang

Review Conclusion

☐ ACCEPTABLE – No Comments.

☒ ACCEPTABLE – Include Post Approval Comments

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

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

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

None

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

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

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

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

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

1.2 POST APPROVAL REVISIONS

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

1. GENERAL COMMENTS (For Container and Carton Label)

a. [redacted] (b) (4)

b. Please revise to read as below to be the same as the reference listed drug:

[redacted] (b) (4)

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

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

Reviewer Comments:

The below comments are from the labeling review C4 based on the submission (s) dated 10/19/2015, 6/10/2016 and Firm's Responses are from Cover Letter on 04/06/2017:

1. CONTAINER LABEL – The following comments are based on the Asacol® HD container label, approved on May 5, 2016.
   a. (b) (4)
   b. Revise the administration direction to read as follows:
      Swallow Mesalamine Delayed-Release Tablets whole. Do not cut, break, or chew the tablets.
   c. Include the text "Dispense in original container" as does the Asacol® HD tablets label.

Firm's Response:

a.

(b) (4)

b.

As recommended by the Agency, we have revised our administration direction to read "**Swallow Mesalamine Delayed-Release Tablets whole. Do not cut, break, or chew the tablets.**"

c.

We acknowledge the Agency's comment.

Reviewer's Assessment: All of the label deficiencies have been addressed by the applicant.

2. CARTON – 100 (10 x 10) Unit-dose Tablets

   See comments under CONTAINER, whichever applicable.

Firm's Response:

We have revised our labels according the comments 1a and 1b for container.

Reviewer's Assessment: All of the label deficiencies have been addressed by the applicant.

3. PRESCRIBING INFORMATION

   HOW SUPPLIED/STORAGE AND HANDLING

   Revise the dispensing statement to read as follows:

   Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle.

Firm's Response:

As recommended by the Agency, we have revised the dispensing statement to read "Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle."

Reviewer's Assessment: All of the label deficiencies have been addressed by the applicant.

4. STRUCTURED PRODUCT LABELING (SPL)

See comments under CONTAINER and PRESCRIBING INFORMATION.

Firm's Response:

As recommended by the Agency, we have revised the dispensing statement to read "Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle" and the revised container label has been incorporated.

Reviewer's Assessment: All of the label deficiencies have been addressed by the applicant.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:
None

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:
NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 021830/S-010 **Supplement Approval Date:** 05/05/2016 **Proprietary Name:** Asacol® **Established Name:** Mesalamine Delayed-Release Tablets **Description of Supplement:** This Prior Approval supplemental new drug application provides for the removal of the excipient dibutyl phthalate (DBT) and replacing it with the alternate (b) (4) dibutyl sebacate (DBS).
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** NA
☐ **OTHER (Describe):** NA

Reviewer Assessment:

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

Reviewer Comments:

None

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels Source:

(b) (4)

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

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	**Monograph ? YES or NO**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
USP	5/15/2017	YES	Mesalamine Delayed-Release Tablets	Packaging and Storage: Preserve in tight containers.
PF	5/15/2017	YES	31(2) Second Interim Revision Announcement: Mesalamine Delayed-Release Tablets	Packaging and storage— Preserve in tight containers.

Reviewer Comments:

Biopharmaceutics review not available. We will ask biopharmaceutics which test method was used for this proposed drug product. Biopharmaceutics notified, 05/26/2017.

Response from Biopharmaceutics Reviewer, 06/21/2017:

There is only one USP method listed for this drug product and the applicant's dissolution method and specs

match the USP method and specs. Therefore, no statement is needed in the description section.

Mesalamine Delayed-Release Tablets

DEFINITION
Mesalamine Delayed-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of mesalamine ($C_7H_7NO_3$).

IDENTIFICATION
• **A. Infrared Absorption** ⟨197K⟩
Sample solution: To about 50 mL of water add a quantity of finely powdered Tablets, nominally equivalent to about 800 mg of mesalamine. Boil the mixture for about 5 min, with constant stirring. Filter the hot solution, and allow the filtrate to cool. Collect the precipitated crystals, and dry at about 110°.
Acceptance criteria: Meet the requirements

ASSAY
• **Procedure**
Mobile phase: Dissolve 4.3 g of sodium 1-octanesulfonate in 1 L of water. Adjust with phosphoric acid to a pH

r_S = peak response of mesalamine from the *Standard solution*
C_S = concentration of USP Mesalamine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of mesalamine in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
• **Dissolution** ⟨711⟩
Solution A: Transfer about 43.35 g of monobasic potassium phosphate and 1.65 g of sodium hydroxide to a 2-L volumetric flask. Dissolve in and dilute with water to volume, and mix. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.0, and mix.
Solution B: Transfer 133.6 g of sodium hydroxide to a 2-L volumetric flask, dissolve in and dilute with water to volume, and mix.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 5/15/2017.

Table 3 provides Orange Book patents for the Model Labeling (NDA 021830) and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter "Carve-out" or "None")**
6893662	Nov 15, 2021	U-141	TREATMENT OF ULCERATIVE COLITIS	iv	01/13/2016	None
8580302	Nov 15, 2021			iv	01/13/2016	None
9089492	Nov 15, 2021			iv	01/13/2016	None

Reviewer Assessment:

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

Reviewer Comments:

None

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

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
NA					

Reviewer Assessment:

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

Reviewer Comments:

NA

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.	acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.	**No Change. Acceptable.**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products
Previous Labeling Review
Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows: NDC 68382-435-28 in bottles of 180 tablets NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose) **Storage** Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. (b) (4)

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products
Currently Proposed Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows: NDC 68382-435-28 in bottles of 180 tablets NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose) **Storage** Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle.
Assessment **Storage statement has been revised to read "Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle." according to the agency's recommendations.** **Acceptable.**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: Cadila Healthcare Ltd. Ahmedabad, India **Distributed by:** **Zydus Pharmaceuticals USA Inc.** Pennington, NJ 08534	**Manufactured by:** Cadila Healthcare Ltd. Ahmedabad, India **Distributed by:** **Zydus Pharmaceuticals USA Inc.** Pennington, NJ 08534	**No Change. Acceptable.**

5. COMMENTS FOR CHEMISTRY REVIEWER

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

Reviewer Comments:
Biopharmaceutics review not available. We will ask biopharmaceutics which test method was used for this proposed drug product. Biopharmaceutics notified, 05/26/2017.

Response from Biopharmaceutics Reviewer, 06/21/2017:
There is only one USP method listed for this drug product and the applicant's dissolution method and specs match the USP method and specs. Therefore, no statement is needed in the description section.

Mesalamine Delayed-Release Tablets

DEFINITION
Mesalamine Delayed-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of mesalamine ($C_7H_7NO_3$).

IDENTIFICATION
• **A. Infrared Absorption ⟨197K⟩**
Sample solution: To about 50 mL of water add a quantity of finely powdered Tablets, nominally equivalent to about 800 mg of mesalamine. Boil the mixture for about 5 min, with constant stirring. Filter the hot solution, and allow the filtrate to cool. Collect the precipitated crystals, and dry at about 110°.
Acceptance criteria: Meet the requirements

ASSAY
• **Procedure**
Mobile phase: Dissolve 4.3 g of sodium 1-octanesulfonate in 1 L of water. Adjust with phosphoric acid to a pH

r_S = peak response of mesalamine from the *Standard solution*
C_S = concentration of USP Mesalamine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of mesalamine in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
• **Dissolution ⟨711⟩**
Solution A: Transfer about 43.35 g of monobasic potassium phosphate and 1.65 g of sodium hydroxide to a 2-L volumetric flask. Dissolve in and dilute with water to volume, and mix. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.0, and mix.
Solution B: Transfer 133.6 g of sodium hydroxide to a 2-L volumetric flask, dissolve in and dilute with water to volume, and mix.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:
NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	**800 mg** 180 Tablets in 1 Bottle	04/06/2017	Satisfactory
Blister	Final	**800 mg** 10 Tablets	04/06/2017	Satisfactory
Carton	Final	**800 mg** 100 Tablets (10 x 10 Unit-Dose)	04/06/2017	Satisfactory
(Other – specify)				
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	02/2017	04/06/2017	Satisfactory
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements	NA	02/2017	04/06/2017	Satisfactory

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 5/25/2017 02:06:24PM
GUID: 5256bdc00002af3bc3fa942a9512a891

Esther Park

Digitally signed by Esther Park
Date: 5/15/2017 09:01:51PM
GUID: 552d387d009750180ac89afefb9b8914

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

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	12/6/2016
ANDA Number(s)	203286
Review Number	4
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
Established Name & Strength(s)	NA
Proposed Proprietary Name	Mesalamine Delayed-release Tablets USP, 800 mg
Submission Received Date	10/19/2015 and 6/10/2016
Labeling Reviewer	Chan Park
Labeling Team Leader	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

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

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on December 6, 2016 based on your submission dated October 19, 2015 and June 10, 2016.

1. CONTAINER LABEL – The following comments are based on the Asacol® HD container label, approved on May 5, 2016.
   a. (b) (4)
   b. Revise the administration direction to read as follows:
      Swallow Mesalamine Delayed-Release Tablets whole. Do not cut, break, or chew the tablets.
   c. Include the text "Dispense in original container" as does the Asacol® HD tablets label.

2. CARTON – 100 (10 x 10) Unit-dose Tablets

   See comments under CONTAINER, whichever applicable.

3. PRESCRIBING INFORMATION

   HOW SUPPLIED/STORAGE AND HANDLING

   Revise the dispensing statement to read as follows:

   Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle.

4. STRUCTURED PRODUCT LABELING (SPL)

   See comments under CONTAINER and PRESCRIBING INFORMATION.

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

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

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

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

http://www.accessdata.fda.gov/scripts/cder/daf

1.2 POST APPROVAL REVISIONS

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

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

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s).

Reviewer Comments: The below comments are from the labeling review C3 based on the submission dated 6/23/2015. There was no deficiency, except the post-approval revision request:

HIGHLIGHTS
It is preferable to delete the designation "USP" from the title.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments: The container was acceptable in the submission of 6/23/2015. However, it is necessary to make further revisions based on the current container label for Asacol® HD Tablets. (Approved 5/5/2016).

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

Reviewer Comments: None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Repository files? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): 021830/S-010

Supplement Approval Date: 5/5/2016

Proprietary Name: Asacol® HD Delayed-release tablets

Established Name; Mesalamine Delayed-release Tablets

Description of Supplement:

This supplement is for removal if the excipient dibytyl phthalate (DBT) and replacing it with alternate dibutyl sebacate.(DBS).

NOTE: The above information is the only one appearing in the approval letter for the NDA021830/S-010, approved 5/5/2016. However, the approved label and labeling contains more revisions in addition to the change described above.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement: Click here to enter text.

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**

Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Labeling Deficiencies determined on December 6, 2016 based on your submission dated October 19, 2015 and June 10, 2016.

1. CONTAINER LABEL – The following comments are based on the Asacol® HD container label, approved on May 5, 2016.
   d. [redacted] (b) (4)
   e. Revise the administration direction to read as follows:
      Swallow Mesalamine Delayed-Release Tablets whole. Do not cut, break, or chew the tablets.
   f. Include the text "Dispense in original container" as does the Asacol® HD tablets label.

2. CARTON – 100 (10 x 10) Unit-dose Tablets

   See comments under CONTAINER, whichever applicable.

3. PRESCRIBING INFORMATION

   HOW SUPPLIED/STORAGE AND HANDLING

   Revise the dispensing statement to read as follows:

   Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant pouch (silica gel) from bottle.

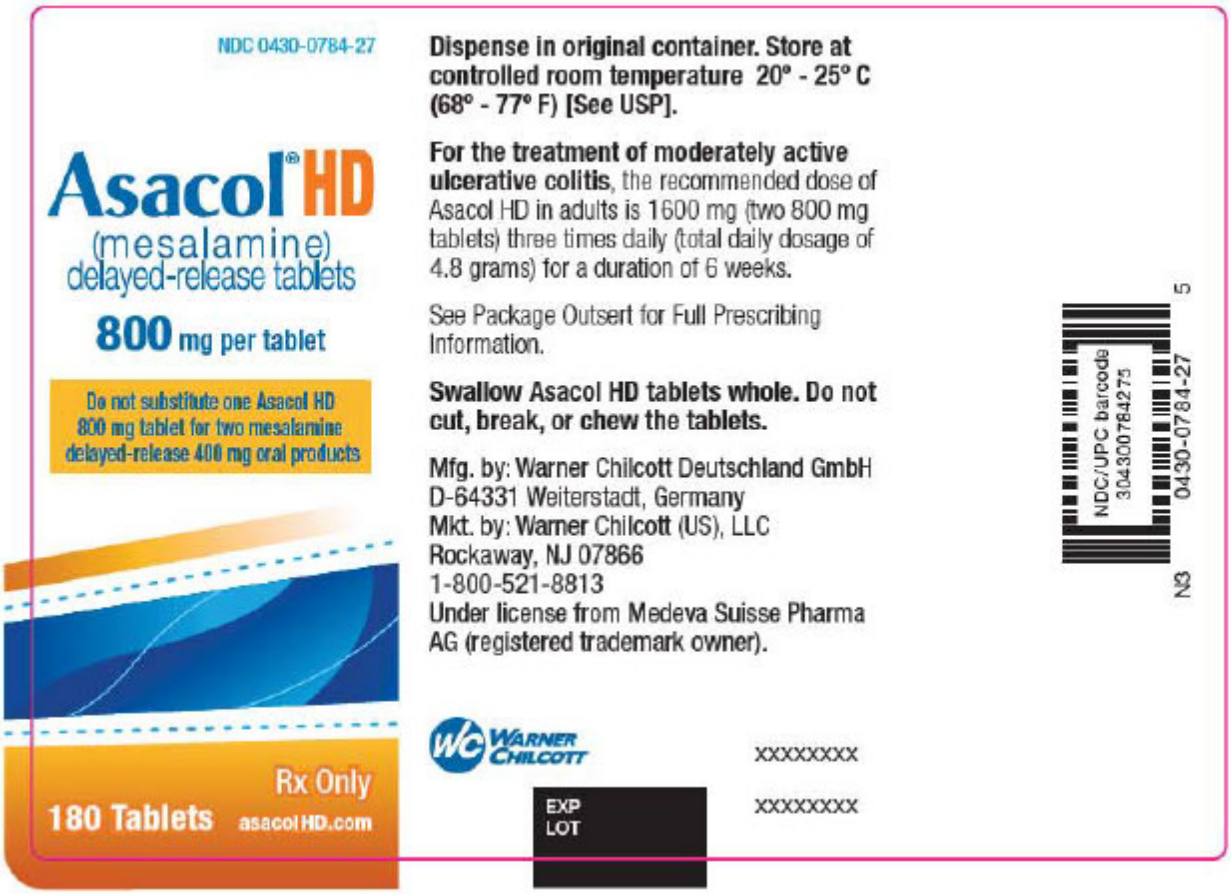
4. STRUCTURED PRODUCT LABELING (SPL)

   See comments under CONTAINER and PRESCRIBING INFORMATION.

3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. [NDA 021830/S-010, **approved May 5, 2016]**

The revised container label appears to be a part of the labeling approved 5/5/2016 as it was attached at the end of the package insert labeling, which was posted on the Drugs@FDA.



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

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	**Monograph ? YES or NO**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
USP	12/6/2016	YES	Mesalamine Delayed-release Tablets	Packaging and storage – Preserve in tight containers
PF	12/6/2016	NA	Click here to enter text.	Click here to enter text.

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/6/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

	Table 3: Impact of Model Labeling Patents on ANDA Labeling					
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**

	Table 3: Impact of Model Labeling Patents on ANDA Labeling					
6893662	11/15/2021	U-141	TREATMENT OF ULCERATIVE COLITIS	IV	1/13/2016	None
8580302	11/15/2021			IV	1/13/2016	None
9089492	11/15/2021			IV	1/13/2016	

Reviewer Assessment:

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

Reviewer Comments:

None

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
NA					

Reviewer Assessment:

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

Reviewer Comments:

None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 5: Comparison of DESCRIPTION Section		
Each mesalamine delayed-release tablet contains 800 mg of mesalamine. In addition, each tablet contains the following inactive ingredients: acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.	**Each mesalamine delayed-release tablet contains 800 mg of mesalamine. In addition, each tablet contains the following inactive ingredients: acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.**	**No change**

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	**Currently Proposed**	**Assessment**
Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows: **NDC 68382-435-28 in bottles of 180 tablets** (b) (4) **NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose**	**Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows:** **NDC 68382-435-28 in bottles of 180 tablets** **NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose)**	(b) (4)

Table 7: Manufactured by statement		
Previously Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: **Cadila Healthcare Ltd.** **Ahmedabad, India** **Distributed by:** **Zydus Pharmaceuticals USA Inc.** **Pennington, NJ 08534**	**Manufactured by:** **Cadila Healthcare Ltd.** **Ahmedabad, India** **Distributed by:** **Zydus Pharmaceuticals USA Inc.** **Pennington, NJ 08534** **Rev.: 05/16**	**No change**

5. COMMENTS FOR CHEMISTRY REVIEWER

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

Reviewer Comments:

None

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:
None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, if you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Date**	**Recommendation**
Container	Final	Bottle of 180s	(b) (4)	Revise
Blister	Final	10s	2/24/2015	Satisfactory
Carton	Final	100 (10 x 10s)	2/24/2015	Revise
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Date**	**Recommendation**
Prescribing Information	Final	5/2016	6/10/2016	Revise
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements		5/2016	6/10/2016	Satisfactory

* Post-approval revision

Chan Park

Digitally signed by Chan Park
Date: 12/06/2016 07:26:15PM
GUID: 508da70600028afeb3d3490c9451e8d2

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 12/15/2016 09:41 24PM
GUID: 508da70800028c5cddf24c815a550d26

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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	6/26/2015
ANDA Number(s)	203286
Review Number	3
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
Established Name & Strength(s)	NA
Proposed Proprietary Name	Mesalamine Delayed-release Tablets USP, 800 mg
Submission Received Date	6/23/2015
Labeling Reviewer	Chan Park
Labeling Team Leader	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments.

☒ ACCEPTABLE – Include Post Approval Comments

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

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

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

None

1.2 POST APPROVAL REVISIONS

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

HIGHLIGHTS
It is preferable to delete the designation “USP” from the title.

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

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. Include the previous review(s) finalized date(s). 6/3/2015

Reviewer Comments: The sponsor addressed all comments adequately.

1. CONTAINER- 180s (b) (4)
   (b) (4)

2. PRESCRIBING INFORMATION
   a. (b) (4) – Revise this section to read as follows:

      HIGHLIGHTS OF PRESCRIBING INFORMATION
      These highlights do not include all the information needed to use MESALAMINE DELAYED-RELEASE TABLETS safely and effectively. See Full Prescribing Information for MESALAMINE DELAYED-RELEASE TABLETS.

      MESALAMINE delayed-release Tablets, (b) (4)

   ii. 11 DESCRIPTION:
      It appears that the imprinting ink is changed from (b) (4) to "Opacode black S-1-17823 in this current submission. Please justify this change with supporting documents, and/or comment.

   iii. 12.3 Pharmacokinetics – (b) (4)

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

Reviewer Comments: See below regarding change of the imprinting ink.

From: Park, Chan H
Sent: Friday, June 26, 2015 12:00 PM
To: Majumder, Quamrul
Subject: ANDA 03286 (Mesalamine)
Importance: High

Hello Quamrul,

It is for your information, In response to the labeling comment regarding the change of the imprinting ink, the sponsor Responded as follows in the labeling amendment dated 6/23/2015. The sponsor will address this in the first annual report, which is believed to be acceptable per the Agency's guidance.

ii. 11 DESCRIPTION:
It appears that the imprinting ink is changed from (b) (4) to "Opacode black S-1-17823 in this current submission. Please justify this change with supporting documents, and/or comment.

RESPONSE:

(b) (4)

The comparative qualitative and quantitative compositions of both inks are provided in the below table for the Agency's ready reference.

(b) (4)

Opacode Black S-1-17823 (Currently in use)	
Ingredient name	**% w/w**
Shellac	(b) (4)
Isopropyl alcohol (USP,	(b) (4)
(b) (4) butyl alcohol NF	
Propylene glycol	(b) (4)
Ammonium hydroxide (b) (4) NF, (b) (4)	

From: Majumder, Quamrul
Sent: Friday, June 26, 2015 12:02 PM
To: Park, Chan H
Subject: RE: ANDA 03286 (Mesalamine)

Hi Chan
Thank you for sharing the info.
We already have sent the question to the firm and awaits their response.

-Thanks,

Quamrul Majumder,

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Repository files? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 021830/S006 **Supplement Approval Date:** 10/18/2013 **Proprietary Name:** Asacol HD Delayed-release tablets **Established Name; Mesalamine Delayed-release Tablets** **Description of Supplement:** This "Prior Approval" supplemental new drug application proposes the addition of information to the pediatric use section of the prescribing information.
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out):
☐ OTHER (Describe):

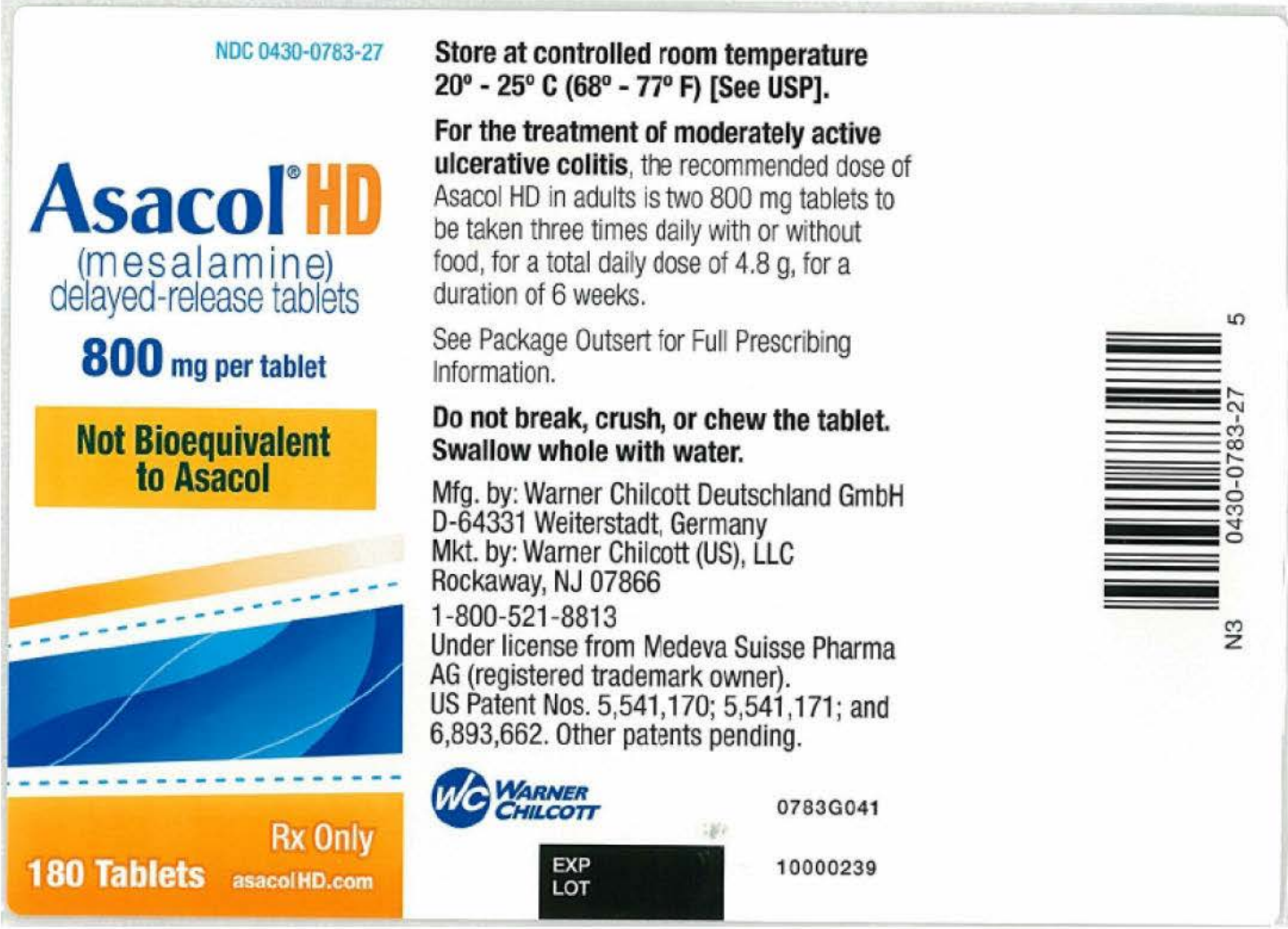
Reviewer Assessment:

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

3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. [DailyMeds, Rev. 4/2015]

/



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

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	6/26/2015	YES	Mesalamine Delayed-release Tablets	Packaging and storage – Preserve in tight containers
PF	6/26/2015	NA	Click here to enter text.	Click here to enter text.

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/26/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

	Table 3: Impact of Model Labeling Patents on ANDA Labeling					
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6893662	11/15/2021	U-141	TREATMENT OF ULCERATIVE COLITIS	IV	7/15/2014	None

	Table 3: Impact of Model Labeling Patents on ANDA Labeling					
6580302	11/15/2021				7/15/2014	None

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section		
Previous Labeling Review	Currently Proposed	Assessment
Each mesalamine delayed-release tablet contains 800 mg of mesalamine. In addition, each tablet contains the following inactive ingredients: acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.	Each mesalamine delayed-release tablet contains 800 mg of mesalamine. In addition, each tablet contains the following inactive ingredients: acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.	No change

Table 6: Comparison of HOW SUPPLIED Section

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	**Currently Proposed**	**Assessment**
Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows: NDC 68382-435-28 in bottles of 180 tablets (b) (4) NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose)	Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows: NDC 68382-435-28 in bottles of 180 tablets (b) (4) NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose	(b) (4)

Table 7: Manufactured by statement		
Previously Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: Cadila Healthcare Ltd. Ahmedabad, India Distributed by: Zydus Pharmaceuticals USA Inc. Pennington, NJ 08534	Manufactured by: Cadila Healthcare Ltd. Ahmedabad, India Distributed by: Zydus Pharmaceuticals USA Inc. Pennington, NJ 08534	No change

5. COMMENTS FOR CHEMISTRY REVIEWER

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

Reviewer Comments:

Click here to enter text.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, if you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Date**	**Recommendation**
Container	Final	Bottle of 180s (b) (4)	(b) (4)	AC
Blister	Final	10s	2/24/2015	AC
Carton	Final	100 (10 x 10s)	2/24/2015	AC
(Other – specify)				
Table 9 Review Summary of Prescribing Information and Patient Labeling				

	Final or Draft or NA	Revision Date and/or Code	Submission Date	Recommendation
Prescribing Information	Final	6/2015	6/23/2015	AC*
Medication Guide				
Patient Information				
SPL Data Elements		6/2015	6/23/2015	AC

* Post-approval revision

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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	6/1/2015
ANDA Number(s)	203286
Review Number	2
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
Established Name & Strength(s)	Mesalamine Delayed-release Tablets USP, 800 mg
Proposed Proprietary Name	NA
Submission Received Date	2/24/2015
Labeling Reviewer	Chan Park
Labeling Team Leader	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

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

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. CONTAINER- 180s (b) (4)

(b) (4)

2. PRESCRIBING INFORMATION

a. (b) (4) – Revise this section to read as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MESALAMINE DELAYED-RELEASE TABLETS safely and effectively. See Full Prescribing Information for MESALAMINE DELAYED-RELEASE TABLETS.

MESALAMINE delayed-release Tablets, (b) (4)

ii. 11 DESCRIPTION:

It appears that the imprinting ink is changed from (b) (4) to "Opacode black S-1-17823 in this current submission. Please justify this change with supporting documents, and/or comment.

iii. 12.3 Pharmacokinetics – (b) (4)

Submit your revised labeling electronically in final print format.

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.

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

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

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

1.2 POST APPROVAL REVISIONS

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

NA

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

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. Include the previous review(s) finalized date(s). 4/23/2013

Reviewer Comment: (b) (4)

1. CONTAINER – (b) (4) 180s, (b) (4)

   a. (b) (4)

   b.

2. BLISTER – 10s

   If space permits, include the phrase "Made in India".

3. INSERT

   a. GENERAL

      i. Please refer to 21 CFR 201.56(d) regarding PLR format for the final printed labeling. Please ensure that the highlight sections and the entire insert can easily be read and that the point type not be smaller than 6.

      ii. Please replace "Asacol-HD" with either "mesalamine delayed-release tablets" (b) (4) depending on the context throughout the text.

      iii. (b) (4)

   b. DESCRIPTION

      (b) (4)

   c. 8 USE IN SPECIFIC POPULATIONS – 8.1 Pregnancy: (b) (4)

      Revise this subsection heading to read "Pregnancy: (b) (4) . We refer you to CFR 201.57(9)(A)(3).

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

Reviewer Comments:

a. (b) (4)

b. The RLD contains "Dibutyl Phthalate (DBP)", which can cause significant adverse events. The ANDA does not contain this as an inactive ingredient, so all information associated with DBP was carved-out from the insert labeling.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Repository files? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 021830/S006 **Supplement Approval Date:** 10/18/2013 **Proprietary Name:** Asacol HD Delayed-release tablets **Established Name; Mesalamine Delayed-release Tablets** **Description of Supplement:** This "Prior Approval" supplemental new drug application proposes the addition of information to the pediatric use section of the prescribing information.
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out):
☐ OTHER (Describe):

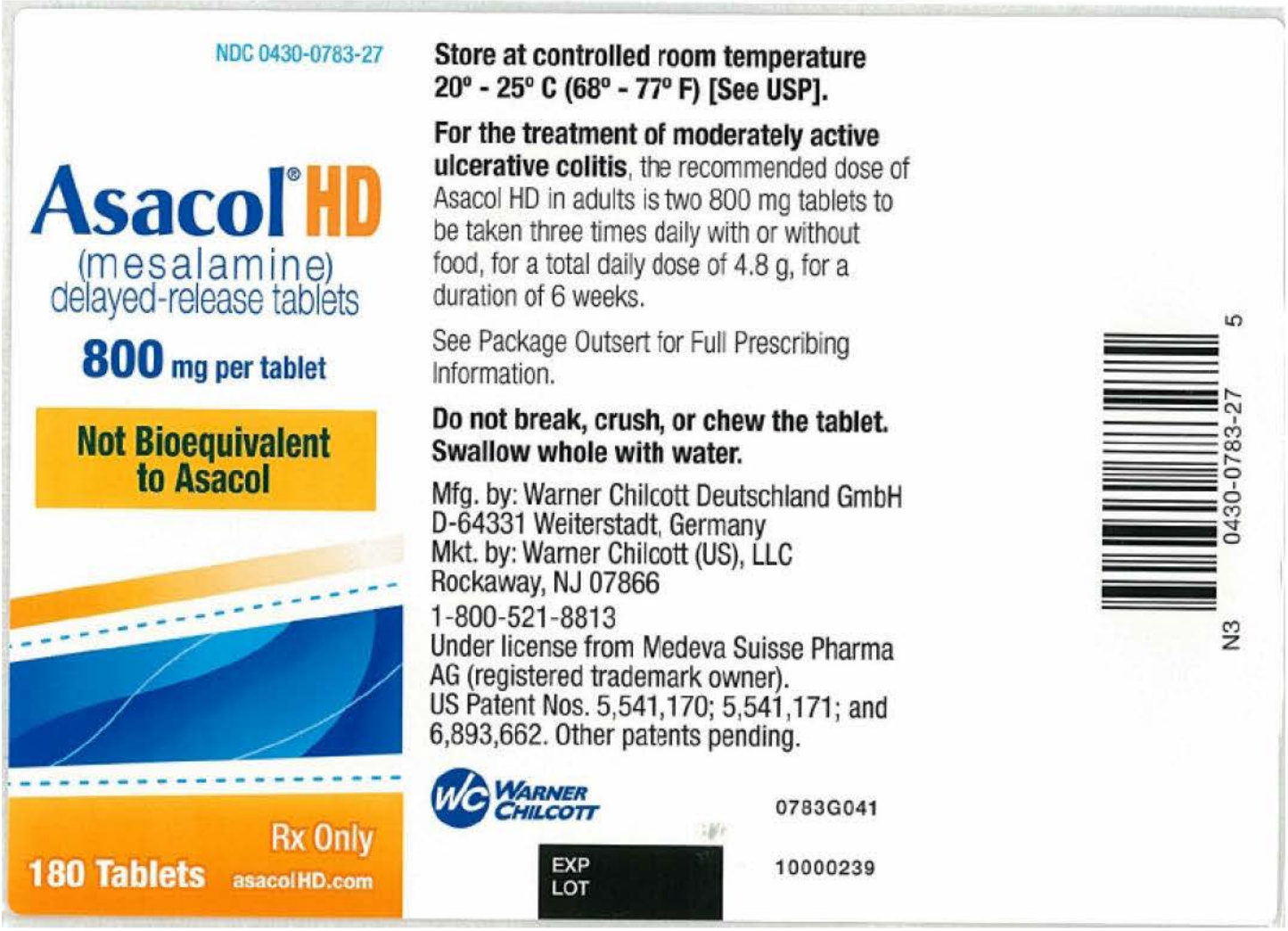
Reviewer Assessment:

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

Reviewer Comments:

3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. [DailyMeds, Rev.4/2015]



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

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	6/3/2015	YES	Mesalamine Delayed-release Tablets	Packaging and storage – Preserve in tight containers
PF	6/3/2015	NA	Click here to enter text.	Click here to enter text.

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/3/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6893662	11/15/2021	U-141	TREATMENT OF ULCERATIVE COLITIS	IV	7/15/2014	None
6580302	11/15/2021				7/15/2014	None

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

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

Are there changes to the manufacturing statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	Each mesalamine delayed-release tablet contains 800 mg of mesalamine. In addition, each tablet contains the following inactive ingredients: acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black S-1-17823 which contains following ingredients: ammonium hydroxide, butyl alcohol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and shellac.	**The imprinting ink changed from (b) (4) to "opacode black S-1-17823.** **(Created an issue to the chemist in the GDRP)**

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	Mesalamine Delayed-release Tablets, USP 800 mg are reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets, imprinted with "435" on one side and plain on other side and are supplied as follows: NDC 68382-435-28 in bottles of 180 tablets (b) (4) NDC 68382-435-77 in cartons of 100 tablets (10 x 10 unit-dose)	(b) (4)

Table 7: Manufactured by statement

Table 7: Manufactured by statement		
Previously Labeling Review	Currently Proposed	Assessment
Manufactured by: Cadila Healthcare Ltd. Ahmedabad, India **Distributed by:** **Zydus Pharmaceuticals USA Inc.** Pennington, NJ 08534	**Manufactured by:** **Cadila Healthcare Ltd.** **Ahmedabad, India** **Distributed by:** **Zydus Pharmaceuticals USA Inc.** **Pennington, NJ 08534**	**No change**

5. COMMENTS FOR CHEMISTRY REVIEWER

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

a. [redacted] (b) (4)

The chemistry review does not make reference to these package configurations.

b. Created an issue in the GDRP for consult to the quality reviewer regarding the change of the imprinting ink described above. Here is the response from the Quality reviewer:

From: Majumder, Quamrul
Sent: Friday, June 05, 2015 11:10 AM
To: Park, Chan H
Subject: RE: ANDA 203286 (Mesalamine)

Chan
You have asked these questions in the GDRP ...How do I add response back ?
So I'm responding in email.
Yes you are right the sponsor had changed the imprinting ink from [redacted] (b) (4) to "opacode black S-1-17823 [redacted] (b) (4)
Packing configuration has been changed and it is acceptable but we still wanted them perform an in-use stability studies on tablets in highest count bottle to determine the effect of repeated opening and closing of pharmacy/patient bottles during routine use by customer and/or patient.

-Thanks,

Quamrul Majumder,

Reviewer Comments:

Click here to enter text.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, if you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Date**	**Recommendation**
Container	Final	180s, (b) (4)	2/24/2015	NAC
Blister	Final	10s	2/24/2015	AC
Carton	Final	100 (10 x 10) Unit-dose Tablets	2/24/2015	AC
(Other – specify)				
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Date**	**Recommendation**
Prescribing Information	Final	8/2014	2/24/2015	NAC
Medication Guide				
Patient Information				
SPL Data Elements		8/2014	2/24/2015	AC

* Post-approval revision

PROFESSIONAL LABELING REVIEW
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 203286

Applicant's Name: Zydus Pharmaceuticals (USA) Inc.

Submission Date: July 12, 2011 (Original)

Established Name: Mesalamine Delayed-release Tablets USP, 800 mg

---

Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☒ Easily correctable (respond within 10 business days)

☐ No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

_ _

Labeling Deficiencies determined on April 21, 2013 based on your submission dated July 12, 2011:

1. CONTAINER (b) (4) [redacted] 180s, (b) (4) [redacted]

   (b) (4) [redacted]

2. BLISTER – 10s

   If space permits, include the phrase “Made in India”.

3. INSERT

   a. GENERAL

      i. Please refer to 21 CFR 201.56(d) regarding PLR format for the final printed labeling. Please ensure that the highlight sections and the entire insert can easily be read and that the point type not be smaller than 6.

ii. Please replace "Asacol-HD" with (b) (4) "mesalamine delayed-release tablets" (b) (4) (b) (4)

iii. (b) (4)

b. DESCRIPTION

(b) (4)

c. 8 USE IN SPECIFIC POPULATIONS – 8.1 Pregnancy: (b) (4)

Revise this subsection heading to read "Pregnancy: (b) (4)
We refer you to CFR 201.57(9)(A)(3).

Submit your revised labeling electronically in final print format.

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.

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

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

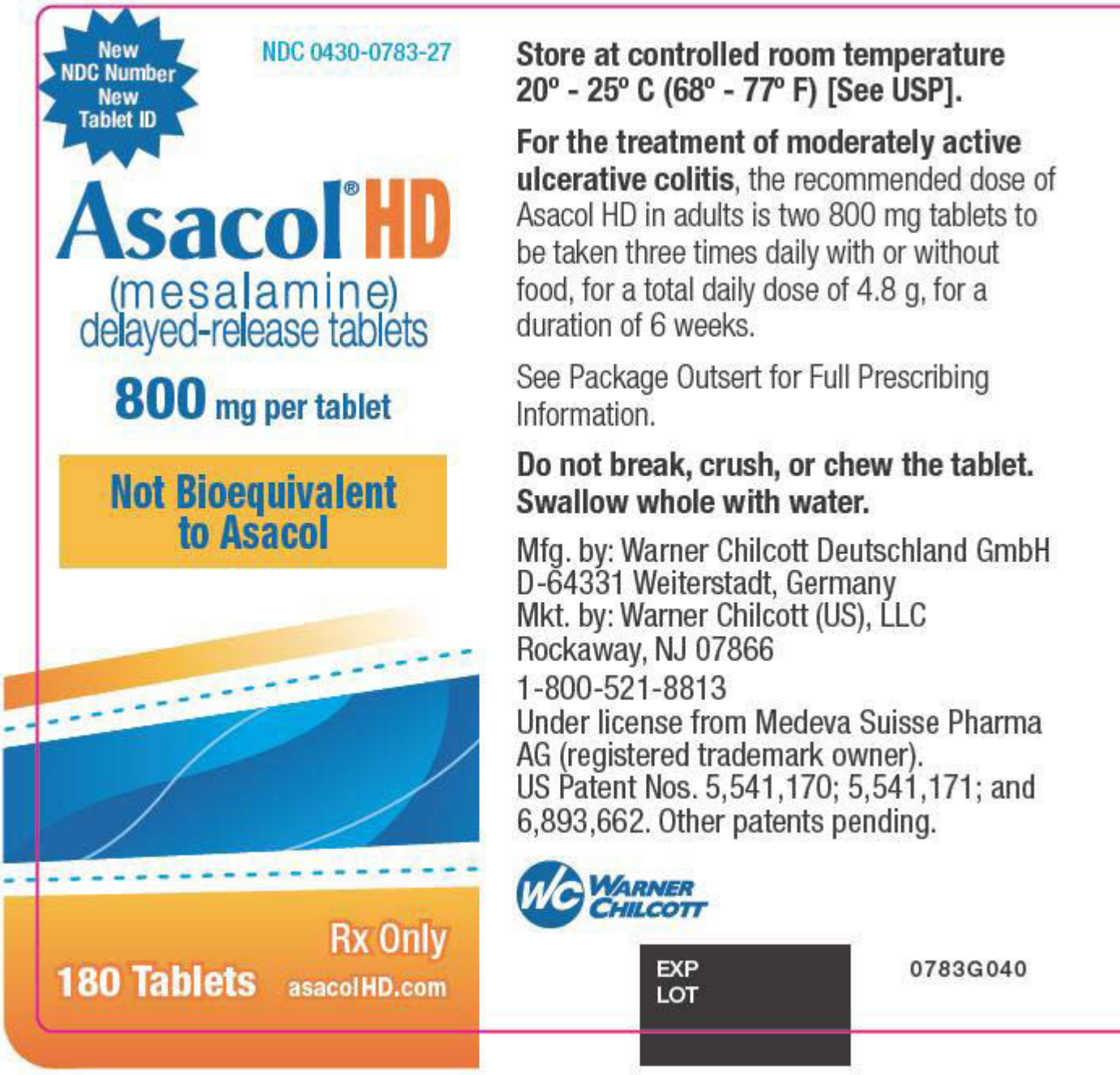
_ _

Note RPM - Labeling comments end here

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING – Asacol HD Delayed-Release Tablets, 800 mg, (NDA 021830/S-005), approved May 24, 2010. It is still current as of the 4/22/2013.



2. This **is FIRST GENERIC for the 800 mg strength.** This drug product is also available in 400 mg and 1.2 gm strength.

3. USP 35 Drug Product Monograph – yes (4/19/2013):
   Packaging and storage – Preserve in tight containers
   PF 36: No new information for the drug product.

4. PATENTS AND EXCLUSIVITIES Patent Data (4/19/2013)

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Certification	Patent Use Code	Labeling Impact
N021830	001	5541170	Jul 30, 2013	III	U - 141	NONE
N021830	001	5541171	Jul 30, 2013	III	U - 141	NONE
N021830	001	6893662	Nov 15, 2021	IV	U - 141	NONE

Exclusivity Data

There is no unexpired exclusivity for this product.

4. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert **is consistent** with the listing of inactive ingredients found in the statement of components and composition.

Insert - Each mesalamine delayed-release tablet contains 800 mg of mesalamine. In addition, each tablet contains the following inactive ingredients: acetyltributyl citrate, colloidal silicone dioxide, ferric oxide red, magnesium stearate, methacrylic acid copolymer type B, microcrystalline cellulose, povidone, sodium starch glycolate, talc and titanium dioxide. The tablet is printed with opacode black (b) (4)

Quality 3.2.p.1

Ingredient (Trade name, if any)	Pharmaceutical Function(s)
Mesalamine, USP	Active pharmaceutical ingredient
Sodium Starch Glycolate, NF (b) (4)	(b) (4)
Colloidal Silicon Dioxide, NF (b) (4)	
Magnesium Stearate, NF	
Microcrystalline Cellulose, NF (b) (4)	
Povidone (b) (4) USP (b) (4)	
Talc, USP	
Methacrylic Acid Copolymer, NF - Type B (Eudragit S (b) (4)	
Acetyltributyl Citrate, NF	
Titanium Dioxide, USP (b) (4)	
Ferric Oxide Red, NF	
Isopropyl Alcohol, USP*	
(b) (4)	
(b) (4)	

(b) (4)

(b) (4)

Maximum Daily Dose: 4.8 mg/day
Strength: 800mg
(b) (4)

(b) (4)

(b) (4)

5. MANUFACTURING FACILITY
Cadila Healthcare Limited
(b) (4)
(b) (4) Ahemdabad (b) (4)
(b) (4) India

6. PRODUCT DESCRIPTION: **Consistent** with Quality 3.2.p.1 section

RLD: (b) (4)

ANDA: Insert - Mesalamine delayed-release tablets are available as reddish-brown colored, capsule-shaped, biconvex, enteric coated tablets imprinted with "435" on one side and plain on other side.

Quality 3.2.P.1.1 (Dosage form)
Reddish brown colored capsule shaped, biconvex enteric coated tablets imprinted with "435" on one side and plain on other side.

7. CONTAINER/CLOSURE SYSTEM:

Count	(b) (4)
180 Tablets	(b) (4) (b) (4) (b) (4)

CRC: Child Resistant Closure; NCRC: Non Child Resistant Closure

Blister Pack (Push through) - 10's Counts

10 Tablets	(b) (4)

(b) (4)

8. PRODUCT LINE:
RLD: (b) (4)
ANDA: Bottles of (b) (4) 180s, (b) (4) and blister pack of 100s (10 x 10s)

9. STORAGE CONDITIONS:
RLD: "(b) (4)
ANDA: "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]."

Stability Test Protocol

Study	Storage Condition	Test Interval
Long Term	25 ± 2°C/ 60 ± 5% RH	0, 3, 6, 9, 12, 18, 24 months
Intermediate*	30 ± 2°C/ 65 ± 5% RH	0, 1, 2, 3, 6, 9 and 12 months
Accelerated	40 ± 2°C/ 75 ± 5% RH	0, 1, 2, 3 months

*The samples at intermediate condition will be analyzed if significant change occurs at any time during 3 months testing at the accelerated storage condition.

10. DISPENSING RECOMMENDATIONS:
(b) (4)

11. MEDWATCH (checked 4/22/2013) - No new alerts or labeling changes.

12. REMS (checked 4/22/2013) - None

13. SPL – DPDE:
Accurate as of the 7/12/2013 submission

14. Tablet Size:

RLD – (b) (4)
ANDA – (b) (4)

Date of Review: April 22, 2013

Primary Reviewer: Chan Park

Team Leader: Koung Lee

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHAN H PARK
04/23/2013

KOUNG U LEE
04/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

CHEMISTRY REVIEWS

CHECKLIST FOR THE CHEMISTRY REVIEW:

ANDA-203286-ORIG-1-AMEND-23; ZYDUS PHARMACEUTICALS USA INC., Mesalamine Tablet- DELAYED ACTION

Function	**Performed By (Initial and Date)**	**Check appropriate box**
Is this package for new strength PAS?	MJN 6/30/2017	☐ Yes ☒ No
DMF adequate?	MJN 6/30/2017	☒ Yes ☐ No *(see comments)
Any outstanding consults?	MJN 6/30/2017	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☒ Yes ☐ No ☐ N/A
Are all facility inspections acceptable?	MJN 6/30/2017	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	MJN 6/30/2017	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A
Is the final review uploaded into the current IT platform?	MJN 6/30/2017	☒ Yes ☐ No

Division	Signature	Date
OPF	Naiqi Ya	7/11/2017

Submission Overall Manufacturing Facility Status

Overall Inspection Recommendation	Completion Date	Submission Status	Project Name
Approve	6/16/2017	Pending	ANDA-203286-ORIG-1-AMEND-23
Withhold	9/8/2016	Complete Response	ANDA-203286-ORIG-1-AMEND-20
Withhold	1/29/2016	Complete Response	ANDA-203286-ORIG-1-AMEND-15
Withhold	6/26/2015	Complete Response	ANDA-203286-ORIG-1-AMEND-9

Naiqi Ya

Digitally signed by Naiqi Ya
Date: 7/11/2017 03:57:48PM
GUID: 508da70200028815b8e6bac755028bd4

Recommendation: CMC adequate pending facilities

ANDA:

☒ **Approval**

☐ **Information Request – Minor**

(_____days for applicant to response)

☐ **Complete Response - Minor**

☐ **Complete Response – Major**

ANDA 203286

Amendment Review

Drug Name/Dosage Form	Mesalamine Delayed Release Tablets, USP
Strength	800 mg
Reviewer(s)	Kamal Tiwari
Applicant	Zydus Pharmaceuticals (USA) Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment	4/6/2017

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
22999	Type II	Cadila Healthcare Limited	Mesalamine USP	Adequate	03/24/2017	Z. Wang

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
CMC (samples requested for appearance and dissolution testing)	Completed.	(b) (4)	5/5/2015	

FACILITIES: Withhold dated 9/8/2016. Currently OMIR is pending (New)

Drug Substance			
Function	**Site Information**	**FEI #**	**Status**
(b) (4)	(b) (4)	(b) (4)	Approve 1/29/2016
Drug Product			
Function	**Site Information**	**FEI #**	**Status**
(b) (4)	Cadila Healthcare Limited (b) (4) (b) (4) Ahemdabad (b) (4) (b) (4) India	3002984011	Withhold - OAI 1/29/2016

This review template is updated on April 15, 2015

P.7

P.8

Labeling & Package CMC Related Concerns: N/A

Overall Reviewer's Assessment and Signature:

CMC of this ANDA is adequate.

Kamal Tiwari; 05/26/2017

Secondary Review Comments and Concurrence:

Naiqi Ya

List of Deficiencies To Be Communicated by Information Request or Complete Response:N/A

Naiqi Ya

Digitally signed by Naiqi Ya
Date: 5/31/2017 09:29:09AM
GUID: 508da70200028815b8e6bac755028bd4

Recommendation:
ANDA:
☐ **Approval**
☐ **Information Request – Minor**
(30 days for applicant to response)
☒ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 203286

Amendment Review

Drug Name/Dosage Form	Mesalamine Delayed Release Tablets, USP
Strength	800 mg
Reviewer(s)	Huiquan Wu
Applicant	Zydus Pharmaceuticals (USA) Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment	10/19/2015
IR Response	3/1/2016
IR Response	6/20/2016
Amendment	8/9/2016

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
22999	II	Cadila Healthcare Limited	Mesalamine USP	Adequate with IR (as of 07/15/2016) A new submission on 08/02/2016 may need to be reviewed by DMF division*	01/06/2016	Z. Wang
			(b) (4)	4		
				4		
				4		
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				4		
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				4		
				4		
				4		

(b) (4)			
	4		
	4		
	4		
	4		
	4		
	4		
	4		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

*The review team alerted the potential need for review of the DMF 22999 submission dated 8/2/2016 to Maya Johnson-Nimo (the RBPM for this application) on Thursday 01/05/2017. As per Maya's response at the same day, that "Please note, DMF 22999 has been reviewed and is adequate. Annual reports do not generally contain technical information, so they are no longer reviewed as stand-alone reviews unless a quality or facility amendment is forwarded. This summary is also captured in panorama if needed. The review is due Jan 31st

(b) (4)

Please let me know if you have any questions." Based on the above recommendation, we will only request the ANDA applicant to update their drug substance specifications in ANDA.

CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
CMC (samples requested for appearance and dissolution testing)	Completed.	(b) (4)	5/5/2015	

FACILITIES: Withhold

Drug Substance			
Function	**Site Information**	**FEI #**	**Status**
(b) (4)	(b) (4)	(b) (4)	Approve 1/29/2016
Drug Product			
Function	**Site Information**	**FEI #**	**Status**
(b) (4)	Cadila Healthcare Limited (b) (4) (b) (4) Ahemdabad (b) (4) (b) (4) India	3002984011	Withhold - OAI 1/29/2016

Review #1 (Not Approvable – MAJOR)

ANDA 203286

Mesalamine Delayed Release Tablets USP, 800 mg

Zydus Pharmaceuticals (USA) Inc.

Quamrul Majumder, Ph.D.
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 293286:

2. REVIEW #: 1

3. REVIEW DATE: 11/9/2013

4. REVIEWER: Quamrul Majumder

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Acknowledgment	09/09/2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	07/12/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Zydus Pharmaceuticals (USA) Inc.
Address:	Cadila Healthcare Limited (b) (4) Ahemdabad (b) (4) India FEI Number: 3002984011
Representative:	Mr. G. Srinivas Zydus Healthcare LLC 73 Route 31 North, Pennington, NJ 08534-3601 Email: gsrinivas@zydususa.com
Telephone:	Tel: 609-730-1900 Fax: 609-730-1999

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

Proprietary Name:
Non-Proprietary Name (USAN):

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) Asacol HD®, NDA No. 21830, manufactured by Warner Chilcott (US) LLC, NJ. The firm has filed Paragraph IV certification for U.S. Patent Nos. 6893662 (exp. Nov. 15, 2021). They have also indicated that according to the Orange Book, there is no unexpired exclusivity for the product.

10. PHARMACOL. CATEGORY: Indicated for mild to moderate ulcerative colitis.

11. DOSAGE FORM: Delayed Release Tablet

12. STRENGTH/POTENCY: 800 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X Rx __ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Please see drug substance section.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
22999	II	Cadila Healthcare Limited	Mesalamine USP		Inadequate	02/20/2014	Z. Wang
(b) (4)	III	(b) (4)			4		
	III				4		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
1	N021830	Asacol® HD

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Inadequate	04/23/2013	PARK, CHAN H
Bioequivalence	Dissolution –Adequate Bio- Adequate In vitro BE Dissolution study-Inadequate	11/15/2013	REN, PING
Toxicology/Clinical	N/A		
EA	CE provided		
Radiopharmaceutical	N/A		
Samples Requested	Yes- for visual evaluation	11/19/2013	Q. Majumder

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
[i.e. manufacturer, contract lab, etc.]	*[Location, address, etc.]*		
(b) (4)			(b) (4)
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)	Cadila Healthcare Limited (b) (4) (b) (4) Ahemdabad (b) (4) India	FEI Number: 3002984011	

Executive Summary Section
Chemistry Review for ANDA 293286

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC deficiency.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(b) (4)

[redacted]

B. Description of How the Drug Product is Intended to be Used

(b) (4)

[redacted]

Executive Summary Section

	IT	QT
DS	0.05%	0.05%
DP	0.10%	0.15%

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval. Major CMC deficiency is recommended as Division of Bioequivalence is asking for dissolution data from a fresh (new) batch due to high dissolution variability.

ADMINISTRATIVE

A. Reviewer's Signature
Quamrul Majumder

B. Endorsement Block

Chemist Name/Date: Q Majumder/ 11/27/2013,12/30/2013
Chemistry Team Leader Name/Date: R. Rajagopalan/ 12/22/2013;12/31/2013;1/2/1014
Project Manager Name/Date: F Nice/2/20/14
Division/P. Capella for S. Rosencrance/07-Jan-2014; 20-Feb-2014 (after DMF review completed)

TYPE OF LETTER: MAJOR Deficiency, Not Approvable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QUAMRUL MAJUMDER
02/20/2014

FRANK J NICE
02/21/2014

RADHIKA RAJAGOPALAN
02/21/2014

PETER CAPELLA on behalf of SUSAN M ROSENCRANCE
02/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	203286		
Drug Product Name	Mesalamine Delayed Release Tablets USP		
Strength(s)	800 mg		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Applicant Address	73, Route 31 North, Pennington, NJ 08534		
US Agent Name and the mailing address	G. Srinivas Zydus Pharmaceuticals USA Inc., 73, Route 31 North, Pennington, NJ 08534		
US agent's Telephone Number	609-730-1900		
US Agent's Fax Number	609-730-1999		
US Agent's Email Address	gsrinivas@zydususa.com		
Original Submission Date(s)	07/12/2011		
Submission Date(s) of Amendment(s) Under Review	02/24/2015 and 10/19/2015, amendments for in vitro dissolution testing		
First Generic	Yes		
Reviewer	Diana Vivian, Ph.D.		
Study Number (s)	# MSN-P0-732	# MSN-P0-733	
Study Type (s)	Fasting	Fed	In vitro BE study
Strength (s)	800 mg	800 mg	800 mg
Clinical Site	Algorithme Pharma Inc.		
Clinical Site Address	1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1		
Analytical Site	(b) (4)		
Analytical Site Address			
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**	
OVERALL REVIEW RESULT	**ADEQUATE**		
REVISED/NEW DRAFT	**NO**		

GUIDANCE INCLUDED			
COMMUNICATION	☐ ECD ☐ IR ☒ NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting Study	800 mg	Adequate
1	Fed Study	800 mg	Adequate
1, 9, 15	In vitro BE Dissolution study	800 mg	Adequate

1 EXECUTIVE SUMMARY

This is a review of a study amendment.

The original application (07/12/2011) contained the results of fasting and fed bioequivalence (BE) studies comparing a test product Mesalamine Delayed Release Tablets, 800 mg, to the corresponding reference product Asacol® HD (Mesalamine Delayed Release) tablets, 800 mg. The results of the 95% upper confidence bound for AUC_{0-t}, $AUC_{8-48,}$ and Cmax in the fasting and fed BE studies were negative. The point estimate (test/reference geometric mean ratio) for AUC_{0-t}, $AUC_{8-48,}$ and Cmax were within the range of 0.80 to 1.25. Hence, the fasting and fed studies met the BE acceptance criteria of reference scaled analysis for log-transformed AUC_{0-t}, $AUC_{8-48,}$ and Cmax of Mesalamine Delayed Release Tablets, 800 mg. The fasting and fed studies were acceptable[1].

In addition to in vivo fasting and fed BE studies, the guidance also recommends comparative in vitro BE dissolution studies (using USP Apparatus II at 50 rpm) to be conducted in pH 4.5, 6.0, 6.5, 6.8, 7.2 and 7.5 phosphate buffer representative of the GI tract pH variations. Yet, in the original application, the firm did not submit any dissolution data for pH 4.5 acetate buffer. Also, the mean values (f2) in pH 6.8 and pH 7.5 phosphate buffer were less than 50 and the lower bound of 90% confidence interval ("CI") for the f2 test comparing test vs. RLD in pH 6.8, pH 7.2, and pH 7.5 phosphate buffer was lower than those comparing the RLD against itself under the same conditions. These values indicated that the dissolution profiles of the test product were significantly different from those of the corresponding reference product under these conditions. Therefore, the in vitro BE (comparative dissolution) studies under pH 6.8, 7.2 and 7.5 buffer were not acceptable. Due to the high variability of the firm-submitted dissolution data conducted in multiple pH media, the firm was requested to repeat comparative dissolution testing on its fresh test product using a larger sample size (e.g. 24 units of test product and two lots of unexpired RLD product) to provide a better estimate of the mean difference, or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculations.

In the amendment dated 02/24/2015, the firm conducted additional dissolution testing in the medium of pH 4.5 acetate buffer and repeated dissolution testing in the media of pH 6.8,7.2, and 7.5 with a larger sample size (n=24) to reduce variability for the purpose of achieving accurate f2 calculations. The firm's data showed the percent drug released from both the test and reference products is less than 5% in the medium of pH 4.5 during a period of 960 min (16 hrs) dissolution testing. The incomplete drug release at this pH is due to the delayed release nature of this product. Therefore, the in vitro dissolution data in the medium of pH 4.5 were accepted. Additionally, the results of the mean f2 values and the lower bound of 90% confidence intervals for f2 values comparing the test vs.

[1] DARRTS: REV-BIOEQ21 (Primary Review) ANDA203286, Final date: 11/15/2013.

reference indicated that the test and reference products have a similar dissolution profile under pH 6.8 and pH 7.2 conditions. [2]

However, as per detailed analysis for the dissolution profile at pH 6.8, (b) (4) (b) (4) (b) (4) pH 6.8 (e.g. pH (b) (4) 6.8, (b) (4)) using a recommended dissolution method on mesalamine (800 mg).

In the current amendment, dated 10/19/2015, (b) (4) meeting between the Division of Bioequivalence (DB) and the Office of Research and Standards (ORS) for related ANDA 091640, (b) (4) (b) (4)

Because of the related DB decision for ANDA 091640 which indicate (b) (4) supporting dissolution data newly submitted by the firm and from the FDA labs, the firm's response is acceptable.

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

[2] GDRP; ANDA-203286-ORIG-1-AMEND-9, Bioequivalence Primary Review, A203286NA022415.doc , dated 5/19/2015.
[3] DARRTS; ANDA 091640, 03/01/2014, REV-BIOEQ-21(Primary Review). Page 89 of 223.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Review of Submission

3.1.1 DBII Deficiency Comment:

At pH 6.8, there is a significant difference in the dissolution profile for the test product between the original (07/12/2011) and amendment (02/24/2015) submissions. Please provide an explanation for this difference. In addition, please submit 12 units dissolution data of the test and reference products in buffers with pH around 6.8 (e.g. (b) (4) 6.8, (b) (4) using the following dissolution method on your test product:

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of

(1) (b) (4)
(2) pH 6.8 Phosphate buffer at 50 rpm
(3) (b) (4)
(4)

Volume: 900 mL
Temperature: 37ºC
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison.

Please submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable. Besides the dissolution summary table in the eCTD format, please submit the individual unit dissolution data and mean values in excel or sas transport format.

Zydus' Response to Deficiency Comment:
Zydus received a similar comment about the dissolution data at pH 6.8 in connection with its pending application for another Mesalamine Delayed-release product, Mesalamine Delayed–release Tablets, 1.2 g (ANDA No. 091640). Apparently, Mesalamine Delayed-release products exhibit extremely high day-to-day variability in dissolution data at around pH 6.8 evaluation stage, which were observed for both the test and reference products. The Agency ultimately accepted Zydus's dissolution data at pH 6.8 for Mesalamine Delayed–release Tablets, 1.2 g as described below.

On May 29, 2015, the Agency sent Zydus a complete response letter for ANDA No. 091640. In that letter, FDA noted:

"Although your test product at 31 month (expired) met the shelf life specification, we noticed that the dissolution data of the fresh test product (1 month) in your submission dated October 23, 2013, is significantly different from that of 31 month old product (submitted in amendment December 6, 2014) under pH 6.8. Using bootstrapping method, the F2 value between the data of your 1 month and 31 month test product at pH 6.8 is only 25.66, Therefore, your dissolution testing data at pH 6.8, (b) (4) *in the current amendment (December 6, 2014) is not acceptable. Please provide your explanation for the observed faster release of the aged product when compared to the fresh product."*

A copy of the Agency's May 29, 2015 complete response letter (Mesalamine Delayed–release Tablets, 1.2 g) is included for the Agency's reference in Module 1.2.
In that same letter, the Agency asked Zydus to conduct additional dissolution testing using 24 units, rather than 12 units, of newly prepared (unexpired) test product and 24 units of reference product at pH 6.8, (b) (4)

On June 5, 2015, Zydus requested a **Post Complete Response Teleconference Meeting** to discuss deficiencies noted in the May 29, 2015 complete response letter for ANDA No. 091640. In that submission, Zydus explained the observed variability in dissolution at pH 6.8 as follows:

"Cadila healthcare Limited conducted method validation for dissolution method with pH 6.8 phosphate buffer based on the deficiency cited in complete response letter dated March 26, 2014 to address day to day variability. Based on the intermediate precision and trend of dissolution data on robustness experiments it was concluded that day to day variability of both test and reference product at pH 6.8 is due to (b) (4) *It was also supported with the consistent in-vitro dissolution data on higher pH (i.e. pH 7.2- OGD method).*

In the subsequent complete response letter issued by the agency dated September 09, 2014, based on the submitted data the agency acknowledged the firm's investigations on day to day variability at pH 6.8 and suggested to re-perform in-vitro dissolution comparison on test product and reference product on ***same day****. Based on agency's recommendation we have generated data on the same day for 24 units of test product of age 31 month complying to our shelf-life specification and two different lots of reference product with 12 units each at pH 6.8,* (b) (4) *Based on this reanalysis F2 was calculated by bootstrapping method as per the guidance.*

In all three pH buffers, satisfactory F2 above 50 was established based on same day analysis. On the basis of firm's investigations and re-analysis data on same day we are concluding that F2 value calculated by agency comparing the dissolution data of 1 month sample and 31 month sample of test product as cited in the recent complete response letter dated May 29, 2015 may not be appropriate since these two dissolution data were

*generated on **two different days**. We believe that lower F2 value between 1 month and 31 month analysis is the result of inherent analytical variability due to day to day variability in pH 6.8. It is also evident from the fact that the drug release data in official OGD method (Firm's Quality control method) on aged sample (31 month) did not show any significant change and the data is well within the shelf-life specification."*

A copy of the Post Complete Response Teleconference Meeting Request Packet (Mesalamine Delayed–release Tablets, 1.2 g) is included for the Agency's reference in Module 1.2.

On June 12, 2015, the Office of Generic Drugs issued a Meeting Request Granted-Written Responses Only. On August 21, 2015, the Office of Generic Drugs issued the following written response:
"The Division of Bioequivalence II (DBII) has re-evaluated the data for the in vitro BE dissolution studies, as well as your rationale for the high variability of dissolution data at pH 6.8. The DBII concludes that the in vitro BE dissolution testing at pH 6.8 is now acceptable. Therefore, DB II agrees with your request to waive the additional data requested in the complete response letter dated May 28, 2015."

A copy of the Agency's Meeting Request Granted- Written Responses Only (Mesalamine Delayed– release Tablets, 1.2g) is included for the Agency's reference in Module 1.2.

As with ANDA No. 091640, Zydus reports that the observed difference in the dissolution data at pH 6.8 for Zydus's Mesalamine Delayed-release Tablets USP 800 mg between the original submission (July 12, 2011) and the February 24, 2015 Amendment is the result of the inherent day to day variability in dissolution at pH 6.8. This day to day variability is observed in both the test and reference products at pH 6.8, and is due to (b) (4) which is soluble at pH ≥ 7.0. Hence, it is not appropriate to compare dissolution data at pH 6.8 for dissolution profiles generated on different days.

Dissolution data of the test and reference products in buffers with pH around 6.8 (e.g. pH (b) (4) 6.8, (b) (4)

Further to the above explanation, and as requested by the Agency, Zydus conducted new dissolution testing on the Test and Reference products of Mesalamine Delayed-release Tablets, 800 mg in buffers with pH around 6.8 (e.g. (b) (4) 6.8, (b) (4). We performed the additional dissolution testing using 24 units of the Test product and 24 units of the Reference product from two batches (12 units per batch), to be consistent with the Agency's request in ANDA No. 091640 (Mesalamine Delayed-release Tablets, 1.2 g) on May 29, 2015 for comparative in vitro dissolution testing. We believe that due to the variability in the dissolution data for Mesalamine Delayed-release tablets around pH 6.8 (as explained above), it is justifiable to use more than 12 units of the tablets to achieve a meaningful comparison of dissolution profiles between the Test and Reference products around this pH range. Therefore, we conducted comparative dissolution testing on 24 units of the Test product (Batch No. EMP 203) and 12 units from each of the two unexpired Reference lots on the same day.

The individual unit dissolution data and mean values along with sas transport format (pH [(b) (4)] pH 6.8, [(b) (4)]) are provided in Module 5.3.1.3 of this Amendment. Please refer Module 2.7.1 for dissolution summary table in eCTD format. The summary dissolution testing results is presented below in Tables 1-4 for the Agency reference.

Table 2: Summary of Dissolution Data for Test and Reference Products Using Methods Defined by the FDA: Pretreatment Stage and Evaluation Stage pH 6.8

Product	TEST PRODUCT Mesalamine Delayed-release Tablets, 800 mg				REFERENCE PRODUCT Asacol HD® (Mesalamine) Delayed-release Tablets, 800 mg			
Batch No.	EMP203 Mfg. Date: April, 2014				457836 S2 (12 units), 457840 S1 (12 units) Expiry Date: 457836 S2 –May, 2017; 457840 S1 –May, 2017			
Manufacturer	Cadila Healthcare Limited, India				Warner Chilcott (US), LLC.			
Test Date: September 04, 2015								
Pretreatment Stage: 2 Hours in 0.1N HCl								
% Dissolved								
Time (Hr)	Mean	Min	Max	%CV	Mean	Min	Max	%CV
2 hr	0.0		(b) (4)	0.0	0.0		(b) (4)	0.0
Evaluation Stage (pH 6.8 Phosphate Buffer)								
% Dissolved								
Time (min)	Mean	Min	Max	%CV	Mean	Min	Max	%CV
10	1.4		(b) (4)	107.9	0.3		(b) (4)	186.7
20	2.3			88.2	1.0			181.0
30	5.6			121.3	5.8			143.1
45	11.6			116.2	15.0			138.7
60	17.6			110.5	25.1			116.9
75	27.2			78.8	33.1			103.4
90	35.8			73.1	38.8			95.0
120	48.7			73.1	47.9			80.2
150	55.0			67.0	57.3			65.8
180	70.9			45.4	66.9			54.3
240	97.1			3.5	87.5			16.4
300	99.5			3.4	94.4			8.6
360	100.9			3.1	97.7			5.7

The above dissolution data demonstrate that the mean dissolution profiles (% dissolved vs. time) of the Test product batch at (b) (4) pH 6.8, (b) (4) evaluation stages are almost identical to the mean profiles of the two Reference product batches.

Due to the high variability in dissolution data of the Test and Reference products, we calculated the f2 (similarity factor) values using a bootstrapping method to compare the dissolution profiles between the Test and Reference products as follows.

Using the bootstrapping method, by creating 10,000 replicates of the Test and Reference product units, the mean percent dissolved at each time point was obtained for each replicate to calculate f2 values. Subsequently, the mean and 90% confidence intervals of the f2 values between Test and Reference products were calculated for each pH at the evaluation stage.

The complete statistical analysis summary report is provided in Module 5.3.1.3 of this Amendment. A summary of the results is presented in the Table below.

Summary of f2 (Similarity Factor) Values Determined by Percentile Bootstrapping Method at each pH Evaluation Stage in the Dissolution of the Mesalamine Delayed-release Tablets, 800 mg

Evaluation Stage pH	Parameters	Observed f2	Average of f2	Median of f2	90% lower CI of f2	90% upper CI of f2
(b) (4)						
6.8	Test vs R1+R2	66.67	55.82	55.61	48.19	63.91
	R1 vs R2	43.63	39.80	39.41	32.96	47.88
(b) (4)						

Test: Test Batch EMP 203 (24 units), R1: Reference Batch 457836 S2 (12 units), R2:Refeence Batch 457840 S1 (12 units)

The above f2 data demonstrate that the dissolution profiles are similar between the Test and Reference products at (b) (4) and (b) (4) because the mean and lower bound of the 90% confidence interval of the f2 values for Test vs. Reference are all greater than 50. The mean f2 value at pH 6.8 or (b) (4) for Test vs. Reference is also greater than 50; however, the lower bound of the confidence interval of the f2 value at pH 6.8 or (b) (4) for Test vs. Reference is less than 50. Nevertheless, the lower bound of the 90% confidence interval of the f2 value at pH 6.8 (b) (4) for Test vs. Reference is greater than that for Reference Batch 1 vs. Reference Batch 2, i.e., 48.19 vs. 32.96 (b) (4) (b) (4)

The f2 values calculated for Reference Batch 1 vs. Reference Batch 2 showed that the dissolution profiles are not even similar between the two Reference batches at pH 6.8 and (b) (4) in addition to (b) (4) in the evaluation stage. This clearly demonstrates the large batch-to-batch variability in the Reference product.

In the Summary Basis of Approval (SBA) of NDA # 204412, Delzicol® (Mesalamine Delayed-release Capsules, 400 mg), the 90% confidence intervals for the f2 values were calculated using percentile and bias-corrected and accelerated (BCA) approaches. Based on this approach, we have calculated the 90% confidence intervals for f2 values using the BCA bootstrap method (Test product vs. RLD Asacol® HD) which is considered to be more reliable (Reference: Summary Basis of Approval, Clinical Pharmacology and Biopharmaceutics Review, Application No. 204412Orig1s000, ONDQA Biopharmaceutics Review, Page 11).

A summary of the analysis results the dissolution data obtained for Test and Reference products of Mesalamine Delayed-release Tables, 800 mg is presented in the table below.

Evaluation Stage pH	Parameters	Observed f2	Average of f2	Median of f2	90% lower CI of f2	90% upper CI of f2 (b) (4)
6.8	Test vs R1+R2	66.67	55.82	55.61	**69.28**	**75.47**
	R1 vs R2	43.63	39.80	39.41	**40.07**	**59.90**
						(b) (4)

Test: Test Batch EMP 203 (24 units), R1: Reference Batch 457836 S2 (12 units), R2: Reference Batch 457840 S1 (12 units)

The above f2 data demonstrate that the dissolution profiles are similar between the Test and Reference products (Asacol® HD) at all pHs in the evaluation stage, ie., (b) (4) pH 6.8, (b) (4) because the mean and lower bound of the 90% confidence interval of the f2 values at all pHs are greater than 50. The complete statistical analysis summary report is provided in Module 5.3.1.3 of this Amendment.

Due to the variability and bias in the Reference product, the BCA (bias corrected accelerated) bootstrapping method is considered to be more reasonable and reliable in calculating the 90% confidence interval for the similarity factor and has been applied in other approved drug products (e.g., Delzicol®).

The 90% lower limits of BCA bootstrapped f2 values for the Test (Mesalamine Delayed-release Tablets USP, 800 mg by Cadila Healthcare Limited) vs. Reference products (Asacol® HD) are greater than 50 in all the dissolution media (at all pHs) tested. Therefore, similarity between the Test and Reference products has been demonstrated. The calculations of f2 values presented above using the bootstrapping method and the BCA bootstrapping method along with individual unit dissolution data and mean values in sas transport format are included in Module 5.3.1.3 of this Amendment.

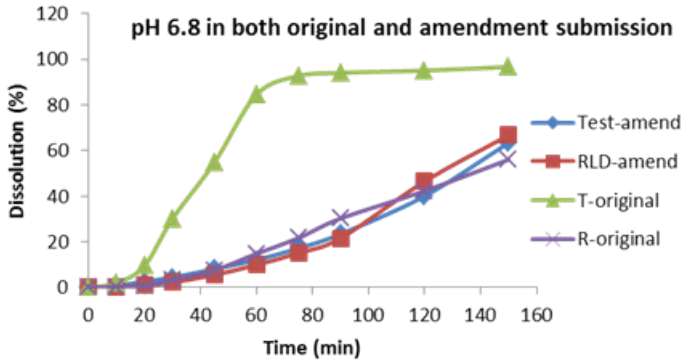
OVERALL CONCLUSION OF DISSOLUTION PROFILES:

Based on the Agency's recommendation, Cadila Healthcare Limited, India has conducted dissolution studies to demonstrate that the dissolution profiles of the Test product,

Mesalamine Delayed-release Tablets USP 800 mg, are similar to those of the Reference product (RLD), Asacol® HD (Mesalamine) delayed-release Tablets 800 mg, at (b) (4) pH 6.8, (b) (4) of the Evaluation Stage on the same day and at the same location. Therefore, the in vitro BE dissolution testing requirements have been satisfied for the Test product Mesalamine Delayed-release Tablets USP 800 mg, manufactured by Cadila Healthcare Limited, India.

Reviewer Comments:

In the first amendment review of ANDA 203286, a large difference was observed in the test product between the original and amendment submission for the dissolution profile at pH 6.8, as shown in the below plot.[4] The firm was asked to explain the large difference in the pH 6.8 test product dissolution between the original submission and the amendment submitted on 02/24/2015. [5]



In its current response to the deficiencies, the firm references the Agency's review of ANDA 091640, Mesalamine Delayed-release Tablets, 1200 mg (also manufactured by Zydus Pharmaceuticals USA Inc.). The RLD for ANDA 091640 is Shire's Lialda® (mesalamine) delayed-release tablets, 1200 mg (NDA 022000).

The formulation of ANDA 091640 contains both (b) (4) (b) (4) (b) (4) According to the proposed labeling for ANDA 091640 and the approved labeling for NDA 022000, this test product "the tablet is coated with a pH dependent polymer

[4] GDRP; ANDA-203286-ORIG-1-AMEND-9, Bioequivalence Primary Review, A203286NA022415.doc , dated 5/19/2015.
[5] V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2015 Meeting Minutes\Non-BMM Internal Meeting Minutes\5 12 2015 ANDA 208236 Mesalamine DR Tab Final.docx

(b) (4)

film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core."[8,9]

The current ANDA references the RLD Asacol® HD (mesalamine delayed release) tablets, 800 mg, manufactured by Warner Chilcott LLC. The formulation for ANDA 203286 contains Eudragit® S (b) (4) The RLD formulation contains Eudragit S (b) (4) and Eudragit L (b) (4) (b) (4) According to the RLD label, "Asacol HD delayed-release tablets have an outer protective coat consisting of a combination of acrylic based resins, Eudragit S (methacrylic acid copolymer (b) (4) NF) and Eudragit L (methacrylic acid copolymer (b) (4) NF). The inner coat consists of an acrylic based resin, Eudragit S, which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon."[13] Formulation details for ANDA 091640, ANDA 203286, and NDA 021830 are presented in Appendix 4.1 of this review.

ANDA 091640 In Vitro Dissolution Review History

For ANDA 091640, the test product showed high day-to-day dissolution variability at pH 6.8. The DBII consulted the ORS on the issue of high dissolution variability under these conditions. Per ORS' response, it may be "okay not to have f2>50 criterion for the pH 6.5 and pH 6.8 condition because the RLD, Lialda, (b) (4) However, since some patients have low pH in the distal small bowel, similar release at pH 6.8 may be desirable. Therefore, considering the variability of the RLD, an alternative to the f2 "would be if the mean of the RLD is within the range of the RLD data at pH 6.8 over the 2-8 hour range." [14] The DB held an internal meeting following this consult to further discuss the issue. [15] Because the test product dissolution for ANDA 091640 was more variability than that seen in other in-house ANDAs, the firm was asked to conduct additional method robustness validation and to repeat dissolution testing at pH 6.8 and (b) (4)

[8] EDR; ANDA 091640, Module 1.14.2.2. Final Package Insert
[9] Drugs@FDA. Search: Lialda. Last accessed: 11/30/2015.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022000s013lbl.pdf
(b) (4)

[13] Drugs @ FDA. Search: mesalamine. Last accessed 11/17/2015.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021830s006lbl.pdf
[14] DARRTS; ANDA 091640, 03/01/2014, REV-BIOEQ-21(Primary Review). Page 84 of 223.
[15] DARRTS; ANDA 091640, 03/01/2014, REV-BIOEQ-21(Primary Review). Page 89 of 223.

In the amendment dated 5/13/2014, the firm observed that dissolution testing is sensitive to minor changes in pH from [redacted] (b) (4) Since the firm used only 6 units for each test during pH robustness testing, the firm was requested to provide additional dissolution testing data for the test and reference product (two lots) at pH 6.8, [redacted] (b) (4) using 24 units each.[16]

In the amendment dated 12/8/2014, the firm provided additional dissolution testing at pH 6.8, [redacted] (b) (4) However, the firm used test product that was 31 months old. This aged test product showed significantly faster release than the previously submitted testing data from 1 month old product. The firm was asked to re-conduct dissolution under these conditions using fresh product and to explain the observed faster release from aged product.[17]

On June 05, 2015, Zydus requested a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response (CR) Letter dated May 29, 2015. In its post CR response, the firm requested to waive the additional in vitro comparative dissolution data at pH 6.8, [redacted] (b) (4) The DB held an internal meeting to discuss the issue, and decided that the firm's dissolution testing was acceptable because of the following: [18,19]

1. Acceptable in vivo BE studies with clinical and PK end points.
2. In vitro BE dissolution testing was acceptable for pH 6.5, 7.2 and 7.5. For pH 6.8, the dissolution is comparable to that of the RLD at 1, 2, 6 and 8 hours except at 4 hours (please note f2 criteria is not necessary to apply to this pH per previous consult to science team).
3. The RLD showed high variability from lot to lot in the current ANDA as well as across ANDAs. The dissolution profiles of the test product (1 month) were similar to at least one batch of the RLD at pH 6.8, i.e. F2>50 (data from more than one lot of the RLD was submitted) and were within the lot-to-lot variability of the RLD not only in the current ANDA but also across ANDAs.
4. The firm demonstrated that high within-batch variability of the test product at pH 6.8 was due to the inherent pH dependent solubility nature of the Eudragit® polymers. This notion is supported by 1) the change of 0.1 in pH above or below pH 6.8 causes dramatic change in the release of the test product and 2) the dissolution profile of test product between 1 month and 31 month (expired) test product is very different under pH 6.8 but NOT under pH 7.2, which suggests the difference of dissolution for 1 month and 31 month is due to variability at transition point, pH 6.8, but not age.

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[16] DARRTS; ANDA 091640, 09/16/2014, REV-BIOEQ-21(Primary Review).
[17] GDRP; ANDA-091640-ORIG-1-AMEND-29, Bioequivalence Primary Review, 091640A12082014.doc , 5/3/2015.
[18] GDRP; ANDA-091640-ORIG-1-AMEND-31, Bioequivalence Primary Review, A91640NA090115.doc , dated 10/26/2015.
[19] V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2015 Meeting Minutes\Non-BMM Internal Meeting Minutes: 7.16.15ANDA91640Post CR MR final date: 07/29/2015.

Both the test product in ANDA 091640 and ANDA 203286 are mesalamine delayed-release tablets with differing strengths and corresponding RLDs. ANDA 091640 is designed to release at pH 6.8, while ANDA 203286 is designed to release at pH 7.0. Similar to ANDA 091640, the following are true of the current application:

1. Acceptable in vivo BE studies with clinical and PK end points.
2. In vitro BE dissolution testing was acceptable for pH 4.5, 6.0, 6.5, 7.2, and 7.5. For pH 6.8, the firm's data submitted on 02/24/15 shows that the test product is comparable to that of the RLD.[20]
3. The RLD showed high variability from lot to lot.
4. The test product is formulated with an outer-layer pH (b) (4) enteric coating which begins to release at pH 7.0 or greater and targets mesalamine delivery to the lower GI tract. The coating composition in the test product contains Eudragit S, which degrades at pH ≥ 7.0. As a result, pH 6.8 can be considered as a transitional pH in drug release. The dissolution profile at this pH is very sensitive to small variation in the medium pH. A small variation in the medium pH in the dissolution testing results in dissolution profiles with wide variability. Thus, the inherent pH dependent solubility nature of the Eudragit polymer S may be a main reason for this batch-batch difference in dissolution profile.

FDA Lab Dissolution Testing of Test and Reference Products

The Office of Pharmaceutical Quality (OPQ) sent test and reference product samples to the FDA lab (Division of Pharmaceutical Analysis) in St. Louis, MO for in-house dissolution testing. The FDA lab sent its report of dissolution testing results on 9/9/2015 (see appended report in Section 4.2 of this review).

The FDA lab conducted dissolution testing using a modified USP monograph with pH 6.0, 6.8, and 7.2 phosphate buffers to evaluate the dissolution variability. Two lots of RLD product (Asacol® HD Lot 457840 S1 and Lot 457836 S2) and one generic product (Mesalamine DR Lot EMP 203) were tested. The FDA lab experiments showed the following results (notably, the lab did not use the bootstrapping procedure for highly variable dissolution f2 analysis):

%Dissolved from Mesalamine DR 800 mg tablets in pH 6.0, 6.8 and 7.2 phosphate buffer in 90 minutes.

	Asacol® HD Lot 457840 S1	Asacol® HD Lot 457836 S2	Mesalamine DR Lot EMP 203	
	Mean ± SD	Mean ± SD	Mean ± SD	**Specification**
pH 6.0	0.0	0.0	0.0	**Mean ≥ 80% in 90 minutes**
pH 6.8	23.6 ± 31.9	20.4 ± 27.6	24.3 ± 24.8	
pH 7.2	93.8 ± 3.7	96.3 ± 1.9	93.6 ± 2.6	

[20] GDRP; ANDA-203286-ORIG-1-AMEND-9, Bioequivalence Primary Review, A203286NA022415.doc , dated 5/19/2015.

Similarity factors (f2) of dissolution profiles for Mesalamine DR 800 mg tablets.

	Asacol® HD Lot 457840 S1	Asacol® HD Lot 457836 S2	Mesalamine DR Lot EMP 203
pH 6.8	reference	77	87
pH 7.2	reference	56	60

Similarity factor (f2) greater than 50 indicates similarity of dissolution profiles.

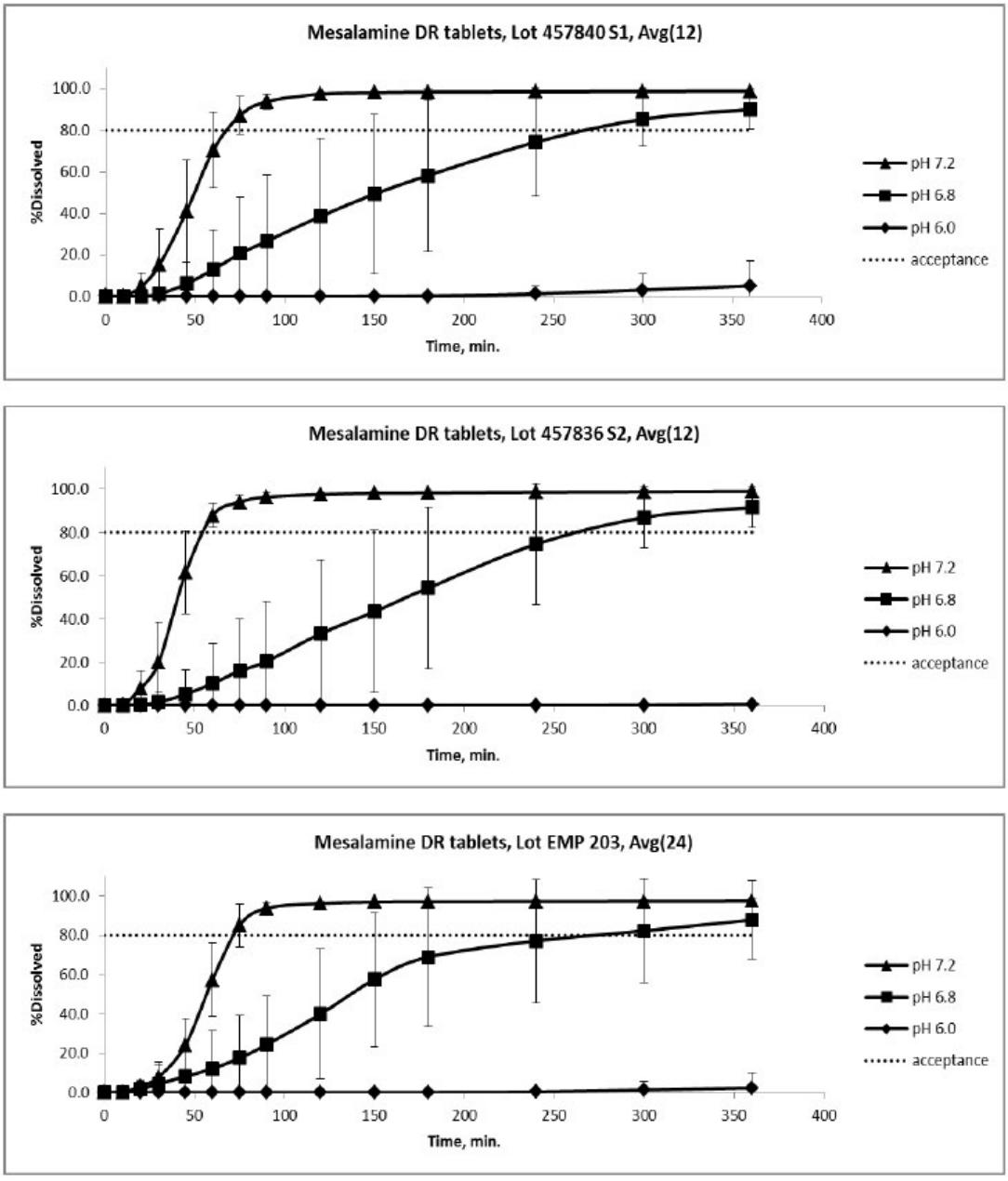


Figure 1. Comparison of dissolution profiles from Mesalamine DR tablets (Paddle; 50 rpm; Mean ± SD).

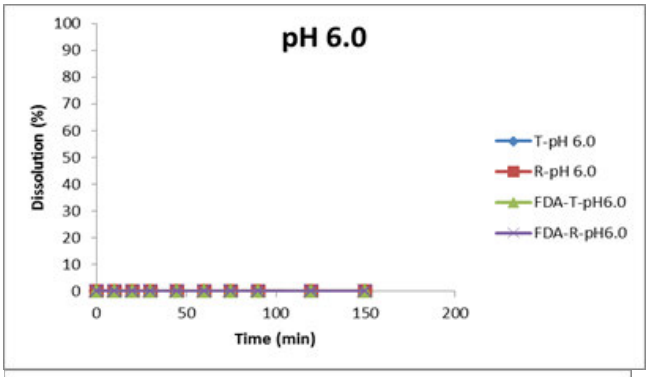
The FDA lab concluded the following:

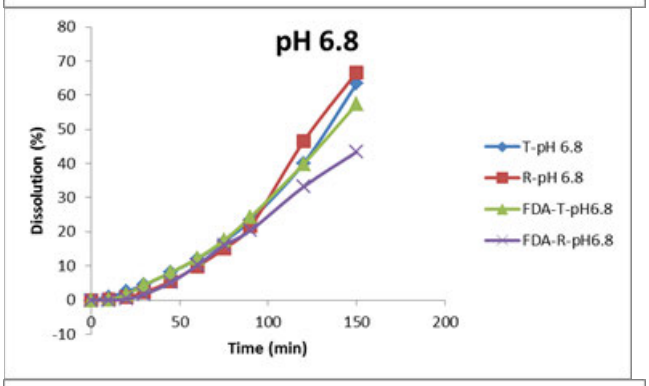
• Based on the tests conducted, the highest variability in dissolution was observed in pH 6.8 phosphate buffer (%RSDs of 102 to 135%) while the lowest variability was observed in pH 7.2 phosphate buffers (%RSDs of 2 to 4%).
• Mesalamine tablets met USP specifications of NLT (b) (4) for each of 6 tablets and Avg(12) and Avg(24) ≥ 80% for tablets in 90 minutes in pH 7.2 phosphate buffer.
• Asacol® HD tablets and generic mesalamine tablets had similar dissolution profiles in pH 6.8 and 7.2 phosphate buffers.
• Both RLD and generic products did not dissolve in pH 6.0 buffer.

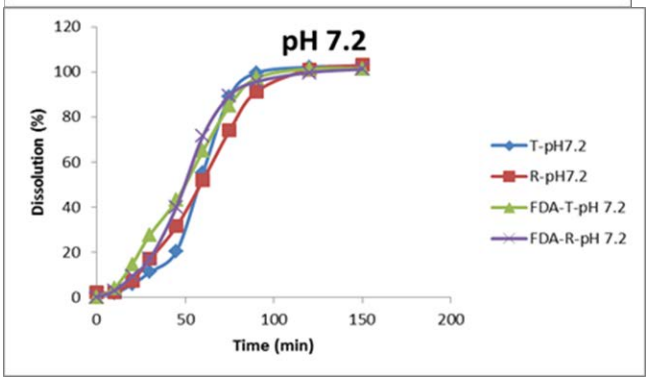
The previous BE reviewer of this ANDA analyzed the data provided by the FDA lab and compared it against the dissolution data previously submitted by the firm (see appended presentation in Section 4.3 of this review). The f2 values/confidence intervals (CIs) in the tables below and the following plots show the reviewer's comparison of the data obtained by the firm and the FDA.

F2 Metric for FDA lab and Firm				
Medium	**Firm T vs. R**	**FDA T vs. R**	**FDA-Firm T vs. T**	**FDA-Firm R vs. R**
pH 6.8 phosphate buffer	71.61	60.24	60.6	48.04
pH 7.2 phosphate buffer	55.87	42.79	75.36	42.32

FDA lab's data in Bootstrapping method							
Study	**pH**	**Strength (mg)**	**Frequent**	**Original f2**	**F2 bootstrap mean**	**Lower CI (Percentile)**	**Upper CI (Percentile)**
T vs. R (R1+R2) (N=24)	6.8	800	10000	83.52	75.43	55.62	94.38
	7.2	800	10000	42.79	43.1	36.1	51.79
T24 vs. R1 (S2)	6.8	800	10000	66.24	67.6	51.0	86.36
	7.2	800	10000	34.52	34.59	30.58	39.16
T24 vs. R2 (S1)	6.8	800	10000	85.1	73.58	54.17	91.17
	7.2	800	10000	52.93	53.84	42.99	68.55
R1 vs. R2 (N=12)	6.8	800	10000	61.25	62.17	47.47	79.39
	7.2	800	10000	47.58	47.92	39.41	58.49
R vs. R* (N=12)	6.8	800	10000	87.1	75.63	58.13	91.24
	7.2	800	10000	61.83	61.78	46.99	80.45







The FDA lab's dissolution profiles at pH 6.0, 6.8, and 7.2 are very similar to those provided by the firm (>50 f2 firm test product vs. FDA lab test product), showing reproducibility for dissolution testing of the test product. The f2 values and the 90% confidence intervals generated using the bootstrapping with the FDA lab's dissolution data indicate the dissolution data at pH 6.8 are acceptable.

Newly-Submitted Dissolution Data

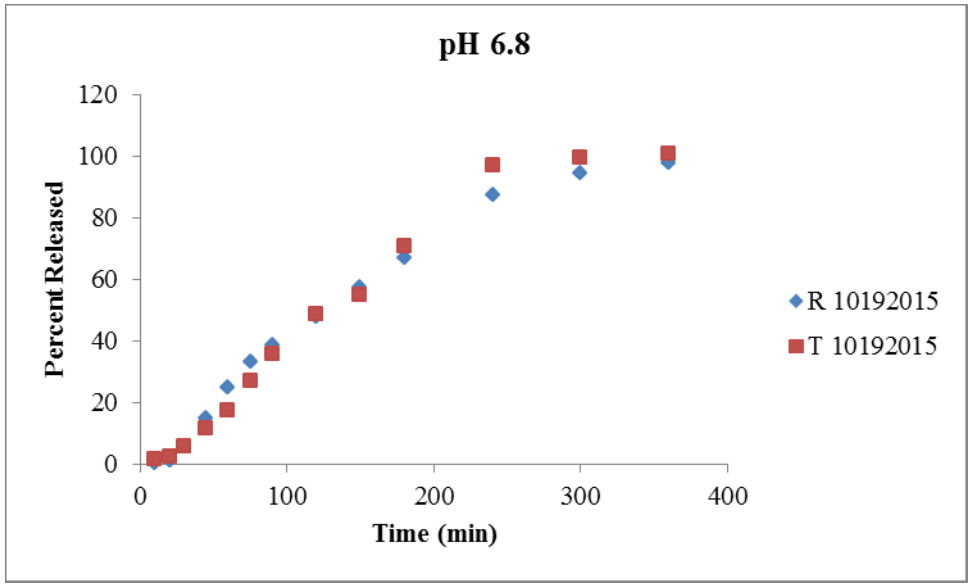
In the current amendment dated 10/19/2015, the firm submitted test and reference product dissolution data in pH (b) (4) 6.8, (b) (4) as requested by the FDA. The firm provided the dissolution summary tables in their response to the deficiency, above. Below, the review compiled plots of test and reference product dissolution at each pH tested and the individual unit data. The firm tested 24 units of test product from batch EMP203 (manufactured 4/2014) and 24 units of reference product from two batches (12 units from batch 457836 S2 and 12 units from batch 457840 S1, expiration date 5/2017 for both batches). All units were pre-treated with 0.1N HCl for 2 hours.

Evaluation Stage: pH 6.8 Phosphate Buffer at 50 rpm, Volume: 900 mL Apparatus II (Paddle)-TEST PRODUCT

Product Name	TEST PRODUCT: Mesalamine Delayed-release Tablets USP, 800 mg												
B. No./Manufacturer	EMP 203 Mfg Date: April, 2014- Cadila Healthcare Limited, India												
Time point	% Dissolved (Minutes)												
	10	20	30	45	60	75	90	120	150	180	240	300	360
Unit-1	(b) (4)												
Unit-2													
Unit-3													
Unit-4													
Unit-5													
Unit-6													
Unit-7													
Unit-8													
Unit-9													
Unit-10													
Unit-11													
Unit-12													
Unit-13													
Unit-14													
Unit-15													
Unit-16													
Unit-17													
Unit-18													
Unit-19													
Unit-20													
Unit-21													
Unit-22													
Unit-23													
Unit-24													
Mean	1.4	2.3	5.6	11.6	17.6	27.2	35.8	48.7	55.0	70.9	97.1	99.5	100.9
Min	(b) (4)												
Max													
% RSD	107.9	88.2	121.3	116.2	110.5	78.8	73.1	73.1	67.0	45.4	3.5	3.4	3.1
Date of analysis:	4th September, 2015												

Evaluation Stage: pH 6.8 Phosphate Buffer at 50 rpm, Volume: 900 mL Apparatus II (Paddle)-REFERENCE

Product Name	REFERENCE PRODUCT: Asacol® HD (mesalamine) delayed-release Tablets 800 mg –Warner Chilcott												
B. No./Manufacturer	457836S2 (1-12 unit) Expiry date: 05/2017, 457840S1 (13-24 unit) Expiry date: 05/2017												
Time point	% Dissolved (Minutes)												
	10	20	30	45	60	75	90	120	150	180	240	300	360
Unit-1	(b) (4)												
Unit-2													
Unit-3													
Unit-4													
Unit-5													
Unit-6													
Unit-7													
Unit-8													
Unit-9													
Unit-10													
Unit-11													
Unit-12													
Unit-13													
Unit-14													
Unit-15													
Unit-16													
Unit-17													
Unit-18													
Unit-19													
Unit-20													
Unit-21													
Unit-22													
Unit-23													
Unit-24													
Mean	0.3	1.0	5.8	15.0	25.1	33.1	38.8	47.9	57.3	66.9	87.5	94.4	97.7
Min	(b) (4)												
Max													
% RSD	186.7	181.0	143.1	138.7	116.9	103.4	95.0	80.2	65.8	54.3	16.4	8.6	5.7
Date of analysis:	4th September, 2015												



The reviewer calculated the below f2 values comparing the test and reference products. F2 values cannot be calculated using mean values if 1) % CV >20% at 20 min and 2) %CV >10% after 20 min (20 min is considered as cutoff point for "early sampling points") and 3) there are less than 3 sampling points for f2 calculation before both test and reference products reach (b) (4)% dissolved. Because of the high dissolution variability, the reviewer calculated the f2 values using a bootstrapping procedure. [21]

F2 values and 90% confidence intervals using a bootstrapping method[22]

Bootstrapping method							
Study	pH	Strength (mg)	Frequency	Original f2 (from mean values)	f2 bootstrap mean	Lower CI (Percentile)	Upper CI (Percentile)
T vs. R (R1+R2) (N=24)	6.8	800	10000	68.92	64.10	44.23	83.73

(b) (4)

All bootstrapping mean f2 values are above 50. The reviewer also calculated the T vs. R f2 confidence intervals for pH 6.8 (b) (4) considering each reference batch separately, as shown below, since the lower bounds of the confidence intervals at these pH conditions were below 46.

Bootstrapping method							
Study	pH	Strength	Frequency	Original f2	f2	Lower CI	Upper CI

[21] Shah et al. In Vitro Dissolution Profile Comparison-Statistics and Analysis of the Similarity Factor, f2. *Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896*

[22] Please see statistical consult review for ANDA 065490 (DARRTS, ANDA-065490, REV-BIOMETRICS-01(General Review), Duan Joan Z, 12/04/2009) and ANDA 065510 (DARRTS, ANDA-065510, REV-BIOMETRICS-01(General Review), Duan Joan Z, 12/04/2009) for a detailed description of the bootstrap method.

		(mg)		(from mean values)	bootstrap mean	(Percentile)	(Percentile)
T vs. R1 (batch 457836 S2)	6.8	800	10000	48.62	51.07	35.67	75.56 (b) (4)
T vs. R2 (batch 457840 S1)	6.8	800	10000	70.26	64.61	45.89	82.38 (b) (4)

For pH 6.8 (b) (4) conditions, the lower bound of the confidence interval is below 46. Per the internal meeting of the OGD vancomycin review team on 3/31/2010[23], the dissolution profiles of the test and reference products are considered similar and acceptable when the f2 for the mean test and reference profiles are >50 and the lower bound of the 90% confidence interval (CI) for the f2 test is >46. In addition, if the lower bound of 90% confidence interval for f2 test is <46, then the dissolution profile differences between the test and reference products may be acceptable if the reference vs. reference difference is larger. Thus, the variability of test versus reference dissolution profiles should not exceed the variability of the reference versus reference dissolution profiles.

The reviewer calculated the reference product variability under these two pH conditions. The reviewer calculated the reference product variability by randomly dividing the 24 units into two groups, and also by considering the f2 of reference product batch #457836 S2 vs. batch #457840 S1.

Bootstrapping method							
Study	**pH**	**Strength (mg)**	**Frequency**	**Original f2 (from mean values)**	**f2 bootstrap mean**	**Lower CI (Percentile)**	**Upper CI (Percentile)**
R vs. R randomly assigned groups	6.8	800	10000	49.71	51.47	34.55	74.60 (b) (4)
R1 vs. R2 by batch	6.8	800	10000	43.09	45.30	31.07	68.88 (b) (4)

This f2 analysis shows that there is high between-batch dissolution variability for the reference product at pH 6.8 (b) (4) Bootstrapping f2 values for each condition were below 50. The lower bound CI for T vs. R was higher than the R vs. R lower bound no matter how the R groups were divided at pH 6.8 (44.23 vs. 34.55 and 31.07). At (b) (4)

[23] DARRTS, ANDA-065478, FRM-MINUTES-01 (Internal Meeting Minutes), 4/28/2010

(b) (4)

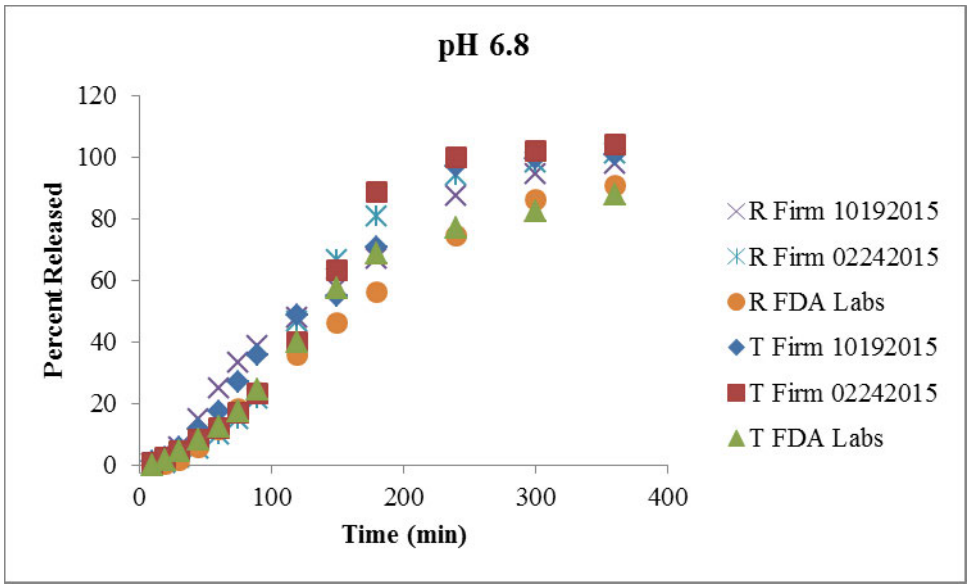
Notably, at (b) (4) drug release in 360 min, while all other units in that batch showed at least (b) (4) release. The reviewer repeated (b) (4) f2 calculations excluding this single unit, as shown below.

Bootstrapping method							
Study	**pH**	**Strength (mg)**	**Frequency**	**Original f2 (from mean values)**	**f2 bootstrap mean**	**Lower CI (Percentile)**	**Upper CI (Percentile)**
T vs. R (R1+R2)	(b) (4)						
T vs. R1 (batch 457836 S2)							
R vs. R randomly assigned groups							
R1 vs. R2 by batch							

(b) (4)

Comparison of New Dissolution Data (10/19/2015) to Data Submitted on 2/24/2015 and FDA Lab Data, pH 6.8

On 2/24/2015, the firm submitted dissolution data at pH 6.8 using 24 units of test product from batch EMP203 (manufactured 4/2014) and 24 units of reference product from two batches (12 units from batch 450645 S2 and 12 units from batch 451550 S3, expiration date 06/2015 and 08/2015, respectively). The FDA lab performed dissolution testing on 24 units of test product from batch EMP203 (manufactured 4/2014) and 24 units of reference product from two batches (12 units from batch 457836 S2 and 12 units from batch 457840 S1, expiration date 5/2017 for both batches), the same batches and number of units as in the current amendment. For all dissolution tests, units were pre-treated with 0.1N HCl for 2 hours before exposure to pH 6.8 buffer.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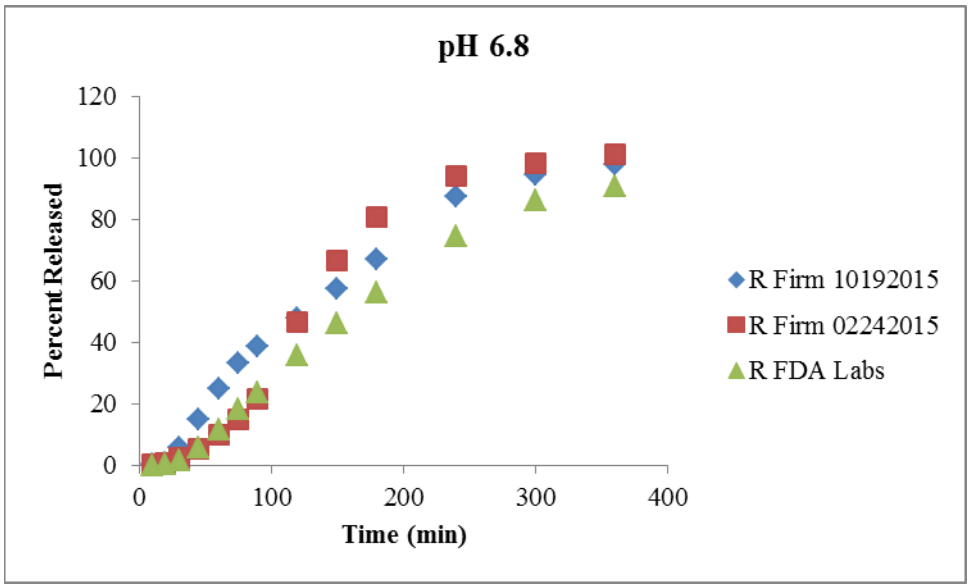
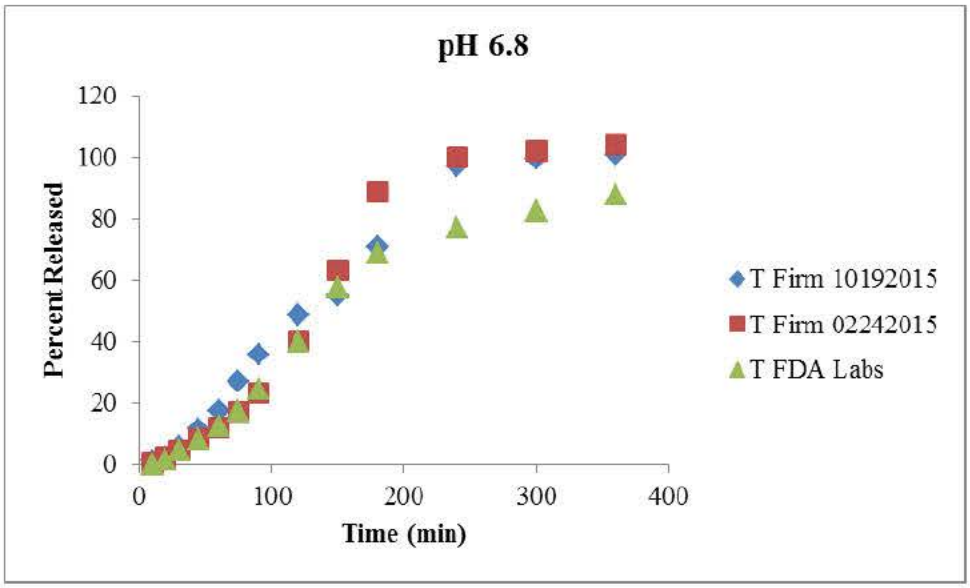
Percent Released
Time (min)
0
20
40
60
80
100
120
0
100
200
300
400
R Firm 10192015
R Firm 02242015
R FDA Labs
T Firm 10192015
T Firm 02242015
T FDA Labs


pH 6.8
Percent Released
Time (min)
0
20
40
60
80
100
120
0
100
200
300
400
R Firm 10192015
R Firm 02242015
R FDA Labs



F2 values comparing to FDA data and firm data submitted on 2/24/2015

Bootstrapping method							
Study*	**pH**	**Strength (mg)**	**Frequency**	**Original f2 (from mean values)**	**f2 bootstrap mean**	**Lower CI (Percentile)**	**Upper CI (Percentile)**
New Firm T vs. FDA T	6.8	800	10000	60.17	60.97	44.04	84.21
New Firm R vs. FDA R	6.8	800	10000	49.41	52.27	35.66	78.87
New Firm T vs. Old Firm T	6.8	800	10000	59.08	60.98	44.92	85.19
New Firm R vs. Old Firm R	6.8	800	10000	46.55	49.00	34.34	73.09

*In the above table, "New Firm" R and T refer to the data the firm submitted on 10/19/2015. "Old Firm" R and T refer to the data the firm submitted on 2/24/2015. FDA R and T refer to the data obtained by the FDA labs.

As shown in the above table, the test product data submitted by the firm on 10/19/2015 shows an f2 bootstrapping mean of approximately 61 and a lower bound CI of approximately 44 when compared against both the data the firm submitted on 2/24/2015 and the independent data generated by the FDA labs. The T vs. T comparisons are more

similar than the R vs. R comparisons, consistent with the trend seen looking solely at the firm's newly submitted data for R vs. R at pH 6.8, shown again below for comparison.

Bootstrapping method- Firm's Newly Submitted Data							
Study	**pH**	**Strength (mg)**	**Frequency**	**Original f2 (from mean values)**	**f2 bootstrap mean**	**Lower CI (Percentile)**	**Upper CI (Percentile)**
R vs. R randomly assigned groups	6.8	800	10000	49.71	51.47	34.55	74.60
R1 vs. R2 by batch	6.8	800	10000	43.09	45.30	31.07	68.88

Overall Conclusions

Because of the related DB decision for ANDA 091640 which indicated that high dissolution variability may be expected in transitional pH media for (b) (4) coated drug products, along with the supporting dissolution data newly submitted by the firm and from the FDA labs, the firm's response is acceptable.

3.2 Deficiency Comments

None.

4 APPENDIX

4.1 Formulation Details

The reference product formulation, Asacol® HD (Mesalamine Delayed Release) tablets, by Warner Chilcott Pharmaceuticals Inc (NDA 021830), is as follows:[24]

Ingredient	Grade	Function	Unit Quantity (mg/tablet)	% w/w[a]
[redacted]				
Mesalamine	USP	Active	800.00	
Lactose monohydrate	NF			
Sodium starch glycolate	NF			
Talc	USP			
Povidone	USP			
Magnesium stearate	NF			
Colloidal silicon dioxide	NF			
[redacted]				
Subtotal			[redacted]	
[redacted]				
Eudragit S [redacted]	NF			
Talc	USP			
Dibutyl Sebacate	NF			
Ferric oxide, red	NF			
Eudragit L [redacted]	NF			
Ferric oxide, yellow	NF			
[redacted]				
Subtotal			[redacted]	
[redacted]				
Polyethylene glycol [redacted]	NF			
[redacted]				
Subtotal			[redacted]	
[redacted]				
Black Ink.				
[redacted]				
		Target Total Tablet Weight	1099 mg	100%
[redacted]				

[24] EDR; NDA 021830, Module 3.2.P.1. Description and Composition of the Drug Product.

The formulation of the 800 mg tablets in the current ANDA is as follows :

Name of Ingredient	Quantity/ Tablet (mg)	Quantity (% w/w)/Tablet[$]
(b) (4)		
Mesalamine, USP	800.000	(b) (4)
Sodium Starch Glycolate, NF (b) (4)	(b) (4)	
Colloidal Silicon Dioxide, NF (b) (4)		
Magnesium Stearate, NF		
(b) (4)		
Microcrystalline Cellulose, NF (b) (4)		
Povidone (b) (4) USP (b) (4)		
(b) (4)		
(b) (4)		
Sodium Starch GlycolateNF, (b) (4)		
Talc, USP (b) (4)		
Colloidal Silicon Dioxide, NF (b) (4)		
Magnesium Stearate, NF		
(b) (4)		
Methacrylic Acid Copolymer, NF - Type B (Eudragit S (b) (4))		
Talc, USP		
Acetyltributyl Citrate, NF		
Titanium Dioxide, USP (b) (4)		
Ferric Oxide Red, NF		
Isopropyl Alcohol, USP*		
(b) (4)		
(b) (4)		
Opacode Black (b) (4)		
Isopropyl Alcohol, USP*		
Total	**1102.400**	**100.000**
(b) (4)		

The formulation of the 1200 mg tablets in ANDA 091640 is as follows :[25]

Ingredient (s)	Mesalamine Delayed-release Tablets, 1.2 g	
	Unit Composition (mg/tablet)	*% w/w[$]*
(b) (4)		
Mesalamine (b) (4) USP	1200.000	(b) (4)
Colloidal Silicon Dioxide (b) (4) NF		(b) (4)
Magnesium Stearate (b) (4) NF		
(b) (4)		
Carboxy methyl cellulose Sodium (b) (4) USP		
Sodium Starch Glycolate (b) (4) NF		
Hypromellose (b) (4) USP		

[25] DARRTS; ANDA 091640, 02/23/2012, REV-BIOEQ-01(General Review).

(b) (4)	q.s	--
Microcrystalline Cellulose (b) (4) NF Colloidal Silicon Dioxide (b) (4) NF Magnesium Stearate (b) (4) NF		(b) (4)
Methacrylic Acid Copolymer (b) (4) NF Methacrylic Acid Copolymer NF Triethyl Citrate (b) (4) NF Talc (b) (4) USP		(b) (4)
		(b) (4)
		(b) (4)
		(b) (4)
Total (Coated Tablets)	**1465.000**	**100.00**
		(b) (4)

4.2 FDA Labs Dissolution Testing Report and Previous Bioequivalence Reviewer's FDA Lab Report Analysis

These two documents are in V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\Email Communications\Mesalamine ANDA 203286

[26] In response to the CMC deficiency letter dated December 3, 2010 the firm changed the (b) (4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203286

APPLICANT: Zydus Pharmaceuticals (USA) Inc.

DRUG PRODUCT: Mesalamine Delayed Release Tablets USP, 800 mg

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

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

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R. Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

ANDA: 203286

Completed Assignment for 203286 ID: 26993

Reviewer:	Vivian, Diana	**Date Completed:**
Verifier:	,	**Date Verified:**
Division:	Division of Bioequivalence	
Description:	Amendment, Mesalamine Delayed Release Tablets USP, 800 mg, Zydus	

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
26993	10/19/2015	Other (REGULAR)	Study Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203286		
Drug Product Name	Mesalamine Delayed Release Tablets USP		
Strength(s)	800 mg		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Address	73, Route 31 North, Pennington, NJ 08534		
Applicant's Point of Contact	G. Srinivas Zydus Pharmaceuticals USA Inc., 73, Route 31 North, Pennington, NJ 08534		
Contact's Telephone Number	609-730-1900		
Contact's Fax Number	609-730-1999		
Original Submission Date(s)	07/12/2011		
First Generic	Yes		
Submission Date(s) of Amendment(s) Under Review	02/24/2015 amendment for in vitro dissolution testing		
Reviewer	Ping Ren, Ph.D.		
Study Number (s)	# MSN-P0-732	# MSN-P0-733	
Study Type (s)	Fasting	Fed	In vitro BE study
Strength (s)	800 mg	800 mg	800 mg
Clinical Site	Algorithme Pharma Inc.		
Clinical Site Address	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1		
Analytical Site	(b) (4)		
Analytical Site Address			
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**		
OVERALL REVIEW RESULT	**Inadequate**		
COMMUNICATION	☐**ECD** ☒**IR**		

	☐NOT APPLICABLE		
DISSOLUTION (QC method)	The dissolution was reviewed separately. Please see details in DARRTS: REV-BIOEQ-02 (Dissolution Review) ANDA203286, Final date: 02/16/2012		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Fasting Study**	**800 mg**	**Adequate**
1	**Fed Study**	**800 mg**	**Adequate**
6	**In vitro BE Dissolution study**	**800 mg**	**Inadequate**

1 EXECUTIVE SUMMARY

The original application (07/12/2011) contained the results of fasting and fed bioequivalence (BE) studies comparing a test product Mesalamine Delayed Release Tablets, 800 mg, to the corresponding reference product Asacol® HD (Mesalamine Delayed Release) tablets, 800 mg. The results of the 95% upper confidence bound for AUC_{0-t}, AUC_{8-48}, and Cmax in the fasting and fed BE studies were negative. The point estimate (test/reference geometric mean ratio) for AUC_{0-t}, AUC_{8-48}, and Cmax were within the range of 0.80 to 1.25. Hence, the fasting and fed studies met the BE acceptance criteria of reference scaled analysis for log-transformed AUC_{0-t}, AUC_{8-48}, and Cmax of Mesalamine Delayed Release Tablets, 800 mg. The fasting and fed studies were acceptable[1].

In addition to in vivo fasting and fed BE studies, the guidance also recommends comparative in vitro **BE** dissolution studies (using USP Apparatus II at 50 rpm) to be conducted in pH 4.5, 6.0, 6.5, 6.8, 7.2 and 7.5 phosphate buffer representative of the GI tract pH variations. Yet, in the original application, the firm did not submit any dissolution data for pH 4.5 Acetate buffer in the current application. Also, the mean values (f2) in pH 6.8 and pH 7.5 phosphate buffer were less than 50 and the lower bound of 90% confidence interval ("CI") for the f2 test comparing test vs. RLD in pH 6.8, pH 7.2, and pH 7.5 phosphate buffer was lower than those comparing the RLD against itself under the same conditions. These values indicated that the dissolution profiles of the test product were significantly different from those of the corresponding reference under these conditions. Therefore, the in vitro BE (comparative dissolution) studies under pH 6.8, 7.2 and 7.5 buffer were not acceptable. Due to the high variability of firm submitted dissolution data conducted in multimedia, the firm was requested to repeat comparative dissolution testing on its **fresh test product** using a larger sample size of tablets (e.g. 24 unites for test and two lots of unexpired RLD product) to provide a better estimate of the mean difference, or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculation.

[1] DARRTS: REV-BIOEQ21 (Primary Review) ANDA203286, Final date: 11/15/2013.

In the current amendment dated 02/24/2015, the firm conducted additional dissolution testing in the medium of pH 4.5 Acetate buffer and repeated dissolution testing in the media of pH 6.8,7.2, and 7.5 with a larger sample size (n=24) to reduce the variability for the purpose of achieving accurate f2 calculation. The result from the current amendment showed the percent drug release from both test and reference products is less than 5% in the medium of pH 4.5 during the period of 960 min (16 hrs) dissolution testing. The incomplete drug release of in vitro dissolution testing is due todelayed release nature of this product. Therefore, the in vitro dissolution data in the medium of pH 4.5 are acceptable. The results of the mean f2 values and the lower bound of 90% confidence intervals for f2 values comparing the test vs. reference indicated that the test and reference products have a similar dissolution profile under pH 6.8 and pH 7.2 conditions.

However, as per detailed analysis for the dissolution profile at pH 6.8, a large difference was observed in the test product between the original and amendment submissions. Moreover, (b) (4) (b) (4) (b) (4) the firm will be asked to provide 12 units dissolution data for the test and reference products in buffers with around pH 6.8 (e.g. pH (b) (4), 6.8, (b) (4), and (b) (4)) using the following dissolution method on Mesalamine (800 mg):

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of

(b) (4)
(2) pH 6.8 Phosphate buffer at 50 rpm
(b) (4)
(b) (4)

Volume: 900 mL
Temperature: 37°C
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison.

Therefore, in vitro comparative dissolution testing at pH 6.8 is inadequate.

In the medium of pH 7.5, the f2 mean value is less than 50 (46.35) and its lower bound of 90% confidence intervals for f2 values is less than 46 (40.72). Moreover, the lower bound of 90% CIs of f2 comparing test vs. RLD for pH 7.5 is lower than those comparing the RLD against itself under the same conditions (42.43 and 54.47). Based on the analysis of

dissolution profile and variability for two different RLD lots (R1 and R2), the failed result for in vitro dissolution study in pH 7.5 with T24 vs. R24 is due to the variability between different reference lots. When T24 was compared with R2, the f2 mean value is more than 50 (57.97) and, its lower bound of 90% confidence intervals for f2 values are more than 46 (51.26). The acceptable result is demonstrated in one of reference lots (R2). Based on the internal meeting minutes (with other offices (Chemistry and Science Team), V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2015 Meeting Minutes\Non-BMM Internal Meeting Minutes) dated 05/12/2015, the in vitro comparative dissolution data in pH 7.5 medium are acceptable.

The firm conducted quality control dissolution testing using the USP method [500 mL of 0.1N HCl (Acid Stage A) for 2 hrs, followed by 900 mL of Phosphate buffer, pH 6.0 (Buffer Stage B) for 1 hr and 900 mL of Phosphate buffer, pH 7.2 (Buffer Stage C) using apparatus 2 (Paddle) at 100 rpm for stage A and B and at 50 rpm for stage C][2]. The firm's proposed specifications are the same as the USP specifications (Acid Stage: NMT 1% in 2 hours; Buffer Stage I: NMT 1% in 1 hour; Buffer Stage II: NLT 80% (Q) in 90 minutes). The quality control dissolution testing with the USP method is acceptable. The DB II acknowledges that the firm will follow the USP method and specifications.

A routine inspection of the clinical site, Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal Quebec, was requested for ANDA202172 on 10/18/2010 and was completed 2/7/2011 with an outcome of NAI.

A routine inspection of the analytical site, (b) (4) was requested for this parent ANDA 203286 on 3/8/2012 and was completed on 05/19-23/2014 with an outcome of NAI[3].

The application is incomplete due to deficiency for in vitro comparative BE dissolution testing at pH 6.8.

[2] DARRTS: REV-BIOEQ-02 (Dissolution Review) ANDA203286, Final date: 02/16/2012.
[3] DARRTS: CONSUT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) ANDA203286, Final date: 07/30/2014.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Mesalamine Delayed Release Tablets USP, 800 mg
Reference Product	Asacol® HD (Mesalamine Delayed Release) tablets
RLD Manufacturer	WARNER CHILCOTT LLC
NDA No.	N021830
RLD Approval Date	May 29, 2008
Indication	Asacol® HD is indicated for the treatment of moderately active ulcerative colitis.

*Asacol® HD was manufactured and marketed by Procter and Gamble (P&G) before February 12, 2010. On February 12, 2010, the firm notified the FDA that the corporate name and/or address had been changed from Procter and Gamble Pharmaceuticals, Inc. to Warner Chilcott Pharmaceuticals Inc[4].

3.2 OGD Recommendations for Drug Product

Number of studies recommended:	3, fasting, fed, and in vitro comparative dissolution study

1.	**Type of study:**	Fasting
	Design:	Single-dose, partially or fully replicated crossover design, in-vivo
	Strength:	800 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study
	Additional Comments:	Other study designs are acceptable if appropriate. Specific recommendations are provided below.

2.	**Type of study:**	Fed
	Design:	Single-dose, partially or fully replicated crossover design, in-vivo
	Strength:	800 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study
	Additional Comments:	Other study designs are acceptable if appropriate. Specific recommendations are provided below.

3.	**Type of study:**	In vitro comparative dissolution study
	Strength	800 mg
	Apparatus:	USP Apparatus 2 (paddle)
	Pretreatment Stage:	2 hours in 0.1 N HCl at 100 rpm

[4] DARRTS: COR-NDAACK-06 (Change of Applicant Name/Address) NDA021830, Final date 02/26/2010.

	Evaluation Stage:	Each of (1) pH 4.5 Acetate buffer at 50 rpm (2) pH 6.0 Phosphate buffer at 50 rpm (3) pH 6.5 Phosphate buffer at 50 rpm (4) pH 6.8 Phosphate buffer at 50 rpm (5) pH 7.2 Phosphate buffer at 50 rpm (6) pH 7.5 Phosphate buffer at 50 rpm
	Volume:	900 mL
	Temperature:	37°C
	Sample times:	0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison
	Additional Comments:	The applicant should use at least 12 tablets per test. The f2 metric will be used to compare dissolution profiles.

Analytes to measure (in plasma):	Mesalamine in plasma
Bioequivalence based on:	90% CI of Mesalamine and acceptable in vitro comparative dissolution study
Waiver request of in-vivo testing:	Not applicable
Source of most recent recommendations:	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320003.pdf The above Guidance is based on FDA's response to (b) (4) Control# 12-0615 on September 20, 2010 reviewed by the scientific team. \\cdsnas\OGDS6\CONTROLS\2012-docs\12-0615.pdf

3.3 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
In vitro comparative dissolution	Yes	6
QC dissolution	Yes	1
Waiver requests	No	N/A
BCS Waivers	No	N/A
Clinical Endpoints	No	N/A
Failed Studies	No	N/A
Amendments	Yes	02/24/2015 amendment for in vitro dissolution testing

3.4 Formulation

Location in appendix	DARRTS: REV-BIOEQ21 (Primary Review) ANDA203286, Final date: 11/15/2013.
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.5 In Vitro Dissolution (quality controls)

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review) ANDA203286, Final date: 02/16/2012
Source of Method (USP, FDA or Firm)	USP
Medium	Acid Stage: 0.1N HCl Buffer Stage I: pH 6.0 Phosphate Buffer Buffer Stage II: pH 7.2 Phosphate Buffer
Volume (mL)	Acid Stage: 500 mL Buffer Stage : 900 mL
USP Apparatus type	USP 2 (Paddle)
Rotation (rpm)	Acid Stage: 100 RPM 2 hours Buffer Stage I: 100 RPM 1 hour Buffer Stage II: 50 RPM 90 minutes
DBE-recommended specifications	Acid Stage: NMT 1% in 2 hours Buffer Stage I: NMT 1% in 1 hour Buffer Stage II: NLT 80% (Q) in 90 minutes
If a modified-release tablet, was testing done on ½ tablets?	No
F2 metric calculated?	No
If no, reason why F2 not calculated	Due to high variability (%CV) for sampling points
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

There is a USP method for this product. The firm conducted dissolution testing using the USP method [500 mL of 0.1N HCl (Acid Stage A) for 2 hrs, followed by 900 mL of Phosphate buffer, pH 6.0 (Buffer Stage B) for 1 hr and 900 mL of Phosphate buffer, pH 7.2 (Buffer Stage C) using apparatus 2 (Paddle) at 100 rpm for stage A and B and at 50 rpm for stage C]. The firm's dissolution testing data with the USP method are acceptable. The firm's proposed specifications are the same as the USP specifications. The quality control dissolution testing is acceptable. The DB II acknowledges that the firm will follow the USP method and specifications.

3.6 Review of Submission

DB Deficiency I (02/24/2014):

We cannot locate the individual data for comparative dissolution testing in 0.1 N HCl followed by pH 4.5 Acetate buffer.

The Firm's Response:

The firm has manufactured a fresh (new) exhibit batch (Batch No. EMP 203) and performed dissolution studies on this batch in 0.1N HCl followed by pH 4.5 acetate buffer.

(b) (4)

The firm has conducted comparative dissolution testing on 24 units of the Test product (Batch No. EMP 203) and two lots of the Reference product (12 units from each Reference lot) on same day and at the same location under same dissolution testing conditions.

Reviewer Comments:

The firm conducted additional dissolution testing in 0.1 N HCl followed by pH 4.5 Acetate buffer. The firm's response is adequate (for submitted data, see Section 4.1).

DB Deficiency II (02/24/2014):

Due to the high variability of your submitted dissolution data conducted in multimedia, an f2 test using mean profiles of test vs. reference listed drug ("RLD") is not sufficient as per the CDER Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms ("Dissolution Guidance"). Therefore, we calculated the f2 metric (an f2 confidence interval) using a bootstrapping method for the dissolution profile comparison. For general information on this approach, please refer to Shah et al. In Vitro Dissolution Profile Comparison-Statistics and Analysis of the Similarity Factor, f2. Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896.

For the test products, the mean values (f2) in pH 6.8 and pH 7.5 phosphate buffer are lower than 50 and the lower bound of 90% confidence interval ("CI") for the f2 test comparing test vs. RLD in pH 6.8, pH 7.2, and pH 7.5 phosphate buffer is lower than those comparing the RLD against itself under the same conditions. These values suggest that the dissolution profiles of the test product are significantly different from those of the corresponding reference under these conditions. Your dissolution data in pH 6.8, 7.2 and 7.5 are not acceptable.

The Firm's Response:

As recommended by the Division of Bioequivalence II (DB II), in Deficiency No. 3 below, the firm has conducted comparative dissolution testing on 24 units of the Test product (Batch

No. EMP 203) and two lots of the Reference product (12 units from each Reference lot) under pH 4.5, 6.8, 7.2, and 7.5 conditions on same day and at the same location.

Reviewer Comments:

The firm repeated in vitro dissolution testing in the media of pH 6.8,7.2, and 7.5 with a larger sample size (n=24) of test product and two lots of RLD product (each lot N=12). The firm's response is adequate (for resubmitted data, see Section 4.1).

DB Deficiency III (02/24/2014):

*To address why the test product is different from the RLD product, please repeat comparative dissolution testing on your **fresh test product** using a **larger sample** of tablets to provide a better estimate of the mean difference, or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculation.*

The dissolution testing should be conducted on at least 24 tablets (more if necessary) of the test product and at least two lots of unexpired RLD product (using 12 tablets per lot) using the following method as specified in the FDA Guidance on Mesalamine (800 mg):

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of
(1) pH 4.5 Acetate buffer at 50 rpm
(2) pH 6.8 Phosphate buffer at 50 rpm
(3) pH 7.2 Phosphate buffer at 50 rpm
(4) pH 7.5 Phosphate buffer at 50 rpm

Volume: 900 mL
Temperature: 37ºC
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison

Please submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable.

The DB II will perform an f2 test on your submitted dissolution data. If the variability of the dissolution data is such that mean data cannot be used for the f2 test, as per the Dissolution Guidance, we will use the above-referenced bootstrapping approach.

For the bootstrapping method, sampling with replacement is used for creating 10,000 replicates of test and reference products. The means of the test and reference units at each time point for each replicate are obtained and used for f2 calculation. The 90%

confidence intervals of the f2 values are calculated using the percentile approach as described in the Shah et al. reference. Similar procedure can be followed for comparing reference vs. reference products.

Please note only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

The Firm's Response:

As recommended by the Division of Bioequivalence II (DB II), the firm has conducted comparative dissolution testing on 24 units of the Test product (Batch No. EMP 203) and two lots of the Reference product (12 units from each Reference lot) under pH 4.5, 6.8, 7.2, and 7.5 conditions on same day and at the same location.

Using the bootstrapping method described above in the Agency's comment letter, by creating 10,000 replicates of the Test and Reference product units, the mean percent dissolved at each time point was obtained for each replicate to calculate f2 (similarity factor). Subsequently, the mean and 90% confidence intervals of the f2 (similarity factor) values between Test and Reference products were calculated for each pH at the evaluation stage. The complete details of the bootstrapping analyses and the bias corrected accelerated (BCA) bootstrapping method to calculate the mean, median and 90% confidence intervals for the f2 values in the dissolution profiles are presented as follows:

Summary of f2 (Similarity Factor) Values Determined by Percentile Bootstrapping Method Described in the FDA Complete Response Letter

Evaluation Stage pH	Parameters	Observed f2	Average of f2	Median of f2	90% lower CI of f2	90% upper CI of f2
4.5	Test vs R1+R2	96.28	95.96	96.10	94.03	97.44
	R1 vs R2	99.88	99.87	99.87	99.83	99.91
6.8	Test vs R1+R2	69.81	61.91	61.76	53.98	70.34
	R1 vs R2	58.94	52.88	52.75	44.85	61.82
7.2	Test vs R1+R2	56.8	54.52	54.20	47.00	63.44
	R1 vs R2	65.1	54.28	53.71	43.15	67.32
7.5	Test vs R1+R2	54.93	54.87	54.71	50.05	60.17
	R1 vs R2	56.55	56.32	55.91	49.6	64.26

Test: Batch EMP 203 (24 units), R1: Batch 450645 S2 (12 units), R2: Batch 451550 S3 (12 units)

Note: The firm calculated f2 distribution and the 90% confidence intervals using the bias corrected accelerated (BCA) bootstrapping method instead of the FDA recommended percentile approach.

Reviewer Comments:

In original application dated 07/12/201, the firm's in vitro comparative dissolution data showed that the test and reference products had a similar dissolution profile under pH 6.0 and pH 6.5 conditions. However, the dissolution profiles of the test product were

significantly different from that of reference product in the medium of pH 6.8, 7.2, and 7.5. Thus, in vitro comparative dissolution testing in pH 6.8, pH 7.2, and pH 7.5 Phosphate buffer was unacceptable. In addition, we could not locate the individual data for comparative dissolution testing in 0.1 N HCl followed by pH 4.5 Acetate buffer. Thus, in vitro comparative dissolution testing was incomplete.

In the current amendment dated 02/24/2015, the firm conducted additional dissolution testing in the medium of pH 4.5 Acetate buffer and repeated dissolution testing in the media of pH 6.8,7.2, and 7.5 with a larger sample size (n=24) to reduce the variability for the purpose of achieving accurate f2 calculation.

Table A. Product information in vitro comparative dissolution testing

Dosage Strength & Form	Test	Reference
800 mg	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMP203 Mfg Date: April, 2014	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: **R1**: 450645 S2 and **R2**: 451550 S3 Expiry : 06/2015 and 08/2015
Sample size	N=24	R1=12, R2=12; R1+R2=24

Test dates for in vitro comparative dissolution testing on both test and reference products:

Test date for the test and reference products in multimedia								
	pH 4.5		pH 6.8		pH 7.2		pH 7.5	
Strength 800 mg	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Test date	12/02/2014	12/02/2014	10/18/2014	10/18/2014	12/12/2014	12/12/2014	10/17/2014	10/17/2014
Exp date	Mach, 2016	06/2015 and 08/2015	Mach, 2016	06/2015 and 08/2015	Mach, 2016	06/2015 and 08/2015	Mach, 2016	06/2015 and 08/2015
Manufacture date	April, 2014		April, 2014		April, 2014		April, 2014	

The review of In Vitro Comparative Dissolution Testing:

a) The calculation of F2 values using means

The means of F2 values (T24 vs. R24)

F2 values between the test and the reference product				
Strength	pH 4.5 buffer	pH 6.8 buffer	pH 7.2 buffer	pH7.5 buffer
800 mg	96.33*	70.64*	54.23*	46.28*

*The percent coefficient of variation (%CV) was more than 20% at the 20 min, or/and more than 10% after 20 min.

REVIEWER'S NOTES:

- The F2 values cannot be calculated using mean values if 1) % CV >20% at 20 min and 2) %CV >10% after 20 min (20 min is considered as cutoff point for "early sampling points") and 3) there are less than 3 sampling points for F2 calculation before both test and reference products reach 85% dissolving[5]. Yet, to confirm the data from bootstrapping approach, reviewer calculates mean f2 values disregarding variability as illustrated in the above table.

- Even though using a **larger sample** of tablets, dissolution data still show high variability (high %CV) in the media of pH 6.8, 7.2, and 7.5. Due to the high variability (high %CV), a comparison of mean profiles with the f2 test is not sufficient per the CDER Guidance for Industry: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms)*. Therefore, a bootstrapping procedure[6] is used to calculate mean values of F2 and an F2 confidence interval (a statistical evaluation of f2, see below).

b) The calculation of F2 values and 90% confidence interval using bootstrapping method[7]

Bootstrapping method							
Study	**pH**	**Strength (mg)**	**Frequent**	**Original f2**	**F2 bootstrap mean**	**Lower CI (Percentile)**	**Upper CI (Percentile)**
T vs. R (R1+R2) (N=24)	4.5			N/A	N/A	N/A	N/A
	6.8	800	10000	82.8	68.9	49.32	88.27
	7.2	800	10000	54.23	51.83	43.64	60.76
	7.5	800	10000	46.35	46.51	40.72	53.12
T24 vs. R1 (N=12) lot#: 4560645	4.5			N/A	N/A	N/A	N/A
	6.8	800	10000	87.13	70.23	49.73	89.8
	7.2	800	10000	55.7	51.22	38.61	65.67
	7.5	800	10000	38.45	38.64	33.28	44.91
T24 vs. R2 (N=12) lot#:	4.5			N/A	N/A	N/A	N/A
	6.8	800	10000	78.62	67.86	48.34	87.25
	7.2	800	10000	50.89	49.15	42.04	56.6

[5] Based on 1) the CDER Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 2) high variability of vancomycin dissolution data, and discussion with bio-management, the reviewer considered the following for the f2 calculation:

- Only one measurement is considered after 85% dissolution of both the products and at least three dissolution time points are available.
- 20 min tentatively appears reasonable to be set as the cutoff of the earlier time point for Vancomycin HCl capsule in vitro BE studies. For the F2 calculation, the percent coefficient of variation before or at the earlier time point (i.e. 20 min) should not be more than 20% and at other time points (i.e. time points after 20 min) should not be more than 10%.

[6] Shah et al. In Vitro Dissolution Profile Comparison-Statistics and Analysis of the Similarity Factor, f2. *Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896*

[7] Please see statistical consult review for ANDA 065490 (DARRTS, ANDA-065490, REV-BIOMETRICS-01(General Review), Duan Joan Z, 12/04/2009) and ANDA 065510 (DARRTS, ANDA-065510, REV-BIOMETRICS-01(General Review), Duan Joan Z, 12/04/2009) for detail description of the bootstrap method.

541550	7.5	800	10000	57.97	58.28	51.26	66.4
R1 vs. R2 (N=12)	4.5			N/A	N/A	N/A	N/A
	6.8	800	1000	90.61	68.99	46.75	92.57
	7.2	800	1000	62.66	57.85	42.43	72.92
	7.5	800	1000	48.35	48.49	42.46	55.87
R vs. R* (N=12)	4.5			N/A	N/A	N/A	N/A
	6.8	800	1000	54.48	57.67	37.8	86.78
	7.2	800	1000	43.83	44.06	28.9	62.31
	7.5	800	1000	78.21	68.97	54.47	85.17

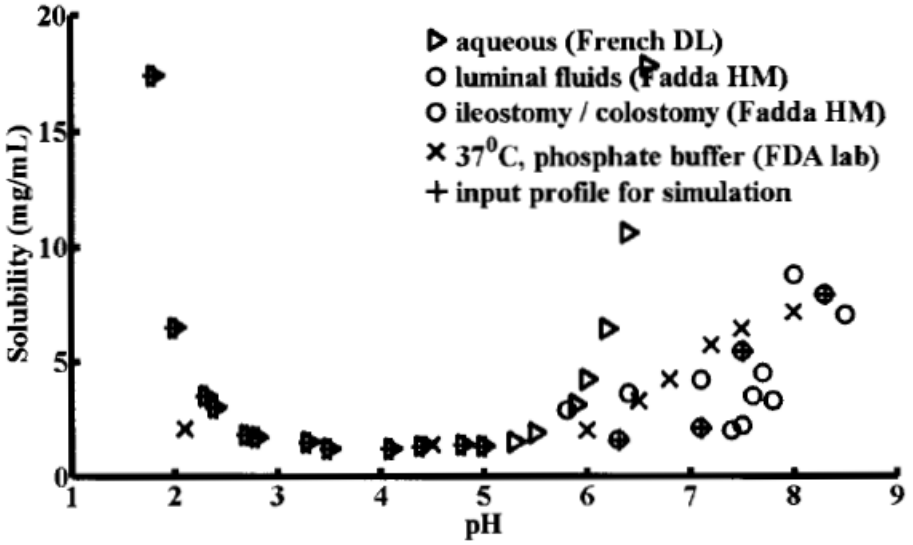
*For R vs. R comparison, the dissolution data was first randomly divided into two groups (12 units vs. 12 units) and with each of the groups obtained from randomization, the bootstrapping procedure was then performed to calculate the f2 confidence intervals for R vs. R comparison in the comparative dissolution testing.

Comments:

1. Per the internal meeting of OGD vancomycin review team on 3-31-2010[8], the dissolution profiles of the test and reference products are considered similar and acceptable when the f2 for the mean test and reference profiles are >50 and the lower bound of 90% confidence interval (CI) for f2 test is >46. In addition, if the lower bound of 90% confidence interval for F2 test is <46, then the difference of dissolution profile differences between test and reference may be acceptable if the reference vs. reference difference is larger. Thus, the variability of test versus reference dissolution profiles should not exceed the variability of the reference versus reference dissolution profiles.

2. As per Control document 12-0615[9], Mesalamine has three ionizable groups. Its aqueous versus pH solubility profiles are a U shape profile with lowest solubility between pH 2.0 to 5.5 illustrated as the following figure:

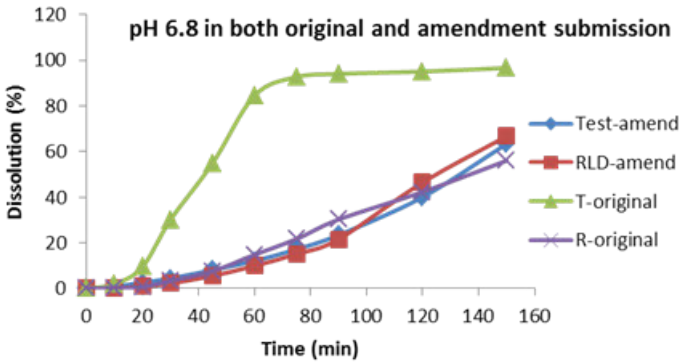
[8] DARRTS, ANDA-065478, FRM-MINUTES-01 (Internal Meeting Minutes), 4/28/2010
[9] Ctr:12-0615: \\cdsnas\OGDS6\CONTROLS\2012-docs\12-0615.pdf.



The pH of the medium in the dissolution testing affects solubility of Mesalamine. Mesalamine is soluble under either acidic environment (pH< 2) or pH above 6 condition. Based on above study, Mesalamine has low drug release in the medium of pH 4.5 due to the enteric coating feature. As a result, the complete dissolution is not expected at the pH 4.5 and the percent drug release from both test and reference products should be very low. The result from the current amendment showed the percent drug release from both test and reference products is less than 5% in the medium of pH 4.5 during the period of 960 min (16 hrs) dissolution testing. Thus, a meaningful comparison of the dissolution data is impossible in pH conditions of 4.5 because of incomplete and variable (high % RSD) dissolution for the test and reference products. The incomplete drug release of in vitro dissolution testing is due to very low solubility of Mesalamine in the medium of pH 4.5. Therefore, the in vitro dissolution data in the medium of pH 4.5 are acceptable.

3. For T24 vs. R24 comparison, the mean f2 values comparing the test vs. reference are greater than 50 in the media of pH 6.8 and 7.2 (82.8 and 54.23, respectively). The lower bound of 90% confidence intervals for f2 values is more than 46 (49.32) in the medium of pH 6.8, while the lower bound of 90% confidence interval for F2 test in the medium of pH 7.2 less than 46 (43.64). However, this value is higher than that comparing the RLD against itself under the same conditions (R1 vs. R2:42.43; R vs R: 28.9). The firm's dissolution data show that the test and reference products have a similar dissolution profile under pH 6.8 and pH 7.2 conditions.

4. However, as per detailed analysis for the dissolution profile at pH 6.8, a large difference was observed in the test product between the original and amendment submission illustrated as below:



The test product is formulated with an outer-layer pH sensitive enteric coating to begin to release at pH 7.0 or greater and to target mesalamine delivery to the lower GI tract. (b) (4) in the test product contains Eudragit S, which degrades at pH ≥ 7.0. As a result, pH 6.8 can be considered as a transitional pH in drug release. The dissolution profile at this pH is very sensitive to small variation in the medium pH. A small variation in the medium pH in the dissolution testing would result in wide variability dissolution profiles. Thus, the inherent pH dependent solubility nature of the Eudragit (b) (4) S may be a main reason for this batch-batch difference in dissolution profile. (b) (4)

(b) (4)

the firm will be asked to provide12 units dissolution data for the test and reference products in buffers around pH 6.8 (e.g. pH (b) (4) 6.8, (b) (4) using the following dissolution method on Mesalamine (800 mg):

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of

(b) (4)

(2) pH 6.8 Phosphate buffer at 50 rpm

(b) (4)

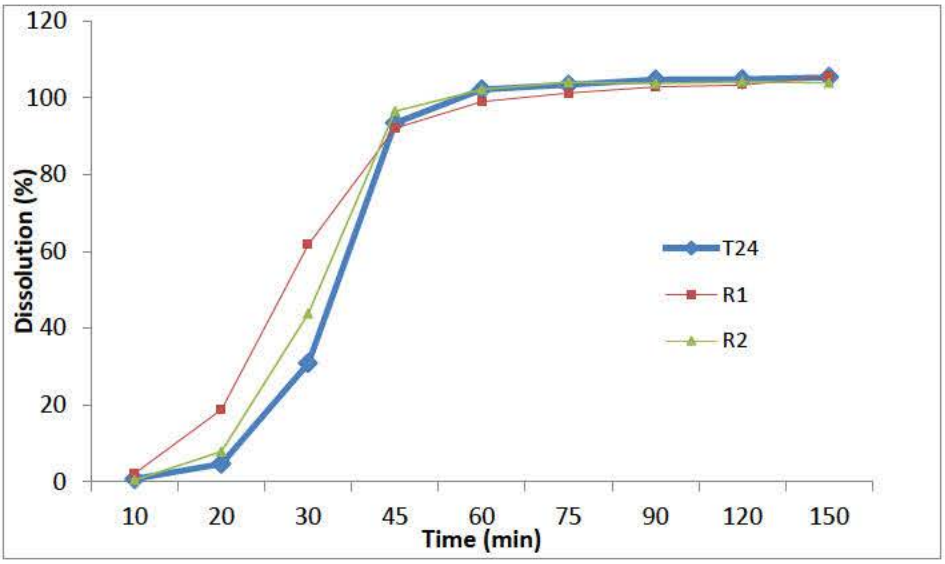
Volume: 900 mL
Temperature: 37ºC
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison.

5. In the medium of pH 7.5, the f2 mean value is less than 50 (46.35) and its lower bound of 90% confidence intervals for f2 values is less than 46 (40.72). Moreover, the lower bound of 90% CIs of f2 comparing test vs. RLD for pH 7.5 is lower than those comparing the RLD against itself under the same conditions (42.43 and 54.47). However, reviewer considers in vitro comparative dissolution testing in the medium of pH 7.5 is acceptable based on the following reasons:

    a) In the current amendment, the firm conducted the dissolution testing on 24 tablets of the test product and two lots of unexpired RLD product (using 12 tablets per lot). Compared T24 vs. R2 (the 2nd RLD batch: lot#541550), the f2 mean value is more than 50 (57.97) and also, its lower bound of 90% confidence intervals for f2 values are more than 46 (51.26). The result demonstrated that the dissolution profile of test product is similar to one of reference lots at pH 7.5.

    b) The reviewer noticed that two lots of reference product have different dissolution profiles and variability. As shown below, the lot R1 (lot# 4560645) releases faster than the lot R2 (lot#541550) and the test product. The lot R2 dissolution profile is more similar to that of test product (f2: 57.97) compared to R1 (38.45). Also, the percent coefficient of variation for R1 is relative higher than that of R2 during the early sampling time (10-60 min), which resulted in lower bound of 90% confidence intervals for f2 value less than 46 for the test product under pH 7.5 condition. Thus, the failed result for in vitro dissolution study in pH 7.5 with T24 vs. R24 was due to the variability in different RLD lot.

Time (min)	10	20	30	45	60	f2
T24	0.7625	4.708333	30.875	93.4375	102.1292	T24 vs.R1
R1-Mean	2.19	18.84	61.72	92.04	99	38.45
%CV	115.27	60.07	24.60	10.32	2.15	
R2-Mean	0.48	7.93	43.84	96.50	102.13	T24 vs.R2
%CV	100.01	48.95	27.54	5.30	1.01	57.97



c) As per detailed analysis for the dissolution profile, the test product displayed slower rate of drug release during the early phase only (10 min to 30 min) than the reference product showed in the table below. Orally administered delayed-release mesalamine tablets act locally within the lumen of the large bowel. Both the test and the reference products should have already dissolved before transiting to jejunum or ileum at pH 7.5.[10] Thus, the dissolution rate difference during the early phase at pH7.5 will not have clinically relevant effect on the drug release locally in the colon.

Early phase dissolution data at pH 7.5

pH 7.5		**Acid**	**Buffer stage**			
		2 hrs	**10 min**	**20 min**	**30 min**	**45 min**
Test	Mean	0	0.76	4.71	30.8	93.4
	%CV	489.9	84.8	84.9	26.9	6.62
RLD	Mean	0	1.33	13.38	52.78	94.27
	%CV	489.9	148	74.5	30.7	8.27

d) In addition, in the fasting and fed BE studies, the mesalamine component of PK parameters of the test and reference were comparable, which further supports that the test product seems not dissolve earlier than the reference product and will reach the colon adequately.

e) The dissolution profiles at pH 7.5 (b) (4) .

[10] Xiaojian Jiang, et al. FDA Bioequivalence Standards, Chapter 12, Bioequivalence for Drug Products Acting Locally within Gastrointestinal, AAPS Advances in the Pharmaceutical Sciences Series, September 6, 2014.

f) The transit time in terminal ileum and colon is 8-48 hours. The slower release in dissolution (0-30 minutes) has no influence on local release in the colon.

Based on the internal meeting minutes (with other offices (Chemistry and Science Team), V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2015 Meeting Minutes\Non-BMM Internal Meeting Minutes) dated 05/12/2015, the in vitro comparative dissolution data in pH 7.5 medium are acceptable.

The in vitro comparative dissolution for Mesalamine Delayed release Tablets is incomplete due to a large difference in the dissolution profile of test product at pH 6.8 between the original and amendment submissions.

3.7 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested in vivo?	N/A
Is in vitro comparative dissolution acceptable?	Yes
Waivers granted?	**N/A**
If not then why?	

3.8 Deficiency

As per detailed analysis for the dissolution profile at pH 6.8, a large difference was observed in the test product between the original and amendment submission. The firm is requested to provide an explanation for this large difference in the dissolution profiles of the test product at pH 6.8 between the original and amendment submission. In addition, the firm will be asked to provide the 12 units dissolution data for the test and reference products in pH buffer at pH 6.8 range (e.g. pH (b) (4) 6.8, (b) (4)) using the following dissolution method on Mesalamine (800 mg):

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of

(b) (4)

(2) pH 6.8 Phosphate buffer at 50 rpm

(b) (4)

Volume: 900 mL
Temperature: 37°C
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison.

3.9 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (MSN-P0-732) conducted by Zydus on its Mesalamine Delayed Release Tablets USP, 800 mg (lot #: EMK150) comparing it to Procter & Gamble, ASACOL® HD (Mesalamine) Delayed Release Tablets, 800 mg (lot #: 442661S3).

2. The Division of Bioequivalence accepts the fed BE study (MSN-P0-733) conducted by Zydus on its Mesalamine Delayed Release Tablets USP, 800 mg (lot #: EMK150) comparing it to Procter & Gamble, ASACOL® HD (Mesalamine) Delayed Release Tablets, 800 mg (lot #: 442661S3).

3. The in vitro comparative dissolution testing using the FDA recommended method as specified in the FDA Guidance on Mesalamine (800 mg) is incomplete due to the above deficiency.

4. The firm's quality controls dissolution testing is acceptable. The dissolution testing should be conducted according to the current USP monograph for Mesalamine Delayed Release Tablets USP, 800 mg.

3.10 Comments for Other OGD Disciplines

Discipline	Comment
N/A	None

4 APPENDIX

4.1 Dissolution Data

4.1.1 In vitro BE Studies in Multiple Media

pH 4.5

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 4.5 Acetate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

Testing Date	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**										**Study Report Location**
					2 hrs	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**120 min**	**150 min**	
12/02/2014	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMP203 Mfg Date: April, 2014	800 mg Tablet	24	Mean	0	0.30	0.28	0.23	0.21	0.37	0.18	0.17	0.22	0.31	
				Range	(b) (4)										
				%CV	489	106.65	125.17	86.33	82.43	57.81	102.84	110.02	112.78	109.43	
12/02/2014	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 450645 S2 and 451550 S3 Expiry : 06/2015 and 08/2015	800 mg Tablet	24	Mean	0	0.06	0.05	0.05	0.04	0.09	0.01	0.00	0.03	0.03	
				Range	(b) (4)										
				%CV	489	159.19	176.93	176.93	199.13	111.05	489.90	N/P	228.42	489.90	
Testing	**Product ID \ Batch No.**	**Dosage**	**No. of**		**Collection Times**										**Study**

Date	(Test - Manufacture Date) (Reference – Expiration Date)	Strength & Form	Dosage Units		180 min	240 min	300 min	360 min	480min	600 min	720min	840 min	960 min	Report Location
12/02/2014	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMP203 Mfg Date: April, 2014	800 mg Tablet	24	Mean	0.25	0.49	0.49	0.62	0.68	0.96	1.29	1.37	1.64	
				Range	(b) (4)									
				%CV	114.9	81.0	132.0	126.9	177.0	152.2	156.2	166.96	168.55	
12/02/2014	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 450645 S2 and 451550 S3 Expiry : 06/2015 and 08/2015	800 mg Tablet	24	Mean	0.10	0.05	0.02	0.08	0.04	0.10	0.08	0.23	0.25	
				Range	(b) (4)									
				%CV	124.9	176	489	172.5	244.3	178.0	186.1	122.4	104.17	

pH 6.8

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 6.8 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times									Study Report Location
					2 hrs	10 min	20 min	30 min	45 min	60 min	75 min	90 min	120 min	
10/18/2014	Mesalamine Delayed Release Tablets USP, 800 mg	800 mg Tablet	24	Mean	0	0.87	2.57	4.44	8.08	12.06	17.15	23.43	40.03	
				Range	(b) (4)									

	Lot No.: EMP203 Mfg Date: April, 2014				(b) (4)									
				%CV	---	59.97	70.21	80.69	88.66	90.72	88.85	85.69	75.35	
10/18/2014	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 450645 S2 and 451550 S3 Expiry : 06/2015 and 08/2015	800 mg Tablet	24	Mean	0	0.24	0.86	2.28	5.51	9.91	15.07	21.54	46.46	
				Range	(b) (4)									
				%CV	---	104.4	106.3	133.3	148.4	157.7	144.6	124.3	64.64	

Testing Date	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
					150 min	**180 min**	**240 min**	**300 min**	**360 min**				
10/18/2014	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMP203 Mfg Date: April, 2014	800 mg Tablet	24	Mean	63.38	88.53	99.98	102.09	104.18				
				Range	(b) (4)								
				%CV	51.75	23.22	6.06	4.43	3.36				
10/18/2014	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 450645 S2 and 451550 S3 Expiry : 06/2015 and 08/2015	800 mg Tablet	24	Mean	66.72	80.81	94.13	98.21	101.34				
				Range	(b) (4)								
				%CV	39.76	21.72	8.61	5.14	2.91				

pH 7.2

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 7.2 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C

Firm's Proposed Specifications															
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210														
Testing Date	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Acid**	**Buffer stage**									**Study Report Location**
					2 hrs	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**120 min**	**150 min**	
12/12/2014	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMP203 Mfg Date: April, 2014	800 mg Tablet	24	Mean	0	1.94	5.80	11.2	20.3	55.35	89.17	99.55	102.1	102.6	
				Range										(b) (4)	
				%CV	---	92.8	99.2	88.9	70.6	35.59	14.77	2.96	1.76	1.68	
12/12/2014	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 450645 S2 and 451550 S3 Expiry : 06/2015 and 08/2015	800 mg Tablet	24	Mean	0	2.28	7.33	16.9	31.4	52.03	73.98	91.18	100.9	102.9	
				Range										(b) (4)	
				%CV	---	152	131	109	96.4	62.58	38.36	11.08	3.63	2.40	

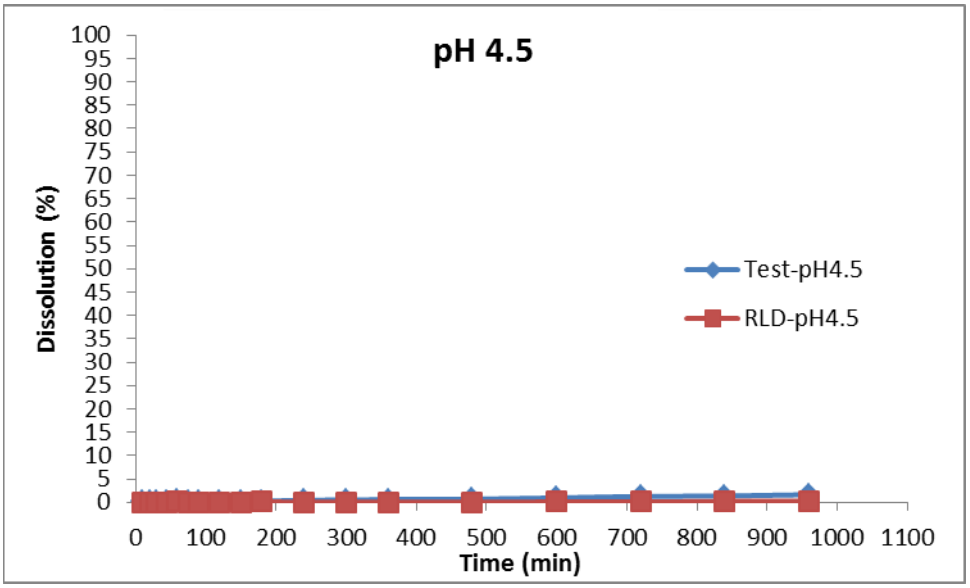
pH 7.5

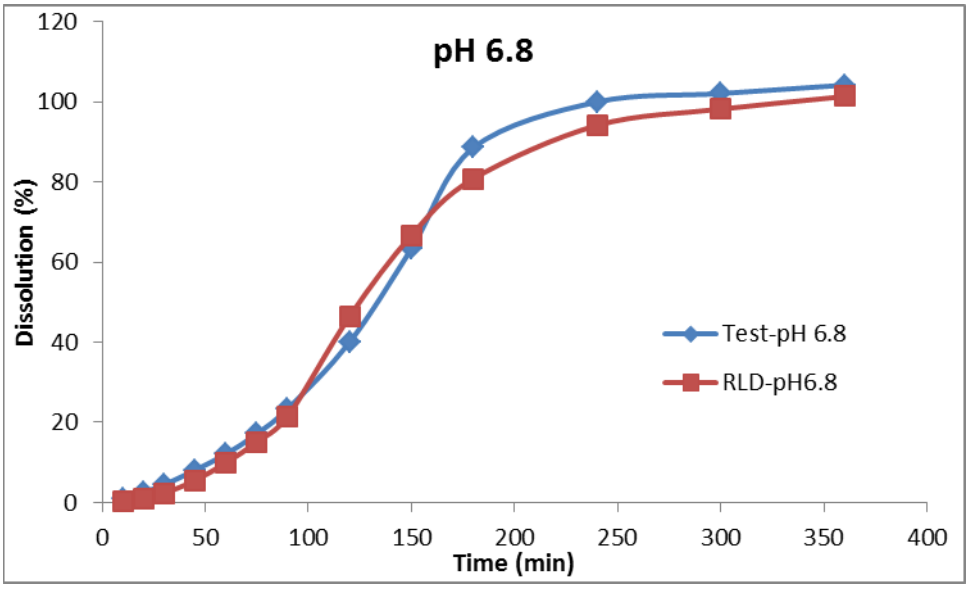
Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 7.5 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C

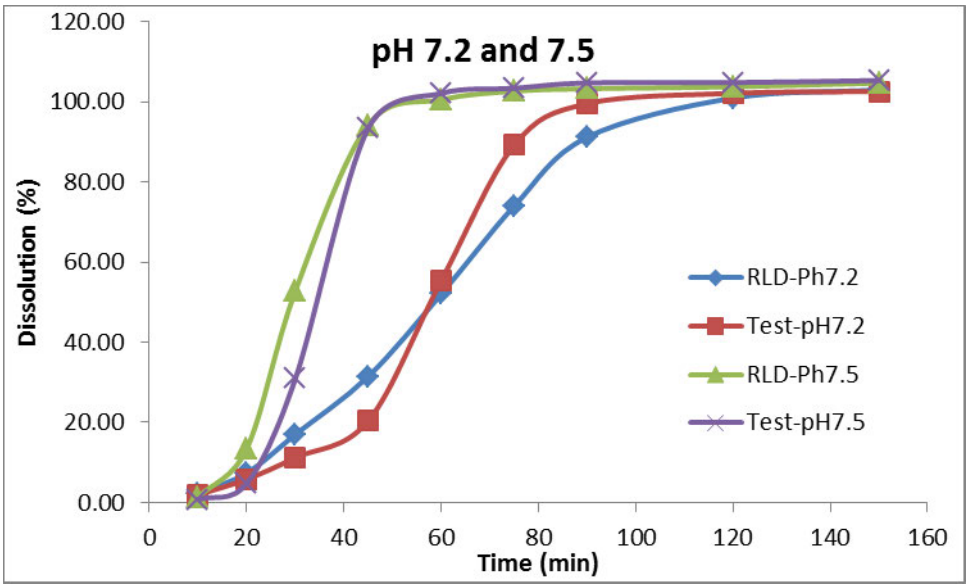
Firm's Proposed Specifications															
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210														
Testing Date	**Product ID \ Batch No. (Test - Manufacture Date)**	**Dosage Strength**	**No. of Dosage**		**Acid**	**Buffer stage**									**Study Report**
					2 hrs	**10**	**20**	**30**	**45**	**60**	**75**	**90**	**120**	**150**	

	(Reference – Expiration Date)	& Form	Units			min	min	min	min	min	min	min	min	min	Location
10/17/2014	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMP203 Mfg Date: April, 2014	800 mg Tablet	12	Mean	0	0.76	4.71	30.8	93.4	102.1	103.4	104.7	104.8	105.3	
				Range										(b) (4)	
				%CV	489.9	84.8	84.9	26.9	6.62	2.10	1.34	0.99	1.18	0.82	
10/17/2014	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 450645 S2 and 451550 S3 Expiry : 06/2015 and 08/2015	800 mg Tablet	12	Mean	0	1.33	13.38	52.78	94.27	100.57	102.66	103.29	103.77	104.7	
				Range										(b) (4)	
				%CV	489.9	148	74.5	30.7	8.27	2.28	2.01	1.06	1.00	1.47	

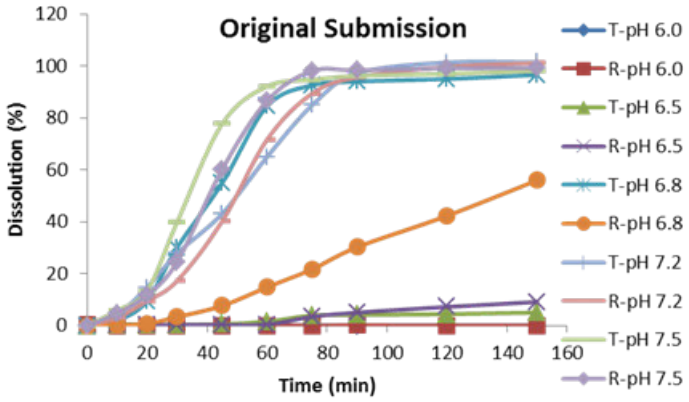
Figure 1. Dissolution Profiles

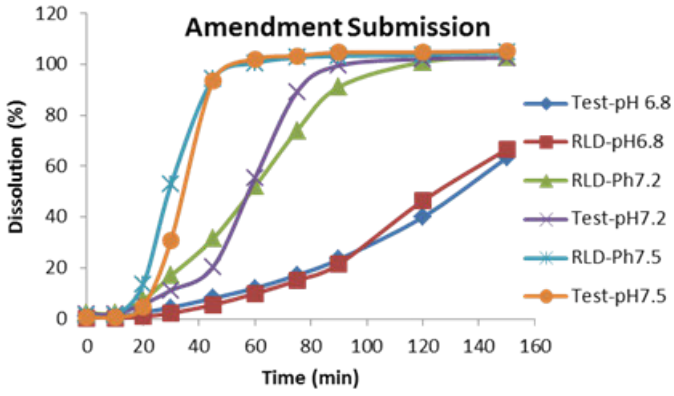


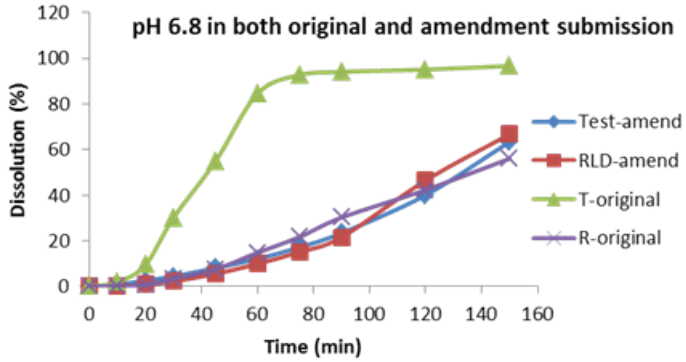


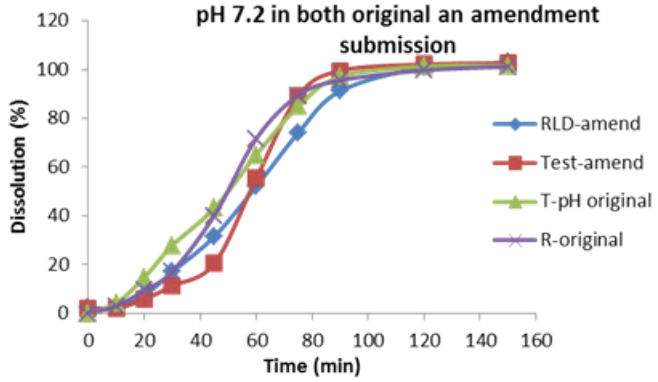


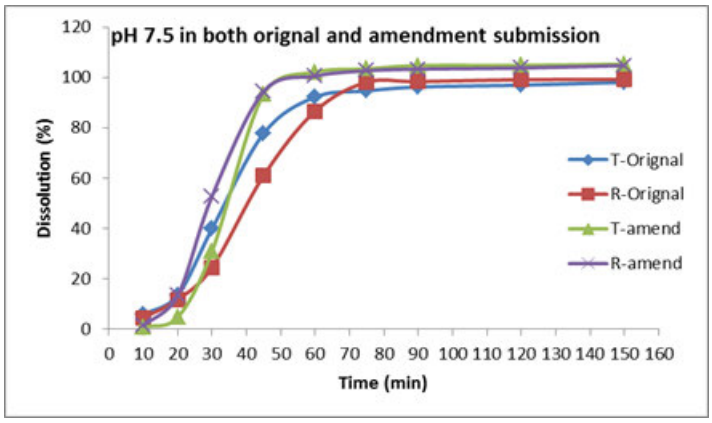
Dissolution profile comparison between the original and amendment submission:






pH 6.8 in both original and amendment submission
Dissolution (%)
Time (min)
Test-amend
RLD-amend
T-original
R-original


pH 7.2 in both original an amendment submission
Dissolution (%)
Time (min)
RLD-amend
Test-amend
T-pH original
R-original


pH 7.5 in both orignal and amendment submission
Dissolution (%)
Time (min)
T-Orignal
R-Orignal
T-amend
R-amend

4.2 Detailed Regulatory History (If Applicable)

None

4.3 Consult Reviews

None

4.4 SAS Output

4.4.1 In vitro dissolution (bootstrap) Codes

pH 6.8

```
/*=========================================================================
=====
/ Program   : f2_analysis.SAS
/ SubMacros :
/ Updated   : 14 Jan 2010
/ Purpose   : Dissolution F2 bootstrapping confidence interval calculations -
Percentile and BCA method
/
/ Notes     :
/
/=========================================================================
====
/ PARAMETERS:  THE FOLLOWING COLUMNS SHOULD BE IN THE INPUT DATASET (EXCEL
FILE).
/-------name------- ------------------------description---------------------
----
NAME OF VARIABLE
      TR               (T, R): TEST OR REFERENCE (CHARACTER)
      LOT              LOT (CHARACTER OR NUMERIC)
      PH               PH (NUMERIC)
      STRENGTH    STRENGTHS OF THE PRODUCTS (NUMERIC)
      UNIT        UNIT NUMBER (NUMERIC) : 12 UNITS PER EACH LOT/PH
      X5               DISSOLUTION RATE PERCENT (NUMERIC) E.G. AT 5 MINUTES
      X10              DISSOLUTION RATE PERCENT (NUMERIC) E.G. AT 10 MINUTES
      .                ..
      .                ..
      X60              DISSOLUTION RATE PERCENT (NUMERIC) E.G. AT 60 MINUTES
/=========================================================================
====
/ AMENDMENT HISTORY:
/ Init --Date--  ---------------------Description-----------------------
/
/=========================================================================
====*/
PROC DATASETS
  LIBRARY=WORK;
  DELETE _ALL_;
RUN;
```

```
*** STEP 1:  LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT REPORTS ***;
%let STUDYDIR= C:\Users\RENP\Desktop\Documents\Completed-ANDA\GI-
COMPLE\203286Mesalamine;

LIBNAME IN "&STUDYDIR";

*** STEP 2:  IF DATA ON EXCEL WORKSHEET, PROVIDE THE EXCEL WORKSHEET NAME AND
RANGE ***;
*** THIS STEP USES DDE - REQUIRES EXCEL DATASET TO BE OPEN ***;
FILENAME RAWDATA DDE 'EXCEL|pH68!R2C1:R49C18';

***** STEP 2:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
*%LET EXCELNAME = 90905DISSOLUTIONDATA.XLS;

***%LET EXCELFILE = &STUDYDIR.\&EXCELNAME;



***** STEP 5:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING STUDY
DATA *****;
/*%let sheetname = Sheet1;

proc import datafile="&excelfile"
            out=revise
            dbms=excel replace;
                  sheet="&sheetname";
                  getnames=yes;
                  mixed=yes;
run;*/


*** IF USING EXCEL DDE OPTION, ENABLE THE FOLLOWING DATA STEP ***;

data revise;
  INFILE RAWDATA;
  INPUT TR $ LOT $ PH STRENGTH UNIT X5 X10 X15 X20 X25 X30 X40 X45 X60 X80
X100 X120 X140;
run;


********************************************************************************
********;
********************** PERCENTILE METHOD
****************************************;
********************************************************************************
********;

proc sort data=revise;by TR ph strength;run;
proc means data=revise noprint;
var X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100 X120 X140;

by TR ph strength ;
output out=revisesum mean=X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100 X120
X140;
run;
```

```
data test0;set revisesum;if TR='T';
tx5=x5;tx10=x10;tx15=x15;tx20=x20;tx25=x25;tx30=x30;tx40=x40;tx45=x45;tx60=x6
0;tx80=x80;tx100=x100;tx120=x120;tx140=x140;
drop TR _type_ X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100 X120 X140;run;

rx5=x5;rx10=x10;rx15=x15;rx20=x20;rx25=x25;rx30=x30;rx40=x40;rx45=x45;rx60=x6
0;rx80=x80;rx100=x100;rx120=x120;rx140=x140;
drop TR _type_ X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100 X120 X140;run;

data original;merge test0 ref0;by ph strength;
run;
data original;set original;
if (rx5>85 or tx5>85) then  do;
sum=(tx5-rx5)**2 ;f2=50*log10(100/sqrt((1+sum/1)));end;
else if (rx10>85 or tx10>85)then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2;f2=50*log10(100/sqrt((1+sum/2)));end;
else if (rx15>85 or tx15>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-
rx15)**2;f2=50*log10(100/sqrt((1+sum/3)));end;
else if (rx20>85 or tx20>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2;
f2=50*log10(100/sqrt((1+sum/4)));end;
else if (rx25>85 or tx25>85) then  do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2;
f2=50*log10(100/sqrt((1+sum/5)));end;
else if (rx30>85 or tx30>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2;
f2=50*log10(100/sqrt((1+sum/6)));end;
else if (rx40>85 or tx40) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2;
f2=50*log10(100/sqrt((1+sum/7)));end;
else if (rx45>85 or tx45>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2;
f2=50*log10(100/sqrt((1+sum/8)));end;
else if (rx60>85 or tx60>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2;
f2=50*log10(100/sqrt((1+sum/9)));end;
else if (rx80>85 or tx80>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-rx80)**2;
f2=50*log10(100/sqrt((1+sum/10)));end;
else if (rx100>85 or tx100>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-
rx80)**2+(tx100-rx100)**2;
f2=50*log10(100/sqrt((1+sum/11)));end;
else if (rx120>85 or tx120>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-
rx80)**2+(tx100-rx100)**2+(tx120-rx120)**2;
f2=50*log10(100/sqrt((1+sum/12)));end;
else do;sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-
rx25)**2
```

```
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-
rx80)**2+(tx100-rx100)**2+(tx120-rx120)**2+(tx140-rx140)**2;
f2=50*log10(100/sqrt((1+sum/13)));end;
f2bar=f2;
keep PH strength f2bar sum ;
run;
quit;


proc sort data=revise;by TR ph strength;run;
proc surveyselect data=revise outhits method=urs n=12 reps=10000 seed=00998
out=reviseboot;
strata TR ph strength;
run;

proc sort data=reviseboot;by TR ph strength replicate;run;

var X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100 X120 X140;

by TR ph strength replicate;
output out=revisebootsum mean=X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100
X120 X140;
run;

data test;set revisebootsum;if TR='T';
tx5=x5;tx10=x10;tx15=x15;tx20=x20;tx25=x25;tx30=x30;tx40=x40;tx45=x45;tx60=x6
0;tx80=x80;tx100=x100;tx120=x120;tx140=x140;
drop TR _type_ X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100 X120 X140;run;
run;
data ref;set revisebootsum;if TR='R';
rx5=x5;rx10=x10;rx15=x15;rx20=x20;rx25=x25;rx30=x30;rx40=x40;rx45=x45;rx60=x6
0;rx80=x80;rx100=x100;rx120=x120;rx140=x140;
drop TR _type_ X5 X10 X15 X20 X25 X30 X40 X45 X60 X80 X100 X120 X140;run;

data boot;merge test ref;by ph strength replicate;
run;
data boot;set boot;


if (rx5>85 or tx5>85) then  do;
sum=(tx5-rx5)**2 ;f2=50*log10(100/sqrt((1+sum/1)));end;
else if (rx10>85 or tx10>85)then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2;f2=50*log10(100/sqrt((1+sum/2)));end;
else if (rx15>85 or tx15>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-
rx15)**2;f2=50*log10(100/sqrt((1+sum/3)));end;
else if (rx20>85 or tx20>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2;
f2=50*log10(100/sqrt((1+sum/4)));end;
else if (rx25>85 or tx25>85) then  do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2;
f2=50*log10(100/sqrt((1+sum/5)));end;
else if (rx30>85 or tx30>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2;
f2=50*log10(100/sqrt((1+sum/6)));end;
else if (rx40>85 or tx40) then do;
```

```
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2;
f2=50*log10(100/sqrt((1+sum/7)));end;
else if (rx45>85 or tx45>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2;
f2=50*log10(100/sqrt((1+sum/8)));end;
else if (rx80>85 or tx80>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-rx80)**2;
f2=50*log10(100/sqrt((1+sum/10)));end;
else if (rx100>85 or tx100>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-
rx80)**2+(tx100-rx100)**2;
f2=50*log10(100/sqrt((1+sum/11)));end;
else if (rx120>85 or tx120>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-
rx80)**2+(tx100-rx100)**2+(tx120-rx120)**2;
f2=50*log10(100/sqrt((1+sum/12)));end;
else do;sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-
rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2+(tx80-
rx80)**2+(tx100-rx100)**2+(tx120-rx120)**2+(tx140-rx140)**2;
f2=50*log10(100/sqrt((1+sum/13)));end;

keep PH strength f2 replicate sum;
run;
quit;


proc sort data=boot;by ph strength;run;
proc summary data=boot;

var f2;
output out=bootout mean=f2_boot_mean p5=f2_5th p95=f2_95th;
by ph strength;


data bootciv;merge bootout original;by ph strength;run;
proc sort data=bootciv;by strength ph;run;

proc  EXPORT DATA= WORK.bootciv
            OUTFILE= "&STUDYDIR.\DA15pH68BOOTF2-PERCENTILE.xlsx"
            DBMS=XLSX REPLACE;
     SHEET="PERCENTILE";
RUN;
```

pH 7.2 and 7.5:

```
/*=============================================================================
=====
/ Program   : f2_analysis.SAS
```

```
/ SubMacros :
/ Updated   : 14 Jan 2010
/ Purpose   : Dissolution F2 bootstrapping confidence interval calculations -
Percentile and BCA method
/
/ Notes     :
/
/=============================================================================
====
/ PARAMETERS:  THE FOLLOWING COLUMNS SHOULD BE IN THE INPUT DATASET (EXCEL
FILE).
/-------name------- -------------------------description---------------------
----
NAME OF VARIABLE
      TR                (T, R): TEST OR REFERENCE (CHARACTER)
      LOT               LOT (CHARACTER OR NUMERIC)
      PH                PH (NUMERIC)
      STRENGTH    STRENGTHS OF THE PRODUCTS (NUMERIC)
      UNIT        UNIT NUMBER (NUMERIC) : 12 UNITS PER EACH LOT/PH
      X5                DISSOLUTION RATE PERCENT (NUMERIC) E.G. AT 5 MINUTES
      X10               DISSOLUTION RATE PERCENT (NUMERIC) E.G. AT 10 MINUTES
      .                 ..
      .                 ..
      X60               DISSOLUTION RATE PERCENT (NUMERIC) E.G. AT 60 MINUTES
/=============================================================================
====
/ AMENDMENT HISTORY:
/ Init --Date--  ---------------------Description-----------------------
/
/=============================================================================
====*/
PROC DATASETS
  LIBRARY=WORK;
  DELETE _ALL_;
RUN;



*** STEP 1:  LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT REPORTS ***;
%let STUDYDIR= C:\Users\RENP\Desktop\Documents\Completed-ANDA\GI-
COMPLE\203286Mesalamine;

LIBNAME IN "&STUDYDIR";

*** STEP 2:  IF DATA ON EXCEL WORKSHEET, PROVIDE THE EXCEL WORKSHEET NAME AND
RANGE ***;
*** THIS STEP USES DDE - REQUIRES EXCEL DATASET TO BE OPEN ***;
FILENAME RAWDATA DDE 'EXCEL|Sheet1!R2C1:R73C14';

***** STEP 2:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
*%LET EXCELNAME = 90905DISSOLUTIONDATA.XLS;

***%LET EXCELFILE = &STUDYDIR.\&EXCELNAME;
```

```
***** STEP 5:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING STUDY
DATA *****;
/*%let sheetname = Sheet1;

proc import datafile="&excelfile"
            out=revise
            dbms=excel replace;
                  sheet="&sheetname";
                  getnames=yes;
                  mixed=yes;
run;*/


*** IF USING EXCEL DDE OPTION, ENABLE THE FOLLOWING DATA STEP ***;

data revise;
  INFILE RAWDATA;
  INPUT TR $ LOT $ PH STRENGTH UNIT X5 X10 X15 X20 X25 X30 X40 X45 X60;
run;


********************************************************************************
********;
********************** PERCENTILE METHOD
*****************************************;
********************************************************************************
********;

proc sort data=revise;by TR ph strength;run;
proc means data=revise noprint;
var x5 x10 x15 x20 x25 x30 x40 x45 x60;

by TR ph strength ;
output out=revisesum mean=x5 x10 x15 x20 x25 x30 x40 x45 x60;
run;

data test0;set revisesum;if TR='T';
tx5=x5;tx10=x10;tx15=x15;tx20=x20;tx25=x25;tx30=x30;tx40=x40;tx45=x45;tx60=x6
0;
drop TR _type_ x5 x10 x15 x20 x25 x30 x40 x45 x60;run;

rx5=x5;rx10=x10;rx15=x15;rx20=x20;rx25=x25;rx30=x30;rx40=x40;rx45=x45;rx60=x6
0;
drop TR _type_ x5 x10 x15 x20 x25 x30 x40 x45 x60;run;

data original;merge test0 ref0;by ph strength;
run;
data original;set original;
if (rx5>85 or tx5>85) then  do;
sum=(tx5-rx5)**2 ;f2=50*log10(100/sqrt((1+sum/1)));end;
else if (rx10>85 or tx10>85)then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2;f2=50*log10(100/sqrt((1+sum/2)));end;
else if (rx15>85 or tx15>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-
rx15)**2;f2=50*log10(100/sqrt((1+sum/3)));end;
else if (rx20>85 or tx20>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2;
```

```
f2=50*log10(100/sqrt((1+sum/4)));end;
else if (rx25>85 or tx25>85) then  do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2;
f2=50*log10(100/sqrt((1+sum/5)));end;
else if (rx30>85 or tx30>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2;
f2=50*log10(100/sqrt((1+sum/6)));end;
else if (rx40>85 or tx40) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2;
f2=50*log10(100/sqrt((1+sum/7)));end;
else if (rx45>85 or tx45>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2;
f2=50*log10(100/sqrt((1+sum/8)));end;
else do;sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-
rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2;
f2=50*log10(100/sqrt((1+sum/9)));end;
f2bar=f2;
keep PH strength f2bar sum ;
run;
quit;


proc sort data=revise;by TR ph strength;run;
proc surveyselect data=revise outhits method=urs n=24 reps=10000 seed=00998
out=reviseboot;
strata TR ph strength;
run;

proc sort data=reviseboot;by TR ph strength replicate;run;
proc means data=reviseboot noprint;
var x5 x10 x15 x20 x25 x30 x40 x45 x60;

by TR ph strength replicate;
output out=revisebootsum mean=x5 x10 x15 x20 x25 x30 x40 x45 x60;


data test;set revisebootsum;if TR='T';
tx5=x5;tx10=x10;tx15=x15;tx20=x20;tx25=x25;tx30=x30;tx40=x40;tx45=x45;tx60=x6
0;
drop TR _type_ x5 x10 x15 x20 x25 x30 x40 x45 x60;run;
run;
data ref;set revisebootsum;if TR='R';
rx5=x5;rx10=x10;rx15=x15;rx20=x20;rx25=x25;rx30=x30;rx40=x40;rx45=x45;rx60=x6
0;
drop TR _type_ x5 x10 x15 x20 x25 x30 x40 x45 x60;run;

data boot;merge test ref;by ph strength replicate;
run;
data boot;set boot;


if (rx5>85 or tx5>85) then  do;
sum=(tx5-rx5)**2 ;f2=50*log10(100/sqrt((1+sum/1)));end;
```

```
else if (rx10>85 or tx10>85)then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2;f2=50*log10(100/sqrt((1+sum/2)));end;
else if (rx15>85 or tx15>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-
rx15)**2;f2=50*log10(100/sqrt((1+sum/3)));end;
else if (rx20>85 or tx20>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2;
f2=50*log10(100/sqrt((1+sum/4)));end;
else if (rx25>85 or tx25>85) then  do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2;
f2=50*log10(100/sqrt((1+sum/5)));end;
else if (rx30>85 or tx30>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2;
f2=50*log10(100/sqrt((1+sum/6)));end;
else if (rx40>85 or tx40) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2;
f2=50*log10(100/sqrt((1+sum/7)));end;
else if (rx45>85 or tx45>85) then do;
sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2;
f2=50*log10(100/sqrt((1+sum/8)));end;
else do;sum=(tx5-rx5)**2+(tx10-rx10)**2+(tx15-rx15)**2+(tx20-rx20)**2+(tx25-
rx25)**2
+(tx30-rx30)**2+(tx40-rx40)**2+(tx45-rx45)**2+(tx60-rx60)**2;
f2=50*log10(100/sqrt((1+sum/9)));end;
keep PH strength f2 replicate sum;
run;
quit;


proc sort data=boot;by ph strength;run;
proc summary data=boot;

var f2;
output out=bootout mean=f2_boot_mean p5=f2_5th p95=f2_95th;
by ph strength;


data bootciv;merge bootout original;by ph strength;run;
proc sort data=bootciv;by strength ph;run;

proc  EXPORT DATA= WORK.bootciv
            OUTFILE= "&STUDYDIR.\DA15pH7BOOTF2-PERCENTILE.xlsx"
            DBMS=XLSX REPLACE;
     SHEET="PERCENTILE";
RUN;
```

4.5 Additional Attachments

None

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 203286

APPLICANT: Zydus Pharmaceuticals (USA) Inc.

DRUG PRODUCT: Mesalamine Delayed Release Tablets USP, 800 mg

The Division of Bioequivalence II (DB II) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

At pH 6.8, there is a significant difference in the dissolution profile for the test product between the original (07/12/2011) and amendment (02/24/2015) submissions. Please provide an explanation for this difference. In addition, please submit 12 units dissolution data of the test and reference products in buffers with pH around 6.8 (e.g. pH (b) (4) 6.8, (b) (4) using the following dissolution method on your test product:

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of

(b) (4)

(2) pH 6.8 Phosphate buffer at 50 rpm

(b) (4)

Volume: 900 mL
Temperature: 37ºC
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison.

Please submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable. Besides the dissolution summary table in the eCTD format, please submit the individual unit dissolution data and mean values in excel or sas transport format.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

ANDA: 203286

Completed Assignment for 203286 ID: 25577

Reviewer: Ren, Ping **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Mesalamine Delayed Release Tablets USP, 800 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
25577	2/24/2014	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1	Edit	Delete
25577	2/24/2014	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1	Edit	Delete
25577	2/24/2014	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1	Edit	Delete
25577	2/24/2014	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1	Edit	Delete
				Total:	4		

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203286		
Drug Product Name	Mesalamine Delayed Release Tablets USP		
Strength(s)	800 mg		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Address	73, Route 31 North, Pennington, NJ 08534		
Applicant's Point of Contact	G. Srinivas Zydus Pharmaceuticals USA Inc., 73, Route 31 North, Pennington, NJ 08534		
Contact's Telephone Number	609-730-1900		
Contact's Fax Number	609-730-1999		
Original Submission Date(s)	07/12/2011		
First Generic	Yes		
Submission Date(s) of Amendment(s) Under Review	03/13/2012 amendment for LTSS		
Reviewer	Ping Ren, Ph.D.		
Study Number (s)	# MSN-P0-732	# MSN-P0-733	
Study Type (s)	Fasting	Fed	In vitro BE study
Strength (s)	800 mg	800 mg	800 mg
Clinical Site	Algorithme Pharma Inc.		
Clinical Site Address	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1		
Analytical Site	(b) (4)		
Analytical Site Address			
OSI Status	**Inadequate pending analytical site inspection**		
OVERALL REVIEW RESULT	**Inadequate pending analytical site inspection and in vitro BE study**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**

DOCUMENT #			
1	Dissolution	800 mg	Adequate
1	Fasting Study	800 mg	Adequate
1	Fed Study	800 mg	Adequate
4	In vitro BE Dissolution study	800 mg	Inadequate

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Mesalamine Delayed Release Tablets, 800 mg, to the corresponding reference product Asacol® HD (Mesalamine Delayed Release) tablets, 800 mg. Each of the BE studies was designed as a single-dose, three-way, partial replicated crossover study in healthy male and female subjects. The applicant provided evidence that, under fasting and fed conditions, the reference product met FDA's criteria to be classified as a highly variable drug with respect to AUCt, AUC_{8-48} and Cmax. The reference-scaled average bioequivalence approach was used to calculate bioequivalence statistics for AUCt, AUC_{8-48} and Cmax in the fasting and fed BE studies. The results are summarized in the tables below.

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Fasting Bioequivalence Study No. MSN-P0-732, N= 83 (Male=51 and Female=32)						
Parameter	**T/R Ratio**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCT (0-120)	1.18	0.6606511	0.8128045	-0.362881	Scaled/PE	PASS
LAUC8-48	1.21	0.6612052	0.8131452	-0.347193	Scaled/PE	PASS
LCMAX	1.23	0.7662244	0.8753424	-0.402449	Scaled/PE	PASS

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Fed Bioequivalence Study No. MSN-P0-733, N= 70 (Male=48 and Female=22)						
Parameter	**T/R Ratio**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCT (0-120)	0.98	0.7193513	0.8481458	-0.422984	Scaled/PE	PASS
LAUC8-48	0.96	0.8018692	0.8954715	-0.467636	Scaled/PE	PASS
LCMAX	1.01	1.3412103	1.1581063	-0.818653	Scaled/PE	PASS

Per guidance, AUC_{0-t} is recommended in place of AUC_{inf} because the Kel could not be accurately measured for mesalamine DR product. In the table above, the 95% upper confidence bound for AUC_{0-t}, AUC_{8-48}, and Cmax in the fasting and fed BE studies are negative. The point estimate (test/reference geometric mean ratio) for AUC_{0-t}, AUC_{8-48},

and Cmax are within the range of 0.80 to 1.25. Hence, the fasting and fed studies meet the BE acceptance criteria of reference scaled analysis for log-transformed AUC_{0-t}, AUC_{8-48}, and Cmax of Mesalamine Delayed Release Tablets, 800 mg. The fasting and fed studies are acceptable.

In addition to in vivo fasting and fed BE studies, the guidance also recommends comparative in vitro **BE** dissolution studies (using USP Apparatus II at 50 rpm) to be conducted in pH 4.5, 6.0, 6.5, 6.8, 7.2 and 7.5 phosphate buffer representative of the GI tract pH variations. Yet, the firm did not submit any dissolution data for pH 4.5 Acetate buffer in the current application. Also, the mean values (f2) in pH 6.8 and pH 7.5 phosphate buffer are less than 50 and the lower bound of 90% confidence interval ("CI") for the f2 test comparing test vs. RLD in pH 6.8, pH 7.2, and pH 7.5 phosphate buffer is lower than those comparing the RLD against itself under the same conditions. These values suggest that the dissolution profiles of the test product are significantly different from those of the corresponding reference under these conditions. Therefore, the in vitro BE (comparative dissolution) studies under pH 6.8, 7.2 and 7.5 buffer are not acceptable. Due to the high variability of firm submitted dissolution data conducted in multimedia, the firm is requested to repeat comparative dissolution testing on its **fresh test product** using a larger sample size of tablets (e.g. 24 unites for test and two lots of unexpired RLD product) to provide a better estimate of the mean difference, or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculation.

The firm conducted quality control dissolution testing using the USP method [500 mL of 0.1N HCl (Acid Stage A) for 2 hrs, followed by 900 mL of Phosphate buffer, pH 6.0 (Buffer Stage B) for 1 hr and 900 mL of Phosphate buffer, pH 7.2 (Buffer Stage C) using apparatus 2 (Paddle) at 100 rpm for stage A and B and at 50 rpm for stage C][1]. The firm's proposed specifications are the same as the USP specifications (Acid Stage: NMT 1% in 2 hours; Buffer Stage I: NMT 1% in 1 hour; Buffer Stage II: NLT 80% (Q) in 90 minutes). The quality control dissolution testing with the USP method is acceptable. The DB II acknowledges that the firm will follow the USP method and specifications.

A routine inspection of the clinical site, Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal Quebec, was requested for ANDA202172 on 10/18/2010 and was completed 2/7/2011 with an outcome of NAI.

A routine inspection of the analytical site, (b) (4)
was requested for this parent ANDA 203286 on 3/8/2012 and is pending.

The application is incomplete pending the results of in vitro comparative dissolution testing and OSI analytical site inspection.

[1] DARRTS: REV-BIOEQ-02 (Dissolution Review) ANDA203286, Final date: 02/16/2012.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Mesalamine Delayed Release Tablets USP, 800 mg
Reference Product	Asacol® HD (Mesalamine Delayed Release) tablets
RLD Manufacturer	WARNER CHILCOTT LLC
NDA No.	N021830
RLD Approval Date	May 29, 2008
Indication	Asacol® HD is indicated for the treatment of moderately active ulcerative colitis.

*Asacol® HD was manufactured and marketed by Procter and Gamble (P&G) before February 12, 2010. On February 12, 2010, the firm notified the FDA that the corporate name and/or address had been changed from Procter and Gamble Pharmaceuticals, Inc. to Warner Chilcott Pharmaceuticals Inc[2].

3.2 PK/PD Information[3]

Mechanism	The mechanism of action of mesalamine is unknown, but appears to be topical rather than systemic. 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 chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.
Bioavailability	The action of mesalamine appears to be topical rather than systemic. Based on cumulative urinary recovery of mesalamine and N-Ac-5-ASA from single dose studies in healthy volunteers, approximately 20% of the orally administered mesalamine in Asacol HD tablets is systemically absorbed, leaving the remainder available for topical action and excretion in the feces.
Food Effect	A high fat meal does not affect the extent of systemic exposure to mesalamine after single-dose administration of Asacol HD, but mesalamine Cmax decreases by 47% and Tmax is delayed by 14 hours under fed conditions.
Tmax	10 to 16 hrs
Metabolism	Plasma concentrations of mesalamine (5-aminosalicylic acid; 5-ASA) and its metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA) are highly variable following administration of Asacol HD tablets. The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver to N-Ac-5-ASA which is excreted mainly by the kidney.
Excretion	The absorbed mesalamine is rapidly acetylated in the gut mucosal wall

[2] DARRTS: COR-NDAACK-06 (Change of Applicant Name/Address) NDA021830, Final date 02/26/2010.
[3] Labeling repository: http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=03a3bff5-e652-4771-9bf7-3b6850423cc5#nlm34090-1

	and by the liver to N-Ac-5-ASA which is excreted mainly by the kidney. Approximately 20% of the orally administered mesalamine in Asacol HD tablets is systemically absorbed, leaving the remainder available for topical action and excretion in the feces.
Half-life	12.6 hrs
Drug Specific Issues (if any)	One Asacol HD 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets. Therefore, one Asacol 800 tablet has not been shown to be interchangeable with two 400 mg Asacol tablets. Instruct patients to swallow the Asacol HD tablets whole, taking care not to break, cut, or chew the tablets, because the coating is an important part of the delayed-release formulation. The most serious adverse reactions: Renal impairment, including renal failure (rare) Acute exacerbation of colitis Hypersensitivity reactions

3.3 OGD Recommendations History

1. The OB lists the following mesalamine modified release products as currently marketed products:

Application No	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant	Approval date
N022000	Yes	Mesalamine	Tablet, Delayed Release; Oral	1.2 g	Lialda®	Shire	Jan 16, 2007
N019651	Yes	Mesalamine	Tablet, Delayed Release; Oral	400 mg	Asacol®	Warner Chilcott Llc	Jan 31, 1992
N021830	Yes	Mesalamine	Tablet, Delayed Release; Oral	800 mg	Asacol HD®	Warner Chilcott Llc	May 29, 2008
N204412	Yes	Mesalamine	Capsule, Delayed release; Oral	400 mg	DELZICOL	Warner Chilcott Llc	Feb 1, 2013
N 020049	Yes	Mesalamine	Capsule, extended release; Oral	500mg (also 250 mg)	Pentasa	Shire	Jul 8, 2004 (May 10, 1993)
N022301	Yes	Mesalamine	Capsule, extended release; Oral	375 mg	APRISO	SALIX PHARMS	Oct 31, 2008

Asacol (delayed-release tablet) was the first mesalamine oral product approved on June 31, 1992 for the treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC. Soon after that, Pentasa (extended-

release capsule, 250 mg) was approved on May 10, 1993 for the induction of remission and for the treatment of patients with mildly to moderately active UC. Pentasa 500 mg strength was approved on July 8, 2004 (NDA 20-049/SCS-015) based on formulation proportionality and an in vivo-in vitro correlation, which has been established for the 250 mg strength (NDA 20-049/SCS-013)[4]. Four newer RLDs were approved recently, namely Lialda (January 16, 2007), Asacol HD (May 29, 2008), Apriso (October 31, 2008) and Delzicol (Feb. 2013), all based on clinical trials.

For Asacol, **prior** to 2010, OGD recommended (b) (4)

(b) (4)

2. Shire Pharmaceuticals (the Pentasa sponsor) filed a Citizen Petition (CP, No. FDA-2008-P-0507) on September 10, 2008, and Warner Chilcott Company (the Asacol and Asacol HD sponsor) filed a CP Docket No. FDA-2010-P-0111) on February 22, 2010. The FDA issued the response to both citizen petitions on August 20, 2010. In the CP response, FDA concluded that 'bioequivalence of mesalamine delayed release tablets (RLD: Asacol and Asacol HD) is recommended to be demonstrated by equivalence of pharmacokinetic profiles and equivalent in vitro drug release (dissolution) under multiple conditions representative of the conditions in the GI tract.'[5]. FDA also concluded that 'the decision about generic products referencing Asacol should also apply to generic products referencing Pentasa and other mesalamine modified release products (Apriso and Lialda)[6].

   The Agency response to the Asacol and Pentasa petitions did not describe the appropriate PK metrics and the comparative dissolution test conditions. The OGD later summarized the appropriate PK metrics and the comparative BE dissolution test conditions recommended for five mesalamine oral products as follows:

   <u>In Vitro BE studies</u>

   Table 1: Recommendations for comparative dissolution testing (Note PB is Phosphate Buffer)

Product	Strength (mg)	Apparatus	Speed (rpm)	Pretreatment Stage	Evaluation Stage	Volume (mL)	Sampling
Asacol Asacol HD	400 800	II (paddle)	100 rpm for pretreatment stage; 50 rpm for evaluation stage.	2 hours in 0.1 N HCl (500 mL)	Each of (1) pH 4.5 Acetate buffer (2) pH 6.0 PB (3) pH 6.5 PB (4) pH 6.8 PB	900	0, 10, 20, 30, 45, 60, 75, 90, 120, 150 min or as

[4] \\cdsnas\OGDS6\CONTROLS\2004-docs\04-293.pdf.
[5] Asacol and Pentasa Citizen Petition Response \\cdsnas\OGDS6\CONTROLS\2008-docs\08-1019.pdf; \\cdsnas\OGDS6\CONTROLS\2010-docs\10-0151.pdf.
[6] \\cdsnas\OGDS6\CONTROLS\2008-docs\08-1019.pdf ; \\cdsnas\OGDS6\CONTROLS\2010-docs\10-0151.pdf

					(5) pH 7.2 PB (6) pH 7.5 PB		needed for profile comparison
Lialda	1200	II (paddle)	[redacted] (b) (4)				
Pentasa	250 / 500	II (paddle)	100 rpm	None	Each of (1) 0.1 N HCl (2) pH 4.5 Acetate buffer (3) pH 6.0 PB (4) pH 6.5 PB (5) pH 6.8 PB (6) pH 7.2 PB (7) pH 7.5 PB	900	1, 2, 4, 6, 8, and 12 hours or as needed for profile comparison
Apriso	375	[redacted] (b) (4)					

Please note that Delzicol was approved after the CP and guidance were issued. The BE recommendation for this RLD is under review.

Selection of partial AUC matrix, AUC8-48 for mesalamine DR tablet (please note this matrix does not apply to Apriso and Pentosa as they are ER capsules)[7]

The original OGD recommendation for partial AUC is AUC0-Tmax and AUCtmax-24 based on simulation data. The recommendation was changed to AUC 8-48 due to the following:

The NDA sponsor [redacted] (b) (4) Asacol 400 mg tablets due to the existence of dibutyl phthalate (DBP). DBP serves as a [redacted] (b) (4) in the Asacol formulation and is believed to have adverse reproducti elopmental effects based on recently publication in animal studies. Warner Chilcott submitted an IND 026093 on 12/29/2010 which included study protocol, PR-08210. In the OCP response, AUC_{8-48} was recommended [redacted] (b) (4)

On October 28, 2011, a meeting was held among OGD, OCP, ONDQA, and ORP to discuss the differences in Asacol BE recommendation. OGD agreed with OND on

[7] The draft pAUC matric for Apriso and Pentosa are AUC0-3 and AUC3-t. They are under review pending CP#FDA-2013-P-0470

the partial AUC_{8-48} based on the following reasons: (1) AUC_{8-48} reflects the absorption in the colon, which is the site of action; (2) the variability of AUC_{Tmax} is too high and it might be over-discriminative (AUC_{8-48} is highly correlated with $AUC_{t)}$. However, since Asacol and other mesalamine oral products are locally acting, it is important to have profile similarity between the reference product and the generic product to ensure they have similar delivery in the gastrointestinal tract. Thus OGD may evaluate other pAUCs during the review process as supportive information. To aid this evaluation and to ensure the best possible characterization of drug absorption by AUC8-48, OGD recommends dense sampling in the time between Tmax and 24 hours.

3. Warner Chilcott Company filed another Citizen Petition (Docket No. FDA-2012-P-1087) on October 14, 2012 requesting changes to the pAUC time interval from AUC8-48 to AUC0-12 and AUC12-48 existing guidance. In the FDA's response issued Mar., 2013, the FDA stated that it *"denies your specific requests that we change our bioequivalence recommendations, though we grant your request that FDA clarify its position on the within-subject variability of Asacol and Asacol HD and the relevance of that variability to use of the reference-scaled approach for demonstrating bioequivalence in highly-variable drug products"*.[8] Therefore, the FDA continues to recommend AUC8-48.

3.4 OGD Recommendations for Drug Product

Number of studies recommended:	3, fasting, fed, and in vitro comparative dissolution study

1.	**Type of study:**	Fasting
	Design:	Single-dose, partially or fully replicated crossover design, in-vivo
	Strength:	800 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study
	Additional Comments:	Other study designs are acceptable if appropriate. Specific recommendations are provided below.

2.	**Type of study:**	Fed
	Design:	Single-dose, partially or fully replicated crossover design, in-vivo
	Strength:	800 mg
	Subjects:	Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study
	Additional Comments:	Other study designs are acceptable if appropriate. Specific recommendations are provided below.

[8] Dockets Search at regulations.gov (http://www regulations.gov/#!home); Search: FDA-2012-P-1087; see FDA/CDER to Warner Chilcott, LLC – Petition Partial Approval and Denial and Acknowledgement Letter to Alvin Howard (Warner Chilcott Company, LLC); Last Accessed Date: 04/03/2013

3.	**Type of study:**	In vitro comparative dissolution study
	Strength	800 mg
	Apparatus:	USP Apparatus 2 (paddle)
	Pretreatment Stage:	2 hours in 0.1 N HCl at 100 rpm
	Evaluation Stage:	Each of (1) pH 4.5 Acetate buffer at 50 rpm (2) pH 6.0 Phosphate buffer at 50 rpm (3) pH 6.5 Phosphate buffer at 50 rpm (4) pH 6.8 Phosphate buffer at 50 rpm (5) pH 7.2 Phosphate buffer at 50 rpm (6) pH 7.5 Phosphate buffer at 50 rpm
	Volume:	900 mL
	Temperature:	37°C
	Sample times:	0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison
	Additional Comments:	The applicant should use at least 12 tablets per test. The f2 metric will be used to compare dissolution profiles.

Analytes to measure (in plasma):	Mesalamine in plasma
Bioequivalence based on:	90% CI of Mesalamine and acceptable in vitro comparative dissolution study
Waiver request of in-vivo testing:	Not applicable
Source of most recent recommendations:	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320003.pdf The above Guidance is based on FDA's response to [redacted](b) (4)Control# 12-0615 on September 20, 2010 reviewed by the scientific team. \\cdsnas\OGDS6\CONTROLS\2012-docs\12-0615.pdf

Additional comments:	**Additional comments regarding the BE study with PK endpoints:** (1). Applicants may consider using a reference-scaled average bioequivalence approach for mesalamine. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability > 30%) for the reference product. For general information on this approach refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs. (2). For both fasting and fed studies, the following PK parameters are recommended to be evaluated: Log-transformed AUC8-48, AUC0-t, and C max , where AUC8-48 is the area under the plasma concentration vs. time curve from 8 to 48 hours, AUC0-t is the area under the curve from 0 hours to the last measurable time point, and C max is the maximum plasma concentration. Applicants should have extensive sampling points around T max to have accurate estimation of C max and T max, and at least four non-zero measurements of concentration are recommended before T max and between T max and 24 hours if possible. Other partial AUCs may be evaluated as supporting material to evaluate similarity of drug release throughout the gastrointestinal tract. (3). As AUC 0-t is recommended in place of AUC 0-∞, the last sampling time point should be at least at 72 hours.

Summary of OGD or DBE History (for details, see Appendix 4.4):	The DB has received and/or reviewed the following ANDAs: (b) (4) 091640 (ZYDUS) (b) (4) 203817 (WATSON) 203574 (MYLAN) (b) (4) The OGD has received and/or reviewed the following Controls: Control # 01-248 (b) (4) Control # 02-167 Control # 02-198 Control # 12-0419 (b) (4) Control # 12-0615 The OGD has received and/or reviewed the following Protocols: 02-010 (b) (4) 06-020 09-042 12-042

3.5 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	N/A
In vitro dissolution	Yes	1
Waiver requests	No	N/A
BCS Waivers	No	N/A
Clinical Endpoints	No	N/A
Failed Studies	No	N/A
Amendments	Yes	03/13/2012 amendment for LTSS 03/13/2012

3.6 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte 1
Bioanalytical method validation report location	Appendix 16.6
Study Report Number	SAP1186007 and SAP1186008

Analyte	Mesalamine
Internal standard (IS)	(b) (4)
Method description	Liquid-Liquid extraction with LC/MS/MS method
Limit of quantitation	1.000 ng/mL
% recovery (and %CV) at each concentration tested	HQC (900.0 ng/mL): 92.18%, %CV: 8.13 MQC-1 (450.0 ng/mL): 88.63%, %CV: 7.76 MQC-2 (50 ng/mL): 87.58%, %CV: 3.57 LQC (3.0 ng/mL): 85.83%, %CV: 9.5
Average recovery of IS (%)	97.8 %
Standard curve concentrations (ng/mL)	1.000, 2.000, 5.000, 20.00, 40.00, 100.0, 250.0, 600.0, 1000, 1200
QC concentrations (ng/mL)	1.000, 3.000, 50.00, 450.0, 900.0, 1200.0
QC Intraday precision range (%)	ULOQ (1200.0 ng/mL): 1.3 to 1.6% HQC (900.0 ng/mL): 1.1 to 1.5% MQC-1 (450.0 ng/mL): 1.1 to 1.7% MQC-2 (50 ng/mL): 0.8 to 1.2% LQC (3.0 ng/mL): 2.0 to 3.6% LLOQ (1.0 ng/mL): 4.0 to 9.4%
QC Intraday accuracy range (%)	ULOQ (1200.0 ng/mL): 94.2 to 103% HQC (900.0 ng/mL): 97 to 101% MQC-1 (450.0 ng/mL): 101 to 106% MQC-2 (50 ng/mL): 105 to 106% LQC (3.0 ng/mL): 100 to 104% LLOQ (1.0 ng/mL): 99.5 to 107%
QC Interday precision range (%)	1.2 % to 7.0 %
QC Interday accuracy range (%)	98.1 % to 106 %
Bench-top stability (hrs)	25 hours @ room temperature
Stock stability (days)	49 days for drug and 15 days for internal standard @ 4°±6 °C
Processed stability (hrs)	70 hours @ room temperature and 92 hours @ 4°± 6°C
Freeze-thaw stability (cycles)	6 freeze thaw cycles
Long-term storage stability (days)	131 days @ -70°C±20°C*
Dilution integrity	DHQC 900.0 ng/mL diluted 10 times: 107.12%, %CV: 0.9 DIQC 6000 ng/mL diluted 10 times: 110.97%, %CV: 1.3
Selectivity	No significant interfering peaks noted in blank plasma samples

* In the amendment dated 03/13/2012, the firm resubmitted the acceptable validation report for the LTSS of 131 days at -70°C±20°C that is sufficient to cover the storage period for fasting (86 days) and fed (116 days) studies.

SOPs submitted	Yes, SOP (b) (4) Assay validation in biological fluids (Chromatographic)
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

Acceptable.

3.7 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range)	Mean Parameters (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/ mL)	AUCi (ng*hr/ mL)	tHalf (hr)	Kel (1/hr)	
Study # MSN-P0-732	To evaluate and compare the relative bioavailability and therefore the bioequivalence of two different formulations of mesalamine after a single oral dose administration under fasting conditions.	Single Center, randomized, laboratory-blinded, three-period, two-treatment, three-sequence, partial replicate single-dose, crossover , fasting, study design	Mesalamine 800 mg delayed-release tablet 1× 800 mg, Oral, [Batch No: EMK150]	90 Enrolled, 90 dosed, 88 completed study (54 males, 34 females) Age: 40 (18-66) years Healthy male & Female subjects.	285.995 (124.105)	16.000 (4.000-48.000)	2859.065 (62.550)	3507.830 (73.766)	12.584 (89.461)	0.137 (131.150)	**Please refer Module 5.3.1.2**
			Asacol® HD 800 mg delayed-release tablet 1× 800 mg, Oral, [Batch No: 442661 S3]		282.187 (187.053)	17.000 (2.000-95.000)	2583.358 (78.284)	3067.042 (72.274)	13.496 (128.171)	0.117 (88.069)	

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range)	Mean Parameters (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/ mL)	AUCi (ng*hr/ mL)	tHalf (hr)	Kel (1/hr)	

Study # MSN-P0-733	To evaluate and compare the relative bioavailability and therefore the bioequivalence of two different formulations of mesalamine after a single oral dose administration under fed conditions.	Single Center, randomized, laboratory-blinded, three-period, two-treatment, three-sequence, partial replicate single-dose, crossover , fed, study design	Mesalamine 800 mg delayed-release tablet 1× 800 mg, Oral, [Batch No: EMK150]	90 Enrolled, 90 dosed, 83 completed study (57 males, 26 females) Age: 38 (20-66) years Healthy male & Female subjects.	657.624 (139.335)	24.000 (7.000-48.170)	3625.090 (80.889)	4256.461 (74.878)	11.550 (88.145)	0.126 (91.693)	**Please refer Module 5.3.1.2**
			Asacol® HD 800 mg delayed-release tablet 1× 800 mg, Oral, [Batch No: 442661 S3]		643.839 (141.041)	24.000 (7.000-48.000)	3556.863 (86.705)	4219.213 (81.900)	11.624 (103.846)	0.119 (84.006)	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Mesalamine Delayed Release Tablets USP
Dose 1 X 800 mg
Summary Of Statistical Analysis - SCALED DATA
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study (Study No. MSN-P0-732)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC_{0-120}	1.18	N/A	N/A	0.6606511	0.8128045	-0.362881	Scaled/PE	PASS
LAUC8-48	1.21	N/A	N/A	0.6612052	0.8131452	-0.347193	Scaled/PE	PASS
LCMAX	1.23	N/A	N/A	0.7662244	0.8753424	-0.402449	Scaled/PE	PASS

Mesalamine Delayed Release Tablets USP
Dose 1 X 800 mg
Summary Of Statistical Analysis - UNSCALED DATA
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study (Study No. MSN-P0-732)

Parameter	Test	Reference	Ratio	90% C.I.	
AUC_{0-120} (hr *ng/ml)	2201.32	1871.79	1.18	100.02	138.29
AUC8-48 (hr *ng/ml)	1829.86	1514.30	1.21	102.06	143.08
Cmax (ng/ml)	182.43	149.86	1.22	101.82	145.53

Mesalamine Delayed Release Tablets USP
Dose 1 X 800 mg
Summary Of Statistical Analysis - SCALED DATA
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fed Bioequivalence Study (Study No. MSN-P0-733)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC_{0-120}	0.98	N/A	N/A	0.7193513	0.8481458	-0.422984	Scaled/PE	PASS
LAUC8-48	0.96	N/A	N/A	0.8018692	0.8954715	-0.467636	Scaled/PE	PASS
LCMAX	1.01	N/A	N/A	1.3412103	1.1581063	-0.818653	Scaled/PE	PASS

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Summary Of Statistical Analysis - UNSCALED DATA Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. MSN-P0-733)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC_{0-120} (hr *ng/ml)	2301.26	2313.92	0.99	74.85	132.15
AUC8-48 (hr *ng/ml)	2003.37	2054.86	0.97	73.04	130.14
Cmax (ng/ml)	274.69	268.54	1.02	74.13	141.15

Table 3. Reanalysis of Study Samples

Fasted Study, Study No. MSN-PO-732 Additional information in Appendix No. 16.5								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in 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
Low internal standard	4	2	0.18	0.04	4	2	0.18	0.04
Above limit of quantitation	2	11	0.09	0.24	2	11	0.09	0.24
Auto injector sample vial broken	1	0	0.04	0.00	1	0	0.04	0.00
Incongruous data	0	1	0.00	0.02	0	1	0.00	0.02
Poor chromatography	1	2	0.04	0.04	1	2	0.04	0.04
Peak in pre-dose sample	0	2	0.00	0.04	0	2	0.00	0.04
Repeat as per SOP for incongruous data	0	2	0.00	0.04	0	0	0.00	0.00
Sample tube broke during extraction	0	4	0.00	0.09	0	4	0.00	0.09

Total	8	24	0.35	0.51	8	22	0.35	0.47

Fed Study, Study No. MSN-PO-733 Additional information in Appendix No. 16.5								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in 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
Above limit of quantitation	16	40	0.74	0.93	16	40	0.74	0.93
Sample not injected	5	10	0.23	0.23	5	10	0.23	0.23
Low internal standard	2	3	0.09	0.07	2	3	0.09	0.07
High internal standard	3	4	0.14	0.09	3	4	0.14	0.09
Auto injector sample vial broken	0	1	0.00	0.02	0	1	0.00	0.02
Auto injector sample vial insert leaked	2	0	0.09	0.00	2	0	0.09	0.00
Poor chromatography	0	1	0.00	0.02	0	1	0.00	0.02
Data acquisition malfunction	0	1	0.00	0.02	0	1	0.00	0.02
Sample tube broke during extraction	1	0	0.05	0.00	1	0	0.05	0.00
Total	29	60	1.34	1.38	29	60	1.34	1.38

Did use of recalculated plasma concentration data change study outcome? No

Comments from the Reviewer:

There were thirty two (0.49%) and eighty nine (2.72%) repeat samples found in the fasting and fed BE studies, respectively. Of them, eight samples were due to Incongruous data, Poor chromatography, Peak in pre-dose sample, and Repeat as per SOP for incongruous data in the fasting study and two samples were due to Poor chromatography and Data acquisition malfunction in the fed study. They were potential PK repeats. The reviewer used a calke and three ways with group SAS program to perform repeat PK statistical analysis using the original values from the samples with potential PK repeats. The study outcomes remained to meet the evaluation criteria of reference-scaled analysis for AUCt, AUC8-48, and Cmax. Therefore, the bioanalytical reanalysis for the fasting and fed BE studies are acceptable.

3.8 Formulation

Location in appendix	Section 4.2, Page 61
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.9 In Vitro Dissolution (quality controls)

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review) ANDA203286, Final date: 02/16/2012
Source of Method (USP, FDA or Firm)	USP
Medium	Acid Stage: 0.1N HCl Buffer Stage I: pH 6.0 Phosphate Buffer Buffer Stage II: pH 7.2 Phosphate Buffer
Volume (mL)	Acid Stage: 500 mL Buffer Stage : 900 mL
USP Apparatus type	USP 2 (Paddle)
Rotation (rpm)	Acid Stage: 100 RPM 2 hours Buffer Stage I: 100 RPM 1 hour Buffer Stage II: 50 RPM 90 minutes
DBE-recommended specifications	Acid Stage: NMT 1% in 2 hours Buffer Stage I: NMT 1% in 1 hour Buffer Stage II: NLT 80% (Q) in 90 minutes
If a modified-release tablet, was testing done on ½ tablets?	No
F2 metric calculated?	No
If no, reason why F2 not calculated	Due to high variability (%CV) for sampling points
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

There is a USP method for this product. The firm conducted dissolution testing using the USP method [500 mL of 0.1N HCl (Acid Stage A) for 2 hrs, followed by 900 mL of Phosphate buffer, pH 6.0 (Buffer Stage B) for 1 hr and 900 mL of Phosphate buffer, pH 7.2 (Buffer Stage C) using apparatus 2 (Paddle) at 100 rpm for stage A and B and at 50 rpm for stage C]. The firm's dissolution testing data with the USP method are acceptable. The firm's proposed specifications are the same as the USP specifications. The quality control dissolution testing is acceptable. The DB II acknowledges that the firm will follow the USP method and specifications.

3.10 In vitro BE studies

(comparative dissolution testing in pH 4.5, 6.0, 6.5, 6.8, 7.2, and 7 .5 media)

Since Mesalamine is a locally-acting drug in the colon, in vitro comparative dissolution testing can be used to ensure that a test and reference product provide equivalent delivery to the site of action. Because of the complexity of GI tract, some differences between the test and reference products could be masked by relying on a PK study alone. In vitro comparative dissolution testing in multi-media are recommended to cover the physiological pH range in the entire GI tract (pH (b) (4) 4.5, 6.0, 6.5, 6.8, 7.2, and 7 .5) according to the FDA guidance on Mesalamine (800 mg).

Table A. Product information in vitro comparative dissolution testing

Dosage Strength & Form	Test	Reference
800 mg	Mesalamine Delayed Release Tablets, 800 mg B. No. EMK150 Mfg. Date: March, 2010 Exp. Date: March, 2012	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg B. No. 442661S3 Exp. Date: March, 2013

Test dates for in vitro comparative dissolution testing on both test and reference products:

Test date for the test and reference products in multimedia								
Strength 800 mg	pH 4.5		pH 6.0		pH 6.5		pH 6.8	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Test date	N/A	N/A	6/27/2011	6/27/2011	6/27/2011	6/27/2011	6/27/2011	6/27/2011
Exp date			03/2012	03/2013	03/2012	03/2013	03/2012	03/2013
Manufacture date			03/2010		03/2010		03/2010	

Test date for the test and reference products in multimedia				
Strength 800 mg	pH 7.2		pH 7.5	
	Test	Reference	Test	Reference
Test date	6/27/2011	6/27/2011	6/27/2011	6/27/2011
Exp date	03/2012	03/2013	03/2012	03/2013
Manufacture date	03/2010		03/2010	

Note: We can not locate the raw data for in vitro comparative dissolution testing for 2 hours in 0.1 N HCl followed by pH 4.5 Acetate buffer. The firm is requested to provide the data of in vitro comparative dissolution testing in pH 4.5 Acetate buffer.

The review of In Vitro Comparative Dissolution Testing:

a) The calculation of F2 values using means

The means of F2 values (T12 vs. R12)

F2 values between the test and the reference product						
Strength	pH 4.5 buffer	pH 6.0 buffer	pH 6.5 buffer	pH 6.8 buffer	pH 7.2 buffer	pH7.5 buffer
800 mg	N/A	99.97*	83.97*	14.7*	58.86*	45.9*

*The percent coefficient of variation (%CV) was more than 20% at the 20 min, or/and more than 10% after 20 min.

REVIEWER'S NOTES:

- The F2 values can not be calculated using mean values if 1) % CV >20% at 20 min and 2) %CV >10% after 20 min (20 min is considered as cutoff point for "early sampling points") and 3) there are less than 3 sampling points for F2 calculation before both test and reference products reach 85% dissolving[9]. Yet, to confirm the data from bootstrapping approach, reviewer calculates mean f2 values disregarding variability as illustrated in the above table.

- Due to the high variability (high %CV) of dissolution data for all the media (pH 6.0 to 7.5), a comparison of mean profiles with the f2 test is not sufficient per the CDER Guidance for Industry: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms)*. Therefore, a bootstrapping procedure[10] is used to calculate mean values of F2 and an F2 confidence interval (a statistical evaluation of f2, see below).

b) The calculation of F2 values and 90% confidence interval using bootstrapping method[11]

Bootstrapping method							
Study	**pH**	**Strength (mg)**	**Frequent**	**Original f2**	**F2 bootstrap mean**	**Lower CI (Percentile)**	**Upper CI (Percentile)**
T vs. R	6.0	800	10000	99.99	99.99	99.97	100.00
	6.5	800	10000	96.93	83.96	65.53	97.48

[9] Based on 1) the CDER Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 2) high variability of vancomycin dissolution data, and discussion with bio-management, the reviewer considered the following for the f2 calculation:

- Only one measurement is considered after 85% dissolution of both the products and at least three dissolution time points are available.
- 20 min tentatively appears reasonable to be set as the cutoff of the earlier time point for Vancomycin HCl capsule in vitro BE studies. For the F2 calculation, the percent coefficient of variation before or at the earlier time point (i.e. 20 min) should not be more than 20% and at other time points (i.e. time points after 20 min) should not be more than 10%.

[10] Shah et al. In Vitro Dissolution Profile Comparison-Statistics and Analysis of the Similarity Factor, f2. *Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896*

[11] Please see statistical consult review for ANDA 065490 (DARRTS, ANDA-065490, REV-BIOMETRICS-01(General Review), Duan Joan Z, 12/04/2009) and ANDA 065510 (DARRTS, ANDA-065510, REV-BIOMETRICS-01(General Review), Duan Joan Z, 12/04/2009) for detail description of the bootstrap method.

(N=12)	6.8	800	10000	16.67	17.83	15.12	20.61
	7.2	800	10000	60.69	54.07	41.73	65.57
	7.5	800	10000	48.79	49.46	37.52	65.58
R vs. R* (N=6)	6.0	800	1000	100.00	99.99	99.98	100.00
	6.5	800	1000	80.31	77.45	57.98	99.70
	6.8	800	1000	63.58	57.32	37.73	81.66
	7.2	800	1000	68.55	63.12	47.65	79.97
	7.5	800	1000	61.28	54.55	38.91	74.14

*For R vs. R comparison, the dissolution data was first randomly divided into two groups (6 units vs. 6 units) and with each of the groups obtained from randomization, the bootstrapping procedure was then performed to calculate the f2 confidence intervals for R vs. R comparison in the comparative dissolution testing.

Comments:

1. Per the internal meeting of OGD vancomycin review team (see the attachment III), the dissolution profiles of the test and reference products are considered similar and acceptable when the f2 for the mean test and reference profiles are >50 and the lower bound of 90% confidence interval (CI) for f2 test is >46. In addition, if the lower bound of 90% confidence interval for F2 test is <46, then the difference of dissolution profile differences between test and reference may be acceptable if the reference vs. reference difference is larger. Thus, the variability of test versus reference dissolution profiles should not exceed the variability of the reference versus reference dissolution profiles.

2. For T vs. R comparison, the mean f2 values comparing the test vs. reference are greater than 50 in the media of pH 6.0 and 6.5 (99.99 and 96.93, respectively) and their lower bound of 90% confidence intervals for f2 values are more than 46 (99.97 and 65.53, respectively). The firm's dissolution data showed that the test and reference products have a similar dissolution profile under pH 6.0 and pH 6.5 conditions. Thus, the dissolution data in pH 6.0 and pH 6.5 media are acceptable.

3. In the medium of pH 7.2, the f2 mean value is greater than 50 (60.69), while its lower bound of 90% confidence intervals for f2 values are less than 46 (41.73). The f2 mean values of test and reference (f2) in all other two media (pH 6.8 and pH 7.5) are less than 50 [(pH 6.8 (16.67) and pH 7.5 (48.79)] and their lower bound of 90% confidence intervals for f2 values are less than 46 (15.12 for pH 6.8 and 37.52 for pH 7.5). Moreover, the lower bound of 90% CIs of f2 comparing test vs. RLD for pH 6.8, pH 7.2, pH 7.5 are lower than those comparing the RLD against itself under the same conditions. These results suggest that the dissolution profiles of the test product are significantly different from that of reference product under these pH conditions. Therefore, in vitro comparative dissolution testing in pH 6.8, pH 7.2, and pH 7.5 Phosphate buffer is unacceptable.

4. As per the RLD labeling, one Asacol HD 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets. Based on OCBP review for NDA

21830[12], Asacol HD (800 mg) has a similar dissolution profile as that of Asacol 400. However, the PK study showed that the administration 800 mg strength caused 36% and 25% decrease in AUC and Cmax, respectively when comparing to the administration of 2 x 400 mg strength,(PK not proportional). Since the Asacol 400 mg and 800 mg have a similar dissolution profile and no other ANDA for 800 mg strength are available in house[13], the reviewer compared the multimedia dissolution data of the RLD this application (RLD Asacol 800 mg) to that of Asacol 400 mg from (b) (4)

(b) (4)

(b) (4) It is possible that the dissolution data for the RLD (Asacol 800 mg) under pH 7.5 condition in the current application may be slightly slower than it should be due to the experiment condition. Giving the fact that f2 value between the test (800 mg strength) and the reference (Asacol HD) in the current application (ANDA 203286) is only slightly below 50 (49.46), repeating the dissolution testing at pH 7.5 with larger sample size may likely to generate a more similar dissolution profile and thus, a greater F2 value (> 50). On the other hand, the repeating dissolution testing at pH 6.8 with large sample size may or may not help to improve F2 values since pH 6.8 is the critical point and the variability around this pH is very high.

Medium	Strength	TRT	Lot #	Time (min)	0	10	20	30	45	60	75	90	120	150
pH6.8														(b) (4)
	800 mg (ANDA 203286)	Test	EMK150	Mean (%)	0	2	10	30	55	85	93	94	95	97
		RLD	442661S3	Mean (%)	0	0	1	3	8	15	22	30	42	56
pH 7.2														(b) (4)
pH 7.5														
	800 mg (ANDA 203286)	Test	EMK150	Mean (%)	0	6	14	40	78	92	95	96	97	98
		RLD	442661S3	Mean (%)	0	5	12	25	60	87	98	98	99	99

5. Because the reason discussed above and also the fact that both test and reference dissolution profiles at various pH media displayed a great deal of variability (high %CV), the firm should use a larger sample size for each dissolution testing and/or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculation. The firm is requested to repeat in vitro comparative dissolution testing in multiple media (pH 6.8, pH 7.2, and pH

[12] DRRATS: REV-CLINPHARM-21 (Primary Review) NDA21830, Final date 08/12/2005.
[13] This is the first generic product for 800 mg strength.

(b) (4)

7.5) on the **fresh test product** using at least 24 units and at least two lots of the unexpired reference product (12 units from each lot) to provide a better estimate of the mean difference.

3.11 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested in vivo?	N/A
Is in vitro comparative dissolution acceptable?	Unacceptable for the media of pH 6.8, pH 7.2, and pH 7.5
Waivers granted?	**N/A**
If not then why?	

3.12 Deficiency Comments

1. We can not locate the comparative dissolution testing data in pH 4.5 Acetate buffer (pretreated with 0.1 N HCl for 2 hours). The firm is requested to provide comparative dissolution testing data in pH 4.5 Acetate buffer using at least 24 units of fresh test product and at least two lots of the unexpired reference product (12 units from each lot) Please submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable.

2. Due to the high variability of firm submitted dissolution data conducted in multimedia, an f2 test using mean profiles of test vs. reference listed drug ("RLD") is not sufficient as per the CDER Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms ("Dissolution Guidance"). Therefore, we calculated the f2 metric (an f2 confidence interval) using a bootstrapping method for the dissolution profile comparison. For general information on this approach, please refer to Shah et al. In Vitro Dissolution Profile Comparison-Statistics and Analysis of the Similarity Factor, f2. Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896.

   The mean values (f2) in pH 6.8 and pH 7.5 phosphate buffer are lower than 50 and the lower bound of 90% confidence interval ("CI") for the f2 test comparing test vs. RLD in pH 6.8, pH 7.2, and pH 7.5 phosphate buffer is lower than those comparing the RLD against itself under the same conditions. These values suggest that the dissolution profiles of the test product are significantly different from those of the corresponding reference under these conditions. Your dissolution data in pH 6.8, 7.2 and 7.5 do not support the bioequivalence of the test product to the RLD and are not acceptable.

3. To address why the test product is different from the RLD product, the firm is recommended to repeat comparative dissolution testing on its **fresh test product**

using a larger sample of tablets to provide a better estimate of the mean difference, or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculation.

The dissolution testing should be conducted on at least 24 tables (more if necessary) from the test product and at least two lots of unexpired RLD product (using 12 tablets per lot) using the following method as specified in the FDA Guidance on Mesalamine (800 mg):

Apparatus: USP Apparatus II (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage:
Each of
(1) pH 4.5 Acetate buffer at 50 rpm
(2) pH 6.8 Phosphate buffer at 50 rpm
(3) pH 7.2 Phosphate buffer at 50 rpm
(4) pH 7.5 Phosphate buffer at 50 rpm

Volume: 900 mL
Temperature: 37ºC
Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison

The firm should submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable.

The DB will perform an f2 test on firm's submitted dissolution data. If the variability of the dissolution data is such that mean data cannot be used for the f2 test, as per the Dissolution Guidance, we will use the above-referenced bootstrapping approach.

For the bootstrapping method, sampling with replacement is used for creating 10,000 replicates of test and reference products. The means of the test and reference units at each time point for each replicate are obtained and used for f2 calculation. The 90% confidence intervals of the f2 values are calculated using the percentile approach as described in the Shah et al. reference. Similar procedure can be followed for comparing reference vs. reference products.

Please note only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

3.13 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (MSN-P0-732) conducted by Zydus on its Mesalamine Delayed Release Tablets USP, 800 mg (lot #:

EMK150) comparing it to Procter & Gamble, ASACOL® HD (Mesalamine) Delayed Release Tablets, 800 mg (lot #: 442661S3).

2. The Division of Bioequivalence accepts the fed BE study (MSN-P0-733) conducted by Zydus on its Mesalamine Delayed Release Tablets USP, 800 mg (lot #: EMK150) comparing it to Procter & Gamble, ASACOL® HD (Mesalamine) Delayed Release Tablets, 800 mg (lot #: 442661S3).

3. The Division of Bioequivalence finds in vitro comparative dissolution testing (study number) unacceptable due to the deficiencies mentioned above. The dissolution testing should be conducted on at least 24 tables (more if necessary) from the fresh test product and at least two lots of unexpired RLD product (using 12 tablets per lot) using the following method as specified in the FDA Guidance on Mesalamine (800 mg):

   Apparatus: USP Apparatus II (paddle)
   Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
   Evaluation Stage:
   Each of
   (1) pH 4.5 Acetate buffer at 50 rpm
   (2) pH 6.8 Phosphate buffer at 50 rpm
   (3) pH 7.2 Phosphate buffer at 50 rpm
   (4) pH 7.5 Phosphate buffer at 50 rpm
   Volume: 900 mL
   Temperature: 37°C
   Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison

4. The firm's quality controls dissolution testing is acceptable. The dissolution testing should be conducted according to the current USP monograph for Mesalamine Delayed Release Tablets USP, 800 mg.

3.14 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	MSN-P0-732
Study Title	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 800 mg Delayed-Release Tablets in Healthy Male and Female Volunteers / Fasting State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1
Principal Investigator	Eric Sicard, M.D. Algorithme Pharma Inc.
Dosing Dates	Group A (Subjects # 001-045): Period 1: 2011/02/25 Period 2: 2011/03/04 Period 3: 2011/03/11 Group B (Subjects # 046-090): Period 1: 2011/02/28 Period 2: 2011/03/07 Period 3: 2011/03/14
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	21 Apr 11 to 22 May 11
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	86 Days (25 Feb 11 to 22 May 11) (Group A) 83 Days (28 Feb 11 to 22 May 11) (Group B)

Table 5. Product information

Product	Test	Reference
Treatment ID	T	R
Product Name	Mesalamine Delayed Release	ASACOL® HD (Mesalamine)

	Tablets USP	Delayed Release Tablets
Manufacturer	Cadila Healthcare Limited, India	Procter & Gamble Pharmaceuticals, Inc.*
Batch/Lot No.	EMK150	442661S3
Manufacture Date	March, 2010	N/A
Expiration Date	August, 2011(Retest date)	March, 2013
Strength	800 mg	800 mg
Dosage Form	Delayed Release Tablets	Delayed Release Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	101.0 %	98.5 %
Content Uniformity (mean, %CV)	Acceptance value as per USP <905> is 3.2	N/A
Dose Administered	800 mg	800 mg
Route of Administration	Oral	Oral

*Asacol® HD was manufactured and marketed by Procter and Gamble (P&G) until Warner Chilcott acquired P&G's portfolio of branded pharmaceutical products, including Asacol® HD on Aug 24, 2009. So in certificate of analysis of reference listed drug and Bioequivalence study reports, Procter and Gamble Pharmaceuticals is indicated as name of manufacturer. However, as per current "Approved Drug Products with Therapeutic Equivalence Evaluation" (Electronic Orange Book), Warner Chilcott is identified as NDA holder for reference listed drug product, ASACOL® HD (Mesalamine) Delayed Release Tablets, 800 mg.

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled: 90** **Dosed: 90** **Completed: 88** **Samples Analyzed: 88** **Data Analyzed: 83***
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	2; 90 subjects were selected for inclusion in the study at the same clinical center. The subjects were divided into two groups, A (Subject 1to 45) and B (Subject 46 to 90) for the test and reference treatments under fasting condition.
Washout Period	7 days
Randomization Scheme	TR1R2: 2, 4, 9, 12, 15, 17, 19, 21, 24, 26, 29, 32, 36, 39, 42, 45, 48, 51, 52, 56, 60, 62, 65, 68, 71, 75, 77, 80, 83, 86, and 90. R1TR2: 3, 5, 8, 11, 14, 16, 22, 25, 30, 31, 35, 38, 41, 43, 46, 49, 50, 54, 55, 59, 63, 66, 69, 72, 73, 78, 79, 84, 85, and 89 R1R2T: 1, 6, 7, 10, 13, 18, 20, 23, 27, 28, 33, 34, 37, 40, 44, 47, 53, 57, 58, 61, 64, 67, 70, 74, 76, 81, 82, 87, and 88.
Blood Sampling Times	Pre-dose (0.0) and 2, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 22, 24, 28, 32, 36, 48, 72, 96 and 120 hours post-dose

Blood Volume Collected/Sample	7 mL/sample
Blood Sample Processing/Storage	Blood samples were collected in pre-cooled K_3 EDTA Vacutainers. Within 30 minutes of blood collection, samples were centrifuged at a temperature of 4°C nominal and at approximately 1500g for 10 minutes. The plasma obtained was separated into duplicate polypropylene culture tubes labeled as Split #1 and Split #2 (in approximately equal volume) within 90 minutes of blood collection, when feasible. The samples were frozen in an upright position and retained in the clinic's freezers at a temperature of -50°C nominal or colder until transferred to the laboratory where they were stored frozen at a temperature of -70°C ± 20°C until assayed.
IRB Approval	Yes, approved on 01/31/2011
Informed Consent	Yes, approved on 01/31/2011
Length of Fasting	12 hrs
Length of Confinement	48 hrs
Safety Monitoring	Medical history, physical examinations, vital sign assessments, 12-lead electrocardiograms (ECG), clinical laboratory assessments, adverse event evaluation, and by general observations.

* As per protocol (MSN-P0-732), Subject# (b) (6) are excluded from the pharmacokinetic & statistical analysis, since these subjects do not have three consecutive samples with levels above LLOQ[15].

Comments on Study Design:

The primary targeted site of action of mesalamine is the colon. However mesalamine can be absorbed throughout the whole GI tract. Previous PK study and continuous systemic exposure of mesalamine after mesalamine oral administration suggested that mesalamine is continuous absorption of mesalamine throughout the GI tract. Thus PK profile similarity will provide information of mesalamine local availability.

The study design is acceptable.

[15] According to guidance, applicants should have extensive sampling points around T max to have accurate estimation of C max and T max, and **at least four non-zero measurements of concentration are recommended** before T max and between T max and 24 hours if possible. Thus, it is reasonable to exclude above subjects without three consecutive samples by the firm per guidance and per firm's protocol. However, to confirm this result, the reviewer also conducted SAS analysis including all these subjects. The study outcomes remain to meet the evaluation criteria of reference-scaled analysis for AUCt, AUC8-48, and Cmax (Please see the review comments in section 4.1.1.4).

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. MSN-P0-732			
		Treatment Groups	
		Test Product N = 88	Reference Product N = 88
Age (years)	Mean ± SD	40 ± 13	40 ± 13
	Range	18 - 66	18 - 66
Age Groups	< 18	0	0
	18 – 40	47 (53.4%)	47 (53.4%)
	41 – 64	40 (45.45%)	40 (45.45%)
	65 – 75	1 (1.1%)	1 (1.1%)
	> 75	0	0
Sex	Male	53 (60.2%)	53 (60.2%)
	Female	35 (39.8%)	35 (39.8%)
Race	Asian	0	0
	Black	11 (12.5%)	11 (12.5%)
	Caucasian	76 (86.4%)	76 (86.4%)
	Hispanic	0	0
	Other (America native)	1 (1.1%)	1 (1.1%)
BMI	Mean + SD	25.09 ± 2.59	25.09 ± 2.59
	Range	19.91 - 29.82	19.91 - 29.82
Other Factors		No	No

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Withdrawn from study for safety reasons (toothache of moderate intensity).	1	No
	Withdrawn from study for safety reasons (toothache of mild intensity).	2	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Study No. MSN-P0-732		
System Organ Class MedDRA Term	**Test (N=88)**	**Reference (N=179)**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n(%)]	7 (8.0)	14 (7.8)
Vessel Puncture Site Reaction [n(%)]	4 (4.5)	3 (1.7)
Vessel Puncture Site Haematoma [n(%)]	2 (2.3)	3 (1.7)
Vessel Puncture Site Pain [n(%)]	0	5 (2.8)
Procedural Dizziness [n(%)]	0	2 (1.1)
Arthropod Bite [n(%)]	0	1 (0.6)
Injury [n(%)]	1 (1.1)	0
Procedural Complication [n(%)]	0	1 (0.6)
Procedural Nausea [n(%)]	0	1 (0.6)
NERVOUS SYSTEM DISORDERS [n(%)]	4 (4.5)	15 (8.4)
Headache [n(%)]	2 (2.3)	10 (5.6)
Somnolence [n(%)]	2 (2.3)	4 (2.2)
Dizziness [n(%)]	0	2 (1.1)
Dysgeusia [n(%)]	0	2 (1.1)
Hypoaesthesia [n(%)]	0	1 (0.6)
GASTROINTESTINAL DISORDERS [n(%)]	3 (3.4)	10 (5.6)
Abdominal Pain [n(%)]	0	3 (1.7)
Nausea [n(%)]	0	3 (1.7)
Abdominal Pain Upper [n(%)]	1 (1.1)	1 (0.6)
Constipation [n(%)]	1 (1.1)	1 (0.6)
Diarrhoea [n(%)]	0	2 (1.1)
Toothache [n(%)]	0	2 (1.1)
Vomiting [n(%)]	1 (1.1)	1 (0.6)
Dry Mouth [n(%)]	1 (1.1)	0
Dyspepsia [n(%)]	0	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS [n(%)]	3 (3.4)	9 (5.0)
Rhinorrhoea [n(%)]	1 (1.1)	4 (2.2)
Upper Respiratory Tract Infection [n(%)]	0	4 (2.2)
Cough [n(%)]	1 (1.1)	2 (1.1)
Oropharyngeal Pain [n(%)]	1 (1.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS [n(%)]	0	7 (3.9)
Fatigue [n(%)]	0	5 (2.8)
Cold Sweat [n(%)]	0	1 (0.6)
Influenza Like Illness [n(%)]	0	1 (0.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS [n(%)]	1 (1.1)	2 (1.1)
Ecchymosis [n(%)]	0	1 (0.6)
Hangnail [n(%)]	0	1 (0.6)
Rash [n(%)]	1 (1.1)	0

Study No. MSN-P0-732		
System Organ Class MedDRA Term	**Test (N=88)**	**Reference (N=179)**
INVESTIGATIONS [n(%)]	1 (1.1)	1 (0.6)
Neutrophil Count Decreased [n(%)]	1 (1.1)	1 (0.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS [n(%)]	1 (1.1)	1 (0.6)
Arthralgia [n(%)]	0	1 (0.6)
Neck Pain [n(%)]	1 (1.1)	0
EYE DISORDERS [n(%)]	1 (1.1)	0
Eye Pruritus [n(%)]	1 (1.1)	0
METABOLISM AND NUTRITION DISORDERS [n(%)]	1 (1.1)	0
Decreased Appetite [n(%)]	1 (1.1)	0
Subjects with at least one AE [n(%)]	17 (19.3)	46 (25.7)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling deviations	(b) (6)	(b) (6)
Blood sampling collection time unknown		
Blood sampling collection not done		
Blood sampling collection inconclusive		
Concomitant medication consumption		
Xanthines deviation		
Early study departure		
Omission of documentation of health status at 120-hour post-dose departure		

The sample of time deviation in the fasting BE study

Subject No.	Period	TRT	Elapsed Time (Hr)	Deviation (min)	Different (%)	Reason
(b) (6)	1	R1	6	50	13.89	A
	1	R1	2	16	13.33	A
	1	R1	4	30	12.50	A
	3	R2	72	451	10.44	D
	1	T	2	11	9.17	A
	1	R1	2	8	6.67	A
	2	R2	4	15	6.25	A
	2	R1	2	7	5.83	A
	3	R2	36	-114	5.28	H
	1	R1	2	6	5.00	A
	2	R2	48	132	4.58	D
	3	R2	48	-115	3.99	H
	1	T	2	4	3.33	A
	2	R2	4	8	3.33	A
	3	R2	48	89	3.09	D
	3	R2	4	7	2.92	A
	1	R1	7	12	2.86	A

A: difficulty with vein/catheter; D: late/absent; H: Personal reason.

Note: There are 654 time deviations in collection of ambulatory blood samples during the fasting BE study. Only 10 (1.53%) time deviations have the difference of sampling time more than 5% from scheduled time. Since all these time deviations are 0 concentration at the corresponding sampling time (except Subject (b) (6) 30.28 ng/mL at 36 hrs), the reviewer still uses scheduled time for PK analysis.

Comments on Dropouts/Adverse Events/Protocol Deviations:

Forty-one (41) (45.6%) of the ninety (90) subjects enrolled in this study experienced a total of ninety-six (96) adverse events. Of them, twenty-three (23) adverse events were reported after the administration of the test product and 73 adverse events were reported after the administration of the reference product. The intensity of adverse events ranged from mild to severe. Six (6) severe adverse events were observed. All adverse events were followed until resolution except two severe adverse events (dry month and increased neutrophil).

Two subjects experienced emesis during the course of a BE study. Subject (b) (6) who received the RLD experienced vomiting at 15:00 hrs and Subject (b) (6) who received the test product experienced vomiting at 1: 00 since last dose. The onset time of vomiting was within two time median of Tmax (Test: 2 X16 hrs; RLD: 2 X 17 hrs). The firm did not delete these subjects in statistical analysis. Yet, the study outcomes remained to meet the acceptance criteria of reference-scaled analysis for AUCt, AUC8-48, and Cmax after excluded these subjects.

Three (3) subjects experienced an adverse event that required the use of concomitant medications during the course of this study. Subject (b) (6) who took acetaminophen, pro-amoxi and ibuprofen for tooth pain in period 1 was withdrawn. Subject (b) (6) who took acetaminophen only were included in PK statistical analysis. There were no

interaction found in the literature research between the mesalamine and acetaminophen. The use of this medication should not affect the bioequivalence assessment.

Ninety (90) normal male and female adults were enrolled in this fasting BE study. Two subjects were withdrawn. The sample time deviation was minor, therefore, scheduled times were used in reviewer's analysis. The overall protocol deviation did not compromise the integrity of the study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Analyte 1										
Parameter	**Standard Curve Samples**									
Concentration (ng, mcg/mL)	1.00	2.00	5.00	20.0	40.0	100	250	600	1000	1200
Inter day Precision (%CV)	2.6	5.0	4.6	3.5	3.4	3.4	2.8	3.0	3.9	4.2
Inter day Accuracy (%Actual)	100	99.2	99.4	101	100	101	101	100	99.4	98.1
Linearity	0.9963310- 0.9999703									
Linearity Range (ng, mcg/mL)	1.000 – 1200									
Sensitivity/LOQ (ng, mcg/mL)	1.000									

Parameter	**Quality Control Samples**			
Concentration (ng, mcg/mL)	QC LOW 3.000	QC MEDIUM-2 50.00	QC MEDIUM-1 450.0	QC HIGH 900.0
Inter day Precision (%CV)	6.5	5.1	5.4	5.3
Inter day Accuracy (%Actual)	99.4	98.7	99.7	99.6

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes, 20.48% of chromatograms were included from Subject (b) (6)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	**Effective Date of SOP**	**SOP Title**
(b) (4)		Sample Reanalysis and reporting criteria

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

I. Combination of group I and II:

Mean plasma concentrations are presented in Table 18 and Figure 1

		Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUCT (0-120)	ng hr/mL	2859.065	62.55	2536.179	63.13	2630.538	90.46	1.13	1.09	0.96
AUC8-48	ng hr/mL	2401.930	66.65	2094.071	59.20	1966.759	66.92	1.15	1.22	1.06
CMAX	ng/mL	285.995	124.10	264.996	146.61	299.379	213.64	1.08	0.96	0.89
TMAX	hr	16.000	.	17.000	.	16.000	.	0.94	1.00	1.06

Composite

Fasting Bioequivalence Study, Study No. MSN-P0-732									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (0-120) (hr *ng/ml)	2859.1	62.55	54.04	7644	2583.36	78.72	6.27	17015	1.11
AUC8-48 (hr *ng/ml)**	2401.9	66.65	54.04	6394	2030.42	63.29	13.3	5875.9	1.18
Cmax (ng/ml)	285.99	124.10	9.75	2374	282.19	187.8	1.58	3959	1.01
Tmax* (hr)	16.000	.	4	48	17		2	95	0.94

* Tmax values are presented as median, range

**Since firm did not calculate AUC8-48 according to new guidance, the reviewer did it.

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals			
Fasting Bioequivalence Study, Study No. MSN-P0-732			
Parameter (units)	Ratio	90% C.I.	BE Limit Expansion (90%CI)
AUC0-t(0-120)(hr *ng/ml)	1.18	100.66-139.12	48.43-206.48
AUC∞ (hr *ng/ml)	1.17	98.63-137.81	55.79-179.25
Cmax (ng/ml)	1.22	102.61-147.3	45.8-218.32

Mesalamine 800 mg delayed-release tablet 1× 800 mg Scaled Average Bioequivalence		
Fasted Bioequivalence Study (MSN-P0-732)		
Parameter	**Ratio**	**95% Upper bound CI**
AUCt	118.34%	-0.3629
AUCi	116.59%	-0.2075
Cmax	122.94%	-0.4024

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Summary Of Statistical Analysis - Unscaled Data Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. MSN-P0-732					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t(0-120) (hr *ng/ml)	2201.32	1871.79	1.18	100.02	138.29
AUC8-48 (hr *ng/ml)	1829.86	1514.30	1.21	102.06	143.08
Cmax (ng/ml)	182.43	149.86	1.22	101.82	145.53

Reference-scaled analysis

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT(0-120)	1.18	N/A	N/A	0.6606511	0.8128045	-0.362881	Scaled/PE	PASS
LAUC8-48	1.21	N/A	N/A	0.6612052	0.8131452	-0.347193	Scaled/PE	PASS
LCMAX	1.23	N/A	N/A	0.7662244	0.8753424	-0.402449	Scaled/PE	PASS

Table 17. Additional Study Information, Fasting Study No. MSN-P0-732

Root mean square error, AUC0-t	0.6649		
Root mean square error, AUC8-48	0.6782		
Root mean square error, Cmax	0.7883		
	Test	**Reference 1**	**Reference 2**
Indicate the number of subjects with the following:			
measurable drug concentrations at 0 hr	0	2*	0
first measurable drug concentration as Cmax	0	0	1**
Were the subjects dosed as more than one group?	2	2	2

*Subject (b) (6) had pre-dose concentration 1.276 ng/mL (period II) and 2.852 ng/mL (period II), respectively. Their pre-dose concentration were much less than 5% of corresponding Cmax (Subject (b) (6) 187.5 ng/mL X 5% = 9.375 ng/mL; Subject (b) (6) 101.5 ng/mL X 5%= 5.075 ng/mL). Thus, these two subjects are included in data analysis.

** Only one sample in Subject (b) (6) was measured with Cmax at the first time point (2 hr post-dose) of a concentration-time curve following the reference 2 treatment. The first time point is far away from Tmax in this fasting BE study, which is 16 hrs in the test and reference 2 products. There is no question about whether it is insufficient early sampling time to measure a true Cmax. Moreover, study outcome meets the evaluation criteria of reference-scaled analysis for AUCt and Cmax for the fasting BE study when excluded Subject (b) (6) The data sets are considered adequate.

II. Analyzing the data for each group separately (Information only)

The firm selected 90 subjects for this fasting BE study. The subjects were divided into two groups, A and B, for this clinical study. Based on the statistical analysis for the group * treatment, all PK parameters showed that the treatment*group interaction term was not significant ($p > 0.1$). As per the DB practice (see Attachment II), the statistical analysis should be performed on groups 1 and 2 data combined. However, reviewer still analyzed the data for each group separately for information propose only.

Group I (Subject 1 to 45):

Mesalamine Delayed Release Tablets USP
Dose 1 X 800 mg
Summary Of Statistical Analysis - Unscaled Data
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. MSN-P0-732

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (0-120) (hr *ng/ml)	2244.21	1968.37	1.14	93.76	138.65
AUC∞ (hr *ng/ml)	2698.10	2522.86	1.07	87.57	130.61
AUC8-48 (hr *ng/ml)	1842.78	1573.65	1.17	95.04	144.28
Cmax (ng/ml)	172.99	146.77	1.18	94.91	146.37

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.16	N/A	N/A	0.4282745	0.6544268	-0.188609	Scaled/PE	PASS
LAUCI	1.07	N/A	N/A	0.1489786	0.3859774	-0.035977	Scaled/PE	PASS
LAUC8-48	1.18	N/A	N/A	0.4612445	0.6791499	-0.187287	Scaled/PE	PASS
LCMAX	1.19	N/A	N/A	0.6378867	0.7986781	-0.292949	Scaled/PE	PASS

Group II (Subject 46 to 90):

Mesalamine Delayed Release Tablets USP
Dose 1 X 800 mg
Summary Of Statistical Analysis - Unscaled Data
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. MSN-P0-732

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2155.80	1777.55	1.21	93.35	157.56
AUC∞ (hr *ng/ml)	2781.95	2246.79	1.24	97.21	157.72

AUC8-48 (hr *ng/ml)	1817.23	1457.79	1.25	95.22	163.20
Cmax (ng/ml)	192.41	152.90	1.26	94.41	167.73

Reference scaled analysis

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.21	N/A	N/A	0.9022135	0.9498492	-0.420495	Scaled/PE	PASS
LAUCI	1.28	N/A	N/A	0.6671145	0.8167708	-0.217885	Scaled/PE	FAIL
LAUC8-48	1.25	N/A	N/A	0.8759331	0.935913	-0.377326	Scaled/PE	PASS
LCMAX	1.26	N/A	N/A	0.9079809	0.9528803	-0.378886	Scaled/PE	FAIL

Note: The results showed that the group I passed BE requirement, while group II failed in Cmax. The bioequivalence was demonstrated in one of the groups. The results for each group separately are adequate per DB recommendation that equivalence can be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence study (see attachment II).

Comments on Pharmacokinetic and Statistical Analysis:

1. Only 2 (0.8%) samples at 0 hr sampling point had pre-dose concentrations in two out of 83 subjects. However, these two pre-dose concentrations (b) (6) are less than 5% of the corresponding Cmax. As per General BA/BE guidance, the firm included these subjects in the statistical analysis.

2. Currently DB does not have a procedure for analyzing the reference-scaled data with groups in the study design. A statistical consult has been requested for the ANDA 091073 regarding analyzing group effect in a reference-scaled average bioequivalence study design.

3. The reviewer first analyzed the group*treatment interaction term using the procedure implemented for the traditional average bioequivalence studies. The statistical analyses showed that the treatment*group interaction term was not significant for Cmax (p = 0.7582), AUCt (p=0.7529), and AUC_{8-48} (p= 0.7602). Therefore, per the DB practice (see Attachment II), the reviewer performed statistical analysis on groups 1 and 2 data combined since they meet the following criteria:

    - the clinical study takes place at one site;
    - all study subjects have been recruited from the same enrollment pool;
    - all of the subjects have similar demographics;
    - all enrolled subjects are randomly assigned to treatment groups at study outset.

4. The current DB's approach calls for using scaled average BE with a point estimate constraint (4.7 Section, Attachment I), in order to be considered bioequivalent to the RLD, the test drug must pass the following two conditions:

   i. A 95% upper confidence bounds for $\left(\overline{Y}_T - \overline{Y}_R\right)^2 - \theta\, s_{WR}^2$ must be less than or equal to 0.
   ii. The point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

   If sWR (the estimated within-subject standard deviation on the log scale for the RLD) is greater than or equal to 0.294 (meaning that sWR squared is greater than or equal to 0.086436), the reference-scaled approach could be used for establishing bioequivalence. In this case, the firm proposed to use the scaled ABE approach in the study protocol if the CV_{WR} of the reference drug was higher than 30% for the PK parameters, AUCT, AUC∞, and Cmax. Since sWRs are greater than 0.294 for AUCt (0.6649), $AUC_{8\text{-}48}$ (0.6782)[16], and Cmax (0.7883), the firm used reference scaled approach for all PK parameters (Table 15). The 95% Upper confidence bounds for AUCt, $AUC_{8\text{-}48}$, and Cmax for Mesalamine in the fasting BE study are all negative (AUCt: -0.362881, $AUC_{8\text{-}48}$: -0.347193, and Cmax: -0.402449). The results of scaled ABE approach calculated by the firm meet the first condition under fasting condition. The point estimates for Mesalamine fall within 0.8-1.25, (AUCt: 1.18, $AUC_{8\text{-}48}$: 1.21, and Cmax: 1.23) when scaled data are used in SAS scaled ABE approach. Thus, they meet the second condition.

5. As per FDA guidance, log-transformed $AUC_{8\text{-}48}$ the PK parameter is recommended to be evaluated for both fasting and fed studies. Moreover, the partial AUC is more discriminative and sensitive to formulation changes than Cmax or total AUC. The reviewer, thus, conducted SAS analysis for $AUC_{8\text{-}48}$ for fasting study in addition to standard calculation of AUC0-t and Cmax. The result indicates that $AUC_{8\text{-}48}$ for the combined group (I and II) or group I all meet BE acceptance criteria using reference-scaled analysis in this fasting BE study.

6. As per protocol (MSN-P0-732), Subject# (b) (6) are excluded from the pharmacokinetic & statistical analysis, since these subjects do not have three consecutive samples with levels above LLOQ. According to guidance, applicants should have extensive sampling points around T max to have accurate estimation of C max and T max, and at least four non-zero measurements of concentration are recommended before T max and between T max and 24 hours if possible. Thus, it is reasonable to exclude above subjects without three consecutive samples by the firm. Moreover, the study outcomes remain to meet the evaluation criteria of reference-scaled analysis for AUCt, AUC8-48, and Cmax when including above subjects as follows:

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA (N=88)

[16] Reviewer adds $AUC_{8\text{-}48}$ in statistical analysis according to Guidance.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.18	96.45	140.32	0.9644225	0.9820501	-0.55688	Scaled/PE	PASS
LAUC8-48	1.18	97.37	142.81	1.031554	1.0156545	-0.598868	Scaled/PE	PASS
LCMAX	1.21	98.58	143.50	0.9359739	0.9674575	-0.522459	Scaled/PE	PASS

The fasting study met the BE acceptance criteria of reference scaled analysis for log-transformed Cmax, AUC0-t, and AUC_{8-48} of Mesalamine Delayed Release Tablets. The fasting BE study is acceptable.

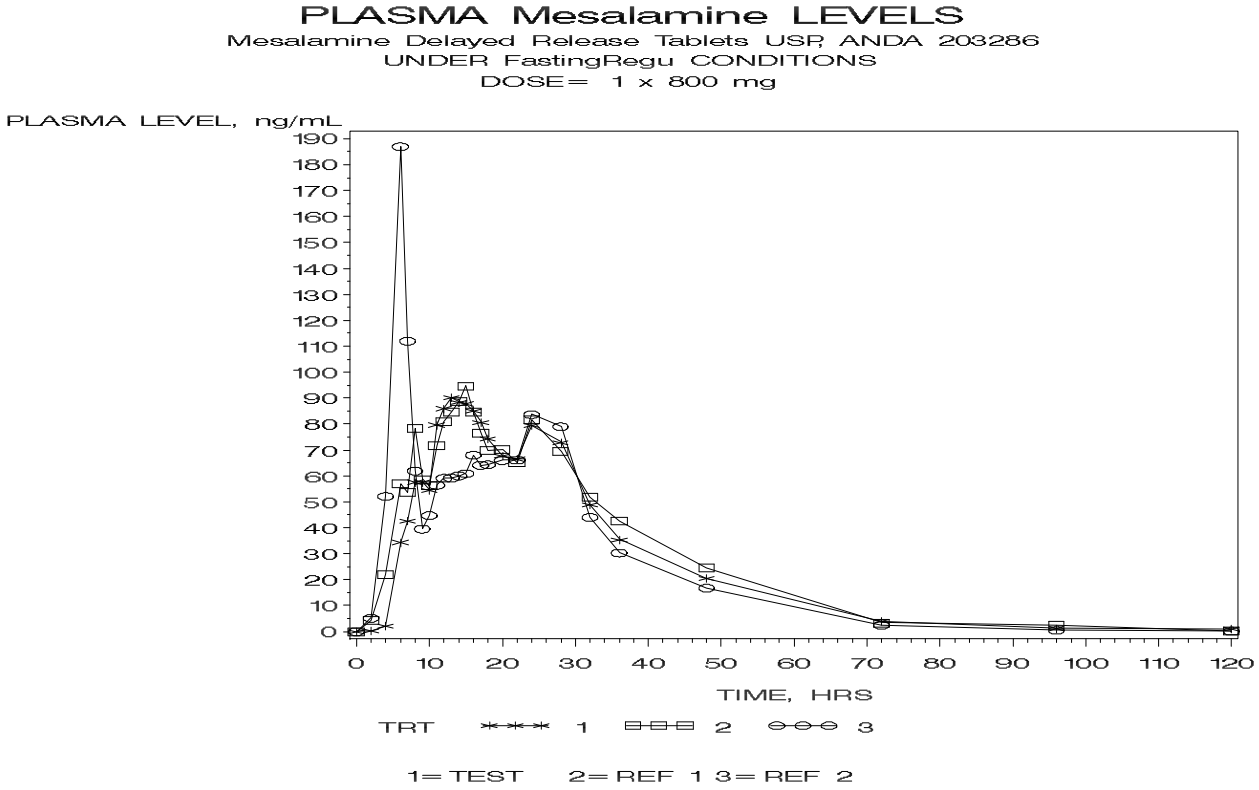
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Acceptable

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=83)		Reference 1 (n=83)		Reference 2 (n=83)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	0.05	686.42	0.00	.	0.00	.	.	.	.
2.00	0.18	590.69	4.17	911.04	5.12	911.04	0.04	0.04	0.82
4.00	2.16	363.64	21.79	613.16	51.51	843.50	0.10	0.04	0.42
6.00	34.34	279.46	56.43	629.99	184.89	348.53	0.61	0.19	0.31
7.00	42.64	275.55	53.26	347.59	110.72	307.76	0.80	0.39	0.48
8.00	57.59	269.41	77.45	334.67	61.52	282.46	0.74	0.94	1.26
9.00	57.58	365.40	57.92	239.19	39.41	215.65	0.99	1.46	1.47
10.00	54.58	189.86	55.67	189.29	44.58	160.60	0.98	1.22	1.25
11.00	79.69	162.41	71.63	156.74	56.29	150.57	1.11	1.42	1.27
12.00	85.93	142.35	82.27	127.53	59.21	141.08	1.04	1.45	1.39
13.00	90.25	130.01	87.76	117.76	59.32	136.94	1.03	1.52	1.48
14.00	88.45	121.98	92.39	113.76	60.06	123.31	0.96	1.47	1.63
15.00	87.77	112.53	99.51	125.91	60.93	109.36	0.88	1.44	1.63
16.00	85.09	108.07	89.86	113.54	67.94	123.08	1.01	1.25	1.26
17.00	80.74	103.61	80.71	103.83	64.24	90.60	1.06	1.26	1.19
18.00	74.38	110.93	72.71	98.48	64.86	92.34	1.06	1.16	1.09
20.00	67.67	108.37	71.37	103.05	66.62	99.51	0.96	1.03	1.07
22.00	66.48	107.37	66.32	102.30	66.61	101.42	1.00	1.00	1.00
24.00	79.50	105.75	81.92	100.60	84.31	106.71	0.97	0.94	0.97
28.00	73.01	97.18	69.70	72.56	79.15	101.02	1.02	0.92	0.88
32.00	48.86	90.72	51.66	96.92	44.65	117.09	0.95	1.09	1.16
36.00	35.44	111.86	42.28	111.78	30.01	129.55	0.84	1.18	1.41
48.00	20.43	144.30	24.59	152.71	16.63	187.69	0.83	1.23	1.48
72.00	3.92	287.82	3.34	323.16	2.46	349.68	1.17	1.59	1.36

	Test (n=83)		Reference 1 (n=83)		Reference 2 (n=83)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
96.00	1.19	258.38	2.52	547.06	0.52	275.01	0.47	2.29	4.85
120.00	1.07	540.67	0.18	574.03	0.15	490.67	5.94	7.13	1.20

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	MSN-P0-733
Study Title	Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 800 mg Delayed-Release Tablets in Healthy Male and Female Volunteers / Fed State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1
Principal Investigator	Eric Sicard, M.D. Algorithme Pharma Inc.
Dosing Dates	Group A (Subjects # 001-003, 005-038, 040-042): Period 1: 2011/03/01 Period 2: 2011/03/08 Period 3: 2011/03/15 Group B (Subjects # 004, 039, 043-090): Period 1: 2011/03/16 Period 2: 2011/03/23 Period 3: 2011/03/30
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	25 May 11 to 25 Jun 11
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	116 Days (01 Mar 11 to 25 Jun 11) (Group A) 101 Days (16 Mar 11 to 25 Jun 11) (Group B)

Table 20. Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Mesalamine Delayed Release Tablets USP	ASACOL® HD (Mesalamine) Delayed Release Tablets
Manufacturer	Cadila Healthcare Limited, India	Procter & Gamble Pharmaceuticals, Inc.

Batch/Lot No.	EMK150	442661S3
Manufacture Date	March, 2010	N/A
Expiration Date	August, 2011(Retest date)	March, 2013
Strength	800 mg	800 mg
Dosage Form	Delayed Release Tablets	Delayed Release Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	101.0 %	98.5 %
Content Uniformity (mean, %CV)	Acceptance value as per USP <905> is 3.2	N/A
Dose Administered	800 mg	800 mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	**Enrolled: 90** **Dosed: 90** **Completed: 83 (7 subject dropped out or withdrawn)** **Samples Analyzed: 83** **Data Analyzed: 70***
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	2, 90 subjects were selected for inclusion in the study at the same clinical center. The subjects were divided into two groups, A (Subject 001-003, 005-038, and 040-042) and B (Subject 004, 039, 043-090) for the test and reference treatments under fed condition.
Washout Period	7 days
Randomization Scheme	TR1R2: 3, 5, 7, 11, 15, 18, 20, 24, 25, 30, 32, 34, 39, 41, 44, 48, 49, 54, 56, 59, 63, 64, 67, 70, 74, 77, 81, 82, 86, and 90. R1TR2: 2, 6, 9, 12, 14, 16, 21, 22, 27, 28, 33, 35, 38, 42, 45, 47, 51, 52, 57, 58, 62, 66, 68, 71, 73, 79, 84, 87, and 89. R1R2T: 1, 4, 8, 10, 13, 17, 19, 23, 26, 29, 31, 36, 37, 40, 43, 46, 50, 53, 55, 60, 61, 65, 69, 72, 75, 76, 78, 80, 83, 85, and 88.
Blood Sampling Times	Pre-dose (0.0) and 2, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 22, 24, 28, 32, 36, 48, 72, 96 and 120 hours post-dose
Blood Volume Collected/Sample	7 mL/sample

Blood Sample Processing/Storage	Blood samples were collected in pre-cooled K_3 EDTA Vacutainers. Within 30 minutes of blood collection, samples were centrifuged at a temperature of 4°C nominal and at approximately 1500g for 10 minutes. The plasma obtained was separated into duplicate polypropylene culture tubes labeled as Split #1 and Split #2 (in approximately equal volume) within 90 minutes of blood collection, when feasible. The samples were frozen in an upright position and retained in the clinic's freezers at a temperature of -50°C nominal or colder until transferred to the laboratory where they were stored frozen at a temperature of -70°C ± 20°C until assayed.
IRB Approval	Yes, approved on 01/31/2011
Informed Consent	Yes, approved on 01/31/2011
Length of Fasting Before Meal	10 hrs
Length of Confinement	48 hrs
Safety Monitoring	Medical history, physical examinations, vital sign assessments, 12-lead electrocardiograms (ECG), clinical laboratory assessments, adverse event evaluation, and by general observations.

* As per protocol (MSN-P0-733), subject# (b) (6) are excluded from the pharmacokinetic & statistical analysis, since these subjects do not have three consecutive samples with levels above LLOQ[17].

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

[17] According to guidance, applicants should have extensive sampling points around T max to have accurate estimation of C max and T max, and **at least four non-zero measurements of concentration are recommended** before T max and between T max and 24 hours if possible. Thus, it is reasonable to exclude above subjects without three consecutive samples by the firm per guidance and per firm's protocol. However, to confirm this result, the reviewer also conducted SAS analysis including all these subjects. The study outcomes remain to meet the evaluation criteria of reference-scaled analysis for AUCt, AUC8-48, and Cmax (Please see the review comments in section 4.1.2.4).

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. MSN-P0-733			
		Treatment Groups	
		Test Product N = 83	Reference Product N = 83
Age (years)	Mean ± SD	38 ± 12	38 ± 12
	Range	20 - 66	20 - 66
Age Groups	< 18	0	0
	18 – 40	43 (51.81%)	43 (51.81%)
	41 – 64	39 (46.99%)	39 (46.99%)
	65 – 75	1 (1.2%)	1 (1.2%)
	> 75	0	0
Sex	Male	57 (68.7%)	57 (68.7%)
	Female	26 (31.3%)	26 (31.3%)
Race	Asian	0	0
	Black	7 (8.4%)	7 (8.4%)
	Caucasian	73 (88.0%)	73 (88.0%)
	Hispanic	0	0
	Other	2 (2.4%)	2 (2.4%)
BMI	Mean + SD	24.51 ± 3.08	24.51 ± 3.08
	Range	18.62 - 29.98	18.62 - 29.98
Other Factors		No	No

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
(b) (6)	Withdrawn from study for safety reasons (haemoglobin decreased of mild intensity).	2	No
	Withdrew consent from study for reasons not related to clinical event.	2	No
	Withdrew consent from study for reasons not related to clinical event.	2	No
	Withdrew consent from study for reasons not related to clinical event.	1	No
	Withdrawn from study for safety reasons (haemoglobin decreased of mild intensity).	2	No
	Withdrawn from study for reasons other	2	No

	than safety (positive ethanol test).		
(b) (6)	Withdrawn from study for safety reasons (injury of moderate intensity).	2	No

Table 24. Study Adverse Events, Fed Bioequivalence Study

Study No. MSN-P0-733		
System Organ Class MedDRA Term	**Test (N=88)**	**Reference (N=174)**
NERVOUS SYSTEM DISORDERS [n(%)]	12 (13.6)	16 (9.2)
Headache [n(%)]	6 (6.8)	9 (5.2)
Somnolence [n(%)]	5 (5.7)	5 (2.9)
Dizziness [n(%)]	1 (1.1)	1 (0.6)
Paraesthesia [n(%)]	0	1 (0.6)
Vision Blurred [n(%)]	0	1 (0.6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS [n(%)]	6 (6.8)	18 (10.3)
Vessel Puncture Site Reaction [n(%)]	2 (2.3)	8 (4.6)
Vessel Puncture Site Haematoma [n(%)]	3 (3.4)	3 (1.7)
Vessel Puncture Site Pain [n(%)]	1 (1.1)	3 (1.7)
Injury [n(%)]	0	2 (1.1)
Procedural Complication [n(%)]	0	1 (0.6)
Procedural Dizziness [n(%)]	0	1 (0.6)
GASTROINTESTINAL DISORDERS [n(%)]	10 (11.4)	12 (6.9)
Abdominal Distension [n(%)]	3 (3.4)	2 (1.1)
Abdominal Pain [n(%)]	2 (2.3)	3 (1.7)
Diarrhoea [n(%)]	1 (1.1)	4 (2.3)
Abdominal Discomfort [n(%)]	2 (2.3)	2 (1.1)
Nausea [n(%)]	2 (2.3)	2 (1.1)
Constipation [n(%)]	0	3 (1.7)
Vomiting [n(%)]	1 (1.1)	1 (0.6)
Dyspepsia [n(%)]	1 (1.1)	0
Gastrooesophageal Reflux Disease [n(%)]	1 (1.1)	0
Lip Dry [n(%)]	0	1 (0.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS [n(%)]	2 (2.3)	5 (2.9)
Fatigue [n(%)]	2 (2.3)	2 (1.1)
Asthenia [n(%)]	0	1 (0.6)
Feeling Cold [n(%)]	0	1 (0.6)
Feeling Hot [n(%)]	0	1 (0.6)
Non-Cardiac Chest Pain [n(%)]	0	1 (0.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS [n(%)]	3 (3.4)	3 (1.7)
Back Pain [n(%)]	2 (2.3)	1 (0.6)
Myalgia [n(%)]	1 (1.1)	1 (0.6)
Musculoskeletal Stiffness [n(%)]	0	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS [n(%)]	2 (2.3)	4 (2.3)
Upper Respiratory Tract Infection [n(%)]	1 (1.1)	2 (1.1)
Oropharyngeal Pain [n(%)]	0	2 (1.1)
Nasal Congestion [n(%)]	1 (1.1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS [n(%)]	2 (2.3)	4 (2.3)
Erythema [n(%)]	1 (1.1)	2 (1.1)

Study No. MSN-P0-733		
System Organ Class MedDRA Term	**Test (N=88)**	**Reference (N=174)**
Alopecia [n(%)]	0	1 (0.6)
Ecchymosis [n(%)]	1 (1.1)	0
Rash [n(%)]	0	1 (0.6)
INVESTIGATIONS [n(%)]	0	5 (2.9)
Haemoglobin Decreased [n(%)]	0	3 (1.7)
Blood Potassium Increased [n(%)]	0	1 (0.6)
Neutrophil Count Increased [n(%)]	0	1 (0.6)
Subjects with at least one AE [n(%)]	24 (27.3)	51 (29.3)

Table 25. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time deviations	(b) (6)	(b) (6)
Blood sampling not done		
Blood collection time not known		
Concomitant medication consumption		
Subject used a moisturizer 3 days prior to dosing		
Subjects were given an optional snack too late and therefore did not fast overnight for at least 10 hours		
Subject received his critical meal 1 minute late.		
The regular breakfast was not standardized compared to other subjects and periods.		
Health status of subject was not questioned before departure from the 48-hour return visit.		
Post-study tests were performed late		

The sample of time deviation in the fed BE study

Subject No.	Period	TRT	Elapsed time (hr)	Deviation (min)	Different (%)	Reason
(b) (6)	2	T	2	9	7.50	A
	1	T	2	5	4.17	A
	1	R1	2	5	4.17	A
	3	R2	6	15	4.17	B
	2	R1	12	25	3.47	A
	2	T	2	4	3.33	A
	3	R2	2	4	3.33	A

A: difficulty with vein/catheter; B: Technical Oversight;

Note: There are 483 time deviations in collection of ambulatory blood samples during the fed BE study. Only 1 (0.21%) time deviation has the difference of sampling time more than 5% from scheduled time. Since this time deviation is 0 concentration at 2 hrs, the reviewer still uses scheduled time for PK analysis.

Comments on Adverse Events/Protocol Deviations:

Forty-nine (49) (54.4%) of the ninety (90) subjects enrolled in this study experienced a total of one hundred and twenty-seven (127) adverse events. Forty-two (42) adverse events were reported after the administration of the Test product and 85 adverse events were reported after the administration of the Reference product. The majority of adverse events were mild in intensity. Six (6) severe adverse events (Test: abdominal pain, headache; Reference: headache, nausea, procedural complication) were observed during the study. All severe adverse events were possibly related to the administration of the tested products except procedural complication in Subject (b) (6)

Two subjects experienced emesis during the course of a BE study. Subject (b) (6) who received the RLD experienced vomiting at 19:45 hrs and was withdrawn due to the safety reason. Subject (b) (6) who received the test product experienced vomiting at 23:00 hrs since last dose. The o set time of vomiting was within two time median of Tmax (Test: 2 X 24 hrs). The firm did not delete this subject in statistical analysis. Yet, the study outcomes remained to meet the evaluation criteria of reference-scaled analysis for AUCt, AUC_{8-48}, and Cmax after excluded Subject (b) (6)

Five (5) subjects experienced adverse events that required the use of concomitant medications during the course of this study. Subject (b) (6) who took acetaminophen only were included in PK statistical analysis. There were no interaction found in the literature research between the mesalamine and acetaminophen. The use of this medication should not affect the bioequivalence assessment. In addition, Subject (b) (6) applied betaderm topical cream for prevention prior to dosing of period 1. Topical betamethasone (corticosteroids) is known to be absorbed into the bloodstream, especially if used for prolonged periods of time on large areas of the body. Yet, this medication was only applied for prevention in limited area at a short time. It was unlikely to have any significant concentration of corticosteroids would be present in the body at the time of clinical study.

Ninety (90) normal male and female adults were enrolled in this fasting BE study. Seven subjects were dropped out or withdrawn. The sample time deviation was minor,

therefore, scheduled times were used in reviewer's analysis. The overall protocol deviation did not compromise the integrity of the study.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Analyte 1										
Parameter	**Standard Curve Samples**									
Concentration (ng, mcg/mL)	1.00	2.00	5.00	20.0	40.0	100	250	600	1000	1200
Inter day Precision (%CV)	3.0	5.7	6.2	3.9	3.8	4.0	3.2	3.7	3.4	3.8
Inter day Accuracy (%Actual)	100	99.9	97.8	100	101	102	101	100	98.6	98.8
Linearity	0.9927569 - 0.9999053									
Linearity Range (ng, mcg/mL)	1.000 – 1200									
Sensitivity/LOQ (ng, mcg/mL)	1.000									

Parameter	**Quality Control Samples**			
Concentration (ng, mcg/mL)	QC LOW 3.000	QC MEDIUM-2 50.00	QC MEDIUM-1 450.0	QC HIGH 900.0
Inter day Precision (%CV)	8.8	5.8	5.7	5.7
Inter day Accuracy (%Actual)	98.3	99.6	102	101

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes, 25.71% of chromatogram were included from Subject (b) (6)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	**Effective Date of SOP**	**SOP Title**
(b) (4)		Sample Reanalysis and reporting criteria

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Acceptable.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Combination of Group I and II:

Mean plasma concentrations are presented in Table 33 and Figure 2

		Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUCT0-120	ng hr/mL	3625.090	80.89	3391.919	88.35	3721.807	85.49	1.07	0.97	0.91
AUC8-48	ng hr/mL	3214.314	88.14	3070.955	94.29	3408.424	90.92	1.05	0.94	0.90
CMAX	ng/mL	657.624	139.33	586.954	133.29	700.724	145.71	1.12	0.94	0.84
TMAX	hr	24.000	.	24.000	.	24.000	.	1.00	1.00	1.00

Fed Bioequivalence Study, Study No. MSN-P0-733									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (0-120) (hr *ng/ml)	3625.09	80.89	8.99	16047	3556.9	86.75	48.62	16333	1.02
AUC8-48 (hr *ng/ml)**	3214.31	88.14	8.99	16047	3239.7	92.37	39.08	16271	0.99
Cmax (ng/ml)	657.624	139.33	1.5	4692	643.84	141.2	5.89	4115	1.02
Tmax* (hr)	24.0	.	7	48	24.0	.	7	48	1

* Tmax values are presented as median, range

**Since firm did not calculate AUC8-48 according to new guidance, the reviewer did it.

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals			
Fed Bioequivalence Study, Study No. MSN-P0-733			
Parameter (units)	Ratio	90% C.I.	BE Limit Expansion (90%CI)
AUC0-t (0-120) (hr *ng/ml)	0.98	73.93-129.66	46.93-213.09
AUC∞ (hr *ng/ml)	0.95	75.61-120.43	49.76-200.98
Cmax (ng/ml)	1.01	73.38-139.16	35.59-280.96

Fed Bioequivalence Study (MSN-P0-733)		
Parameter	Ratio	95% Upper bound CI

AUCt (0-120)	97.91%	-0.4230
AUCi	95.42%	-0.3489
Cmax	101.05%	-0.8187

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Summary Of Statistical Analysis - Unscaled Data Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. MSN-P0-733					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (0-120) (hr *ng/ml)	2301.26	2313.92	0.99	74.85	132.15
AUC8-48 (hr *ng/ml)	2003.37	2054.86	0.97	73.04	130.14
Cmax (ng/ml)	274.69	268.54	1.02	74.13	141.15

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT (0-120)	0.98	N/A	N/A	0.7193513	0.8481458	-0.422984	Scaled/PE	PASS
LAUC8-48	0.96	N/A	N/A	0.8018692	0.8954715	-0.467636	Scaled/PE	PASS
LCMAX	1.01	N/A	N/A	1.3412103	1.1581063	-0.818653	Scaled/PE	PASS

Table 32. Additional Study Information

Root mean square error, AUC0-t	1.0044		
Root mean square error, AUC8-48	1.0392		
Root mean square error, Cmax	1.2279		
	Test	**Reference 1**	**Reference 2**
Indicate the number of subjects with the following:			
measurable drug concentrations at 0 hr	0	0	0
first measurable drug concentration as Cmax	0	0	0
Were the subjects dosed as more than one group?	Yes	Yes	Yes

Analyzing the data for each group separately (Information only)

The firm selected 90 subjects for this fed BE study. The subjects were divided into two groups, A and B, for this clinical study. Based on the statistical analysis for the group * treatment, all PK parameters showed that the treatment*group interaction term was not significant ($p > 0.1$). As per the DB practice (see Attachment II), the statistical analysis could be preformed on groups 1 and 2 data combined if the follows meet:

- the clinical study takes place at one site;

- all study subjects have been recruited from the same enrollment pool;
- all of the subjects have similar demographics;
- all enrolled subjects are randomly assigned to treatment groups at study outset.

However, reviewer still analyzed the data for each group separately for information propose only.

Group I

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Summary Of Statistical Analysis - Unscaled Data Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. MSN-P0-733					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	2228.89	2155.69	1.03	67.28	158.90
AUC∞ (hr *ng/ml)	3316.92	3279.09	1.01	73.89	138.48
AUC8-48 (hr *ng/ml)	1922.41	1933.50	0.99	63.84	154.85
Cmax (ng/ml)	245.49	232.14	1.06	66.17	169.00

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.01	67.28	158.90	0.4987066	0.7061916	-0.172687	Scaled/PE	PASS
LAUCI	0.96	73.89	138.48	0.200811	0.4481194	-0.072209	Scaled/PE	PASS
LAUC8-48	0.97	63.84	154.85	0.5527487	0.7434707	-0.183996	Scaled/PE	PASS
LCMAX	1.06	66.17	169.00	0.8522732	0.9231864	-0.332368	Scaled/PE	PASS

Group II

Mesalamine Delayed Release Tablets USP Dose 1 X 800 mg Summary Of Statistical Analysis - Unscaled Data Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. MSN-P0-733					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	2377.48	2479.76	0.96	65.22	140.93
AUC∞ (hr *ng/ml)	2757.39	2705.82	1.02	72.16	143.91
AUC8-48 (hr *ng/ml)	2089.52	2181.08	0.96	64.84	141.54
Cmax (ng/ml)	307.19	310.72	0.99	62.65	156.00

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.96	65.22	140.93	0.9369318	0.9679524	-0.469613	Scaled/PE	PASS
LAUCI	0.92	72.16	143.91	0.8967651	0.9469768	-0.432247	Scaled/PE	PASS
LAUC8-48	0.96	64.84	141.54	1.061619	1.030349	-0.547592	Scaled/PE	PASS
LCMAX	0.98	62.65	156.00	1.8337085	1.3541449	-1.00806	Scaled/PE	PASS

Comments on Pharmacokinetic and Statistical Analysis:

1. The reviewer first analyzed the group*treatment interaction term using the procedure implemented for the traditional average bioequivalence studies. The statistical analyses performed by the reviewer on the data pooled from the two study groups after including the group*treatment in the statistical analysis showed that the treatment*group interaction term was not significant for Cmax (p = 0.8631), AUCt (p=0.8299), AUC_{8-48} (p= 0.9156), and AUCinf (p = 0.9968). Therefore, per the DB practice (see Attachment II), the reviewer performed statistical analysis on groups 1 and 2 data combined since they meet the following criteria:

    - the clinical study takes place at one site;
    - all study subjects have been recruited from the same enrollment pool;
    - all of the subjects have similar demographics;
    - all enrolled subjects are randomly assigned to treatment groups at study outset.

2. The current DB's approach calls for using scaled average BE with a point estimate constraint (4.7 Section, Attachment I), in order to be considered bioequivalent to the RLD, the test drug must pass the following two conditions:

    i. A 95% upper confidence bounds for $\left(\overline{Y}_T - \overline{Y}_R\right)^2 - \theta\, s_{WR}^2$ must be less than or equal to 0.
    ii. The point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

    If sWR (the estimated within-subject standard deviation on the log scale for the RLD) is greater than or equal to 0.294 (meaning that sWR squared is greater than or equal to 0.086436), the reference-scaled approach could be used for establishing bioequivalence. In this case, the firm proposed to use the scaled ABE approach in the study protocol if the CV_{WR} of the reference drug was higher than 30% for the PK parameters, AUCT, AUC∞, and Cmax. Since sWRs are greater than 0.294 for AUCt (1.0044), AUC_{8-48} (1.0392.), AUC∞ (0.8323), and Cmax (1.2279), the firm used reference scaled approach including all the subjects (Table 30). The 95% Upper confidence bounds for AUCt, AUC_{8-48}, AUC∞, and Cmax for Mesalamine in the fed BE study are all negative (AUCt: -0.422984, AUC_{8-48}: -0.467636., AUC∞: -0.348853, and Cmax: -0.818653). The results of scaled ABE

approach calculated by the firm meet the first condition under fed condition. The point estimates for Mesalamine fall within 0.8-.125, (AUCt: 0.98, AUC_{8-48}:0.96, AUC∞: 0.95, and Cmax: 1.01) when scaled data are used in SAS scaled ABE approach, since they are within the limitation of 0.80-1.25, they meet the second condition.

3. As per FDA guidance, log-transformed AUC8-48 the PK parameter is recommended to be evaluated for both fasting and fed studies. Moreover, the partial AUC is more discriminative and sensitive to formulation changes than Cmax or total AUC. The reviewer, thus, conducted SAS analysis for AUC_{8-48} for the fed study. The result indicates that the AUC_{8-48} for combined group I and II, group I, or group II all meet BE acceptance criteria using reference-scaled analysis in this fed BE study.

4. As per protocol (MSN-P0-733), subject# (b) (6) are excluded from the pharmacokinetic & statistical analysis, since these subjects do not have three consecutive samples with levels above LLOQ. According to guidance, it is reasonable to exclude above subjects by the firm. Moreover, the study outcomes remain to meet the evaluation criteria of reference-scaled analysis for AUCt, AUC_{8-48}, and Cmax when including above subjects as follows:

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA (N= 83)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.93	66.00	131.97	1.6232786	1.2740795	-0.97212	Scaled/PE	PASS
LAUC8-48	0.93	66.98	133.90	1.5943101	1.2626599	-0.951851	Scaled/PE	PASS
LCMAX	0.93	69.27	134.68	1.6217231	1.2734689	-0.980643	Scaled/PE	PASS

The fed study met the BE acceptance criteria of reference scaled analysis for log-transformed Cmax, AUC0-t, and AUC_{8-48} of Mesalamine Delayed Release Tablets. The fed BE study is acceptable.

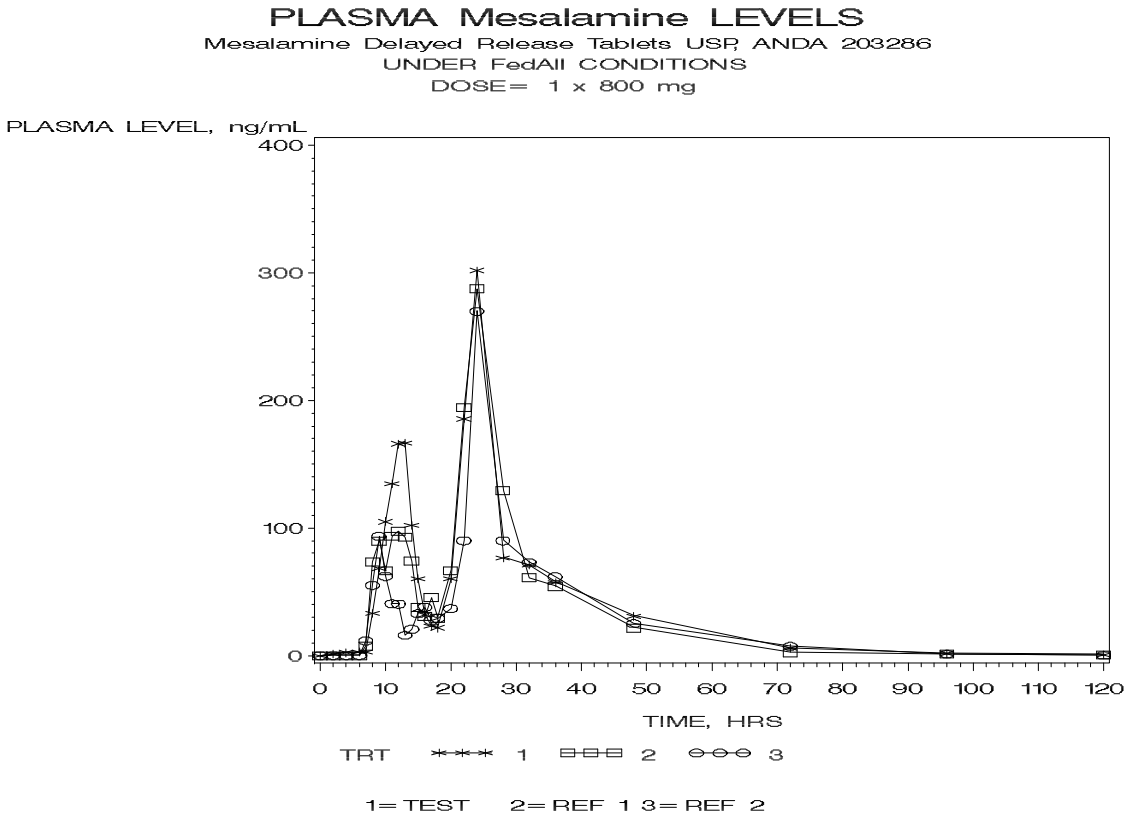
Summary/Conclusions, Single-Dose Fed Bioequivalence Study: Acceptable

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=70)		Reference 1 (n=70)		Reference 2 (n=70)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	0.00	.	0.00	.	0.00	.	.	.	.
2.00	1.29	753.23	0.12	593.17	0.12	589.37	10.93	10.42	0.95
4.00	2.52	787.62	0.13	590.64	0.14	535.84	19.25	18.24	0.95

	Test (n=70)		Reference 1 (n=70)		Reference 2 (n=70)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
6.00	3.14	671.29	0.13	594.52	0.14	518.12	24.69	22.32	0.90
7.00	2.89	491.40	7.42	552.91	11.58	486.62	0.39	0.25	0.64
8.00	33.28	414.73	73.36	508.61	55.17	441.52	0.45	0.60	1.33
9.00	68.57	305.72	90.13	452.48	93.64	396.63	0.76	0.73	0.96
10.00	104.99	304.07	66.63	433.11	62.24	414.59	1.58	1.69	1.07
11.00	135.09	326.25	93.79	457.90	40.72	454.97	1.44	3.32	2.30
12.00	166.20	289.87	97.78	458.92	40.51	418.30	1.70	4.10	2.41
13.00	166.48	293.52	92.74	490.30	15.91	234.79	1.80	10.47	5.83
14.00	102.49	360.38	73.98	396.61	20.68	294.25	1.39	4.96	3.58
15.00	60.52	383.56	38.06	399.29	32.92	356.75	1.59	1.84	1.16
16.00	31.95	249.46	30.76	334.58	37.88	373.01	1.04	0.84	0.81
17.00	23.18	194.87	45.47	413.51	27.76	222.54	0.51	0.84	1.64
18.00	21.94	198.03	29.60	219.33	29.23	196.86	0.74	0.75	1.01
20.00	60.19	270.73	66.92	308.11	36.87	165.68	0.90	1.63	1.82
22.00	185.65	266.76	194.75	262.45	90.14	172.30	0.95	2.06	2.16
24.00	301.89	252.71	287.77	196.92	270.00	253.43	1.05	1.12	1.07
28.00	76.86	105.16	129.16	311.02	90.18	96.60	0.60	0.85	1.43
32.00	71.00	105.59	61.20	110.99	73.04	103.77	1.16	0.97	0.84
36.00	57.52	96.31	54.42	147.41	61.77	97.71	1.06	0.93	0.88
48.00	31.13	127.52	21.89	156.40	25.16	147.75	1.42	1.24	0.87
72.00	6.17	352.29	2.52	270.26	7.39	217.14	2.45	0.83	0.34
96.00	1.72	429.70	1.03	290.77	1.17	266.48	1.66	1.46	0.88
120.00	0.83	552.77	0.37	358.72	0.27	389.77	2.22	3.10	1.39

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Name of Ingredient	Quantity/ Tablet (mg)	Quantity (% w/w)[$]
(b) (4)		
Mesalamine, USP	800.000	(b) (4)
Sodium Starch Glycolate, NF	(b) (4)	
Colloidal Silicon Dioxide, NF	(b) (4)	
Magnesium Stearate, NF	(b) (4)	
(b) (4)		
Microcrystalline Cellulose, NF	(b) (4)	
Povidone, USP	(b) (4)	
(b) (4)		
(b) (4)		
Sodium Starch Glycolate, NF,	(b) (4)	
Talc, USP	(b) (4)	
Colloidal Silicon Dioxide, NF	(b) (4)	
Magnesium Stearate, NF	(b) (4)	
Total	(b) (4)	
Methacrylic Acid Copolymer, NF - Type B (Eudragit S	(b) (4)	
Talc, USP	(b) (4)	
Acetyltributyl Citrate, NF		
Titanium Dioxide, USP	(b) (4)	
Ferric Oxide, NF (RED)	(b) (4)	
Isopropyl Alcohol, USP*		
(b) (4)		
(b) (4)		
Opacode Black	(b) (4)	
Isopropyl Alcohol, USP*		

Total	**1102.400**	**100.000**

(b) (4)

(b) (4)

Inactive ingredient(s)	Listing In the Inactive Ingredients Database	Mesalamine Delayed Release Tablets USP, 800 mg	Levels recommended in Inactive Ingredients Database(mg) (Oral route)
Sodium Starch Glycolate, NF	Yes	(b) (4)	
Colloidal Silicon Dioxide, NF	Yes		
Magnesium Stearate, NF	Yes		
Microcrystalline Cellulose, NF	Yes		
Povidone (b) (4) USP	Yes		
Talc, USP	Yes		
Methacrylic Acid Copolymer, NF - Type B (Eudragit S (b) (4)	Yes		
Acetyltributyl Citrate, NF	Yes		
Titanium Dioxide, USP	Yes		
Ferric Oxide Red, NF	Yes		
(b) (4)			

Note: ANDA079148[18] contains (b) (4) of Povidone (b) (4) in its 1000 mg Metformin Hydrochloride Tablets USP. Per the RLD labeling, dosages up to 2550mg daily have been administered. The daily amount of Povidone (b) (4) Thus, the daily amount of Povidone (b) (4) of ANDA021428.

[18] DARRTS: REV-BIOEQ-01 (General Review) ANDA079148, Final date: 03/26/2008.

The Regulatory Support Branch sent a pharm/tox consult to DGP on 7/28/2011 for evaluation of proposed Eudragit S (b) (4) The consult review (ANDA 203286; Consult No. 2011-0543) was completed on 9/11/2011. The maximum daily Eudragit S (b) (4) intake from Mesalamine Delayed Release Tablets would be (b) (4) The proposed amount of Eudragit S (b) (4) The conclusion of the consult is that "there are no safety concerns for the sponsor's proposed amount of Eudragit S (b) (4) in Mesalamine Delayed Release Tablets (800 mg), and the proposed amount of Eudragit S (b) (4) is acceptable."

ANDA075604[19] contains (b) (4) mg of Acetytributyl citrate in its 20 mEq Potassium Chloride Extended-release Tablets. Per the RLD labeling, doses of 40-100 mEq per day or more are used for the treatment of potassium depletion. The daily amount of Acetytributyl citrate is 100 mEq/20 mEq X (b) (4) Thus, the daily amount of Acetytributyl citrate in the test formulation (4800 mg/800 mg X (b) (4) is below a level of ANDA075604.

(b) (4)

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A

[19] Control 01-151: \\cdsnas\OGDS6\CONTROLS\2001-docs\01-151.pdf

Comments on the drug product formulation:	Acceptable

Comment:

(b) (4)

4.3 Dissolution Data

4.3.1 In vitro Quality Control Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02 (Dissolution Review) ANDA203286, Final date: 02/16/2012

Table 34. Dissolution Data

Dissolution Conditions	Apparatus:	USP-II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 6.0 Phosphate buffer (for 1 hours) followed by pH 7.2 Phosphate buffer
	Volume:	900 mL
	Temperature:	37 C ± 0.5 C
Firm's Proposed Specifications	Acid Stage: Not more that 1% dissolved in 2 hours. Buffer Stage I: Not more that 1% dissolved in 1 hours. Buffer Stage II: Not less than 80 % (Q) of the labeled amount of Mesalamine is dissolved in 90 minutes.	
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test-Manufacture Date) (Reference–Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (Minutes)							Study Report Location
						2 hour	1 hour	15	30	45	60	90	
Study Report #:	June 27, 2011	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMK150 Mfg Date: March, 2010	800 mg Tablet	12	Mean	0.0	0.1	18.4	46.4	73.5	85.9	100.6	Refer Module 5 3 1 3
					Range	(b) (4)							
					%CV	233.5	159.5	82.1	60.0	41.9	31.7	6.2	
Study Report #:	June 27, 2011	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 442661S3 Expiry : 03/2013	800 mg Tablet	12	Mean	0.0	0.1	14.1	30.7	60.8	82.0	99.6	
					Range	(b) (4)							
					%CV	233.5	184.6	142.8	104.0	45.2	18.4	1.2	

4.3.2 In vitro BE Studies in Multiple Media

pH 6.0

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 6.0 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Acid	Buffer stage									Study Report Location
					2 hrs	10 min	20 min	30 min	45 min	60 min	75 min	90 min	120 min	150 min	
June 27, 2011	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMK150 Mfg Date: March, 2010	800 mg Tablet	12	Mean	0.03	0.1	0	0	0	0	0	0	0	0	
				Range	(b) (4)										
				%CV	180	233	--	--	147	--	--	346.4	--	346.4	
June 27, 2011	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 442661S3 Expiry : 03/2013	800 mg Tablet	12	Mean	0.1	0	0	0	0	0	0	0.1	0	0	
				Range	(b) (4)										
				%CV	88.3	---	346	233	233	346.4	233.5	104.4	346.4	346.4	

pH 6.5

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)

	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 6.5 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

Testing Date	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**										**Study Report Location**
					2 hrs	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**120 min**	**150 min**	
June 27, 2011	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMK150 Mfg Date: March, 2010	800 mg Tablet	12	Mean	0	0.4	0.3	0.2	0.5	1.5	3.9	4.1	4.4	5	
				Range	(b) (4)										
				%CV	---	123	157	197	230	303.8	326	318	331.4	327.6	
June 27, 2011	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 442661S3 Expiry : 03/2013	800 mg Tablet	12	Mean	0	0.2	0.2	0.3	0.3	0.4	3.4	5	7.2	9.1	
				Range	(b) (4)										
				%CV	---	68.4	83.1	64.1	60.3	59.7	203.9	231	235.1	222.3	

pH 6.8

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 6.8 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		
Dissolution Testing Site	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

(Name, Address)														
Testing Date	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**									**Study Report Location**
					2 hrs	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**120 min**	**150 min**	
June 27, 2011	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMK150 Mfg Date: March, 2010	800 mg Tablet	12	Mean	0	1.9	9.5	30.1	54.8	84.5	92.6	94	95	96.6	
				Range	(b) (4)										
				%CV	180	87.5	34.5	14.1	15.9	5.9	2.6	1.4	1.1	1.5	
June 27, 2011	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 442661S3 Expiry : 03/2013	800 mg Tablet	12	Mean	0	0.3	0.7	3.3	7.6	14.8	21.7	30.2	42.3	56	
				Range	(b) (4)										
				%CV	---	75.4	82.2	98	100	85.4	90.9	82.6	74.2	60.5	

pH 7.2

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 7.2 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		
Dissolution Testing Site (Name, Address)		Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210

Testing Date	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Acid**	**Buffer stage**								**Study Report Location**
					2 hrs	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**120 min**	**150 min**	
June 27,	Mesalamine Delayed Release Tablets USP, 800 mg	800 mg Tablet	12	Mean	0	4.2	14.7	27.8	43.1	65	84.9	97.2	101.4	101.5	
				Range	(b) (4)										

2011	Lot No.: EMK150 Mfg Date: March, 2010				(b) (4)										
				%CV	---	144.	98.6	85.9	81.7	48	18.2	3	1.7	0.7	
June 27, 2011	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 442661S3 Expiry : 03/2013	800 mg Tablet	12	Mean	0	3	9.4	17.2	40.1	71.7	89.4	95.6	99.7	101.2	
				Range	(b) (4)										
				%CV	346	111	67.1	59.6	36.4	11.9	4.9	3.6	1.7	1	

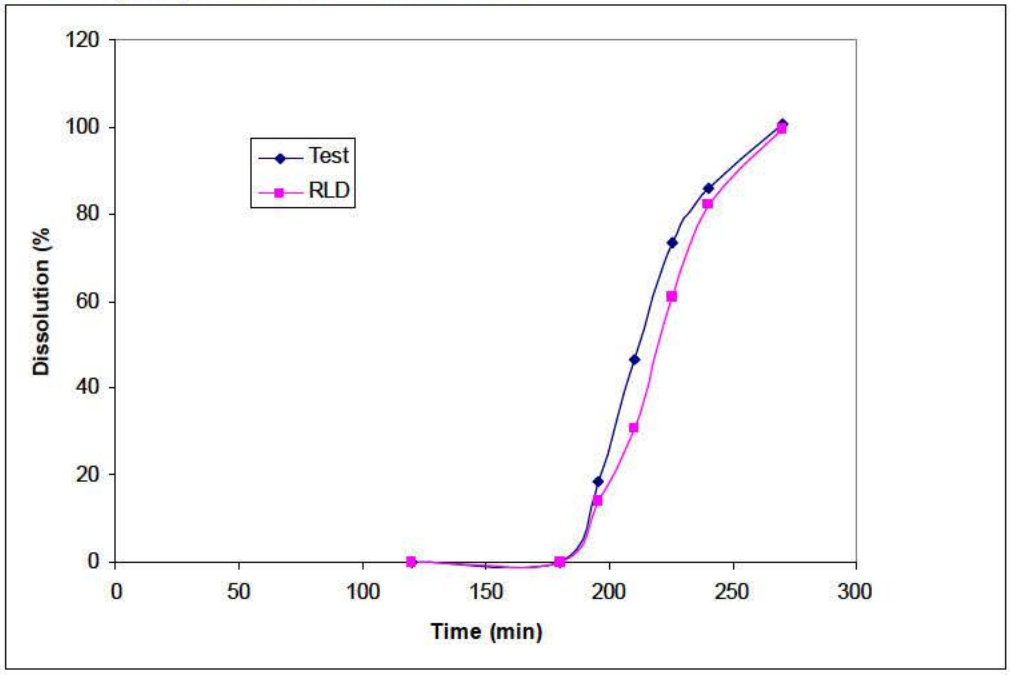
pH 7.5

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	100 rpm for acid stage and 50 rpm for buffer stage
	Medium:	0.1N HCl pH 1.2 (for 2 hours) followed by pH 7.5 Phosphate buffer
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

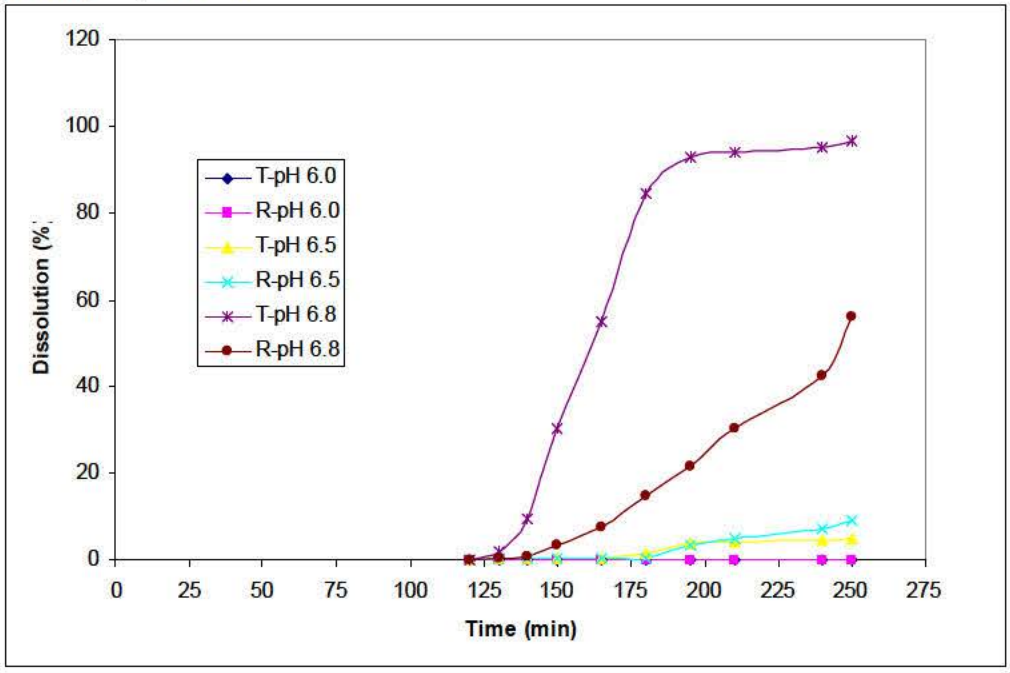
Testing Date	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Acid**	**Buffer stage**								**Study Report Location**
					2 hrs	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**120 min**	**150 min**	
June 27, 2011	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMK150 Mfg Date: March, 2010	800 mg Tablet	12	Mean	0	5.8	13.5	39.8	77.7	92.2	94.7	96.2	97	98.1	
				Range	(b) (4)										
				%CV	---	101	48.1	47.5	19.2	2.5	2.5	1.6	0.9	0.9	
June 27, 2011	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 442661S3 Expiry : 03/2013	800 mg Tablet	12	Mean	0	4.7	11.7	24.5	60.1	86.6	98.1	98.4	99.1	99.3	
				Range	(b) (4)										
				%CV	147	98.7	109	70.9	32.4	7.5	3.6	2.5	1.7	1.1	

Figure 3. Dissolution Profiles

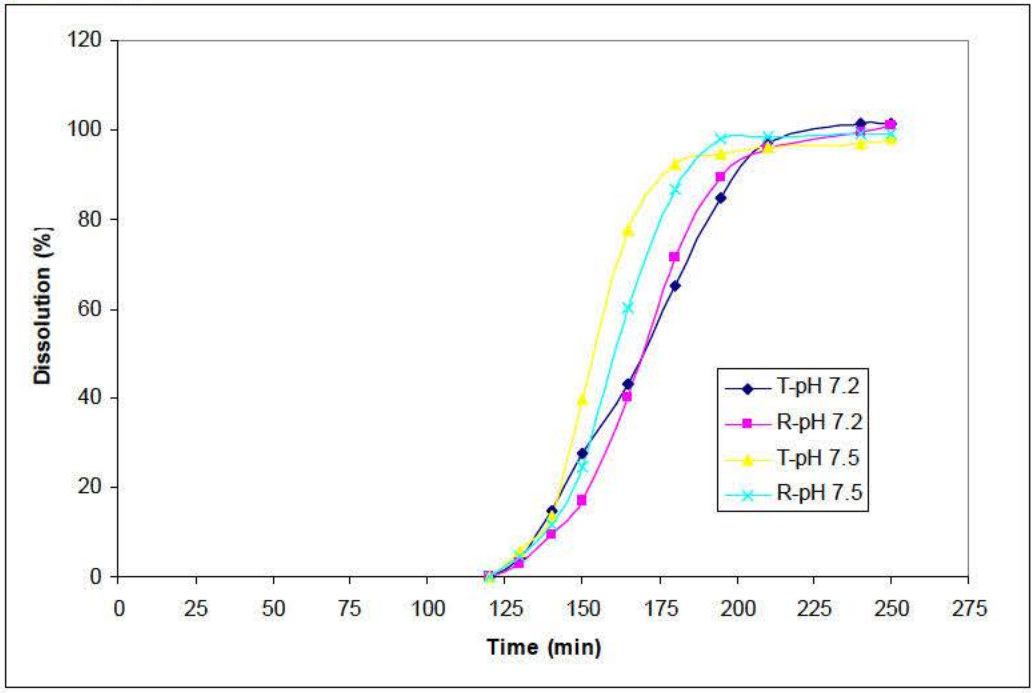
In vitro Quality Control Dissolution Profile:



In vitro BE Studies Profiles:
pH 6.0, 6.5, and 6.8



pH 7.2 and 7.5


120
100
80
60
40
20
0
Dissolution (%)
0
25
50
75
100
125
150
175
200
225
250
275
Time (min)
T-pH 7.2
R-pH 7.2
T-pH 7.5
R-pH 7.5

4.4 Detailed Regulatory History (If Applicable)

None

4.5 Consult Reviews

None

4.6 SAS Output

4.6.1 Fasting Study Codes

```
/*=============================================================================
=====
/ Program   : HVScale3Period.SAS
/ SubMacros :
/ Updated   : 15 Aug 2009
/ Purpose   : To analyze three period reference-scaled bioequivalence
studies.
/
/ Notes     : EXCEL DATA FILE MUST BE OPEN WHEN RUNNING THIS PROGRAM.
/               : OUTPUT FILE (WORD DOCUMENT) CONTAINING SUMMARY TABLES IS
CREATED.
/
/=============================================================================
====
/ PARAMETERS:  THE FOLLOWING COLUMNS SHOULD BE IN THE INPUT DATASET (EXCEL
FILE).
/-------name------- ------------------------description---------------------
----
NAME OF VARIABLE
      SUBJ        SUBJECT NUMBER
      TRT               TREATMENT - CHARACTER (EITHER A OR B) A=TEST; B=REF
      SEQ               SEQUENCE NUMBER - NUMERIC (EITHER 1, 2, OR 3)
      PER               PERIOD NUMBER - NUMERIC (EITHER 1, 2, 3, OR 4)
      AUCT        AREA UNDER CURVE 0-T
      AUCI        AREA UNDER CURVE 0-INF
      CMAX        CMAX
      TMAX        TMAX
      KEL               ELIMINATION RATE CONSTANT
      THALF       HALF LIFE

      sequence 1        T     R     R
      sequence 2        R     T     R
      sequence 3        R     R     T

GROUP EFFECT:
Line 176:  If trt*grp interaction is not significant,
remove TRT*GROUP term from line 176.
```

```
/=============================================================================
====
/ AMENDMENT HISTORY:
/ Init --Date--  ---------------------Description-----------------------
/
/=============================================================================
====*/
options nofmterr nocenter nodate symbolgen mlogic macrogen mprint ps=65
ls=80;

*****STEP 1: ENTER ANDA INFORMATION *****;
%let drug= Mesalamine Delayed Release Tablets USP;
%let anda=203286;
%let studytype=Fasting;

*****STEP 2: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;


***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Documents and Settings\renp\My Documents\203286Mesalamine;

***** STEP 4:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
%let excelfile = &studydir\203286SAS.xls;

***** STEP 5:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING STUDY
DATA *****;
%let sheetname = FasK;

proc import datafile="&excelfile"
            out=base
            dbms=excel replace;
                  sheet="&sheetname";
                  getnames=yes;
                  mixed=yes;
run;



libname studylib "&studydir";

***** STEP 5:  PROVIDE NAMES OF THE VARIABLES TO READ IN FROM EXCEL FILE
*****;
***** PROVIDE STANDARD VARIABLE NAMES FROM THE PARAMETER LIST ABOVE *****;
***** VARIABLE NAMES: SUBJ TRT(A,B) SEQ(1,2) PER(1,2,3) AUCT AUCINF CMAX TMAX
KEL THALF ******;


data base;
  set base;
  /*sequence 1          T     R     R
      sequence 2        R     T     R
      sequence 3        R     R     T
  */
```

```
  IF SEQU="TR1R2" THEN SEQ=1;
  ELSE IF SEQU="R1TR2" THEN SEQ=2;
  ELSE IF SEQU="R1R2T" THEN SEQ=3;


  IF TREAT="T" THEN TRT="A";
  ELSE IF TREAT IN("R1","R2") THEN TRT="B";



run;

proc print data=base;
run;


*************************************************************************
;
          ***** DO NOT CHANGE ANYTHING BELOW THIS LINE *****;
*************************************************************************
;

data pk;
  set base;

  LAUCT=log(auct);
  LAUCINF=log(auci);
  LCMAX=log(cmax);

run;




data pkn;
  set pk;
run;

data full;
  set pkn;

run;

proc sort
  data=pkn;
  by seq subj per;



data test; set pkn; if trt='A'; latt=LAUCT; lait=LAUCINF; lct=LCMAX;
run;

data ref; set pkn; if trt='B';
run;

  /*sequence 1          T     R     R
```

```
      sequence 2        R     T     R
      sequence 3        R     R     T
  */
/*** ORIGINAL DON'S CODE ***
data ref1; set ref; if (seq=1 and per=1) or (seq=2 and per=2) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;
***/
data ref1; set ref; if (seq=1 and per=2) or (seq=2 and per=1) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;

data ref2; set ref; if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and
per=2); lat2r=LAUCT; lai2r=LAUCINF; lc2r=LCMAX;
run;


title "ref1";
proc print data=ref1;
run;

title "ref2";
proc print data=ref2;
run;
title;

data scavbe; merge test ref1 ref2; by seq subj;
ilat=latt-(0.5*(lat1r+lat2r));  *auct;
ilai=lait-(0.5*(lai1r+lai2r));  *auci;
ilc=lct-(0.5*(lc1r+lc2r));      *cmax;

dlat=lat1r-lat2r;  *auct;
dlai=lai1r-lai2r;  *auci;
dlc=lc1r-lc2r;     *cmax;
keep seq subj per trt ilat dlat ilai dlai ilc dlc;
run;

proc print data=scavbe;
title1 'dataset for scaled average BE';
run;

%macro calc(param,no);

      PROC MIXED data=pkn;
      CLASSES GROUP SEQ SUBJ PER TRT;
      MODEL &param = GROUP SEQ GROUP*SEQ PER(GROUP) TRT TRT*GROUP /
DDFM=SATTERTH;
      RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
      REPEATED/GRP=TRT SUB=SUBJ;

      lsmeans trt; /* DEV */
      ods output lsmeans=lsm&param(keep=trt estimate); /* DEV */
      ods output Estimates=unsc&no;
      title1 'unscaled BE 90% CI - guidance version';
      run;

      DATA UPARAM&NO(KEEP=PARAMETER LCI UCI);
```

```
        SET UNSC&NO;

        ESTIMATE = 100 * EXP(ESTIMATE);
        PARAMETER = "&PARAM";
        LCI = 100 * EXP(LOWER);
        UCI = 100 * EXP(UPPER);
      RUN;

   *** for scaled dataset***;
      DATA UNSC&PARAM;
        SET UNSC&NO;
      RUN;

%mend calc;

%calc(LCMAX,1);
%calc(LAUCT,2);


**** ESTIMATES ****;
DATA LSMLAUCT;
  SET LSMLAUCT;
  PARAMETER = "LAUCT";
RUN;

DATA LSMLAUCINF;
  SET LSMLAUCINF;
  PARAMETER = "LAUCI";
RUN;

DATA LSMLCMAX;
  SET LSMLCMAX;
  PARAMETER = "LCMAX";
RUN;

DATA UESTIMATE;
  SET LSMLAUCT LSMLAUCINF LSMLCMAX;
RUN;

DATA UESTIMATE;
  SET UESTIMATE;

  GEOMEAN = EXP(ESTIMATE);
RUN;

PROC SORT
  DATA=UESTIMATE;
  BY PARAMETER;
RUN;

PROC TRANSPOSE
  DATA=UESTIMATE
  OUT=TRANSUEST(DROP=_NAME_);
  VAR GEOMEAN;
  BY PARAMETER;
  ID TRT;
RUN;
```

```
DATA UEST;
  SET TRANSUEST;

  RATIO = ROUND((A/B),.01);
RUN;

DATA UALL;
  SET UPARAM1 UPARAM2 UPARAM3;
RUN;

PROC SORT
  DATA=UALL;
  BY PARAMETER;
RUN;

PROC SORT
  DATA=UEST;
  BY PARAMETER;
RUN;

DATA UPARAMS;
  MERGE UEST
        UALL;
  BY PARAMETER;
RUN;

*** PROPER ORDER AUCT, AUCI, CMAX ***;
DATA UPARAMS;
  SET UPARAMS;

  IF PARAMETER = "LAUCT" THEN ORDER=1;
  ELSE IF PARAMETER = "LAUCI" THEN ORDER=2;
  ELSE IF PARAMETER = "LCMAX" THEN ORDER=3;
RUN;

PROC SORT
  DATA=UPARAMS;
  BY ORDER;
RUN;




proc template;
  define style mystyle1;
  parent = styles.rtf;
    REPLACE fonts /

      'docFont' = ("Arial", 8pt)
     'TitleFont2' = ("Arial",8pt,Bold)
      'TitleFont' = ("Arial",8pt,Bold)
      'StrongFont' = ("Arial",8pt,Bold)
      'EmphasisFont' = ("Arial",8pt)
      'FixedEmphasisFont' = ("Arial",8pt)
      'FixedStrongFont' = ("Arial",8pt,Bold)
      'FixedHeadingFont' = ("Arial",8pt,Bold)
```

```
        'BatchFixedFont' = ("Arial",8pt)
        'FixedFont' = ("Arial",8pt)
        'headingEmphasisFont' = ("Arial",8pt,Bold);

    style SysTitleAndFooterContainer from Container /

      cellpadding = 2
      cellspacing = 2
      borderwidth = 0;

      REPLACE Body from Document /
        bottommargin = 1.0in
        topmargin = 1.0in
        rightmargin = 1in
        leftmargin = 1in;
  END;
run;




/*
data unsc1; set unsc1; unscabe_lower=exp(lower); unscabe_upper=exp(upper);
keep unscabe_lower unscabe_upper; run;
*/


***** SCALED ANALYSIS *****;

%MACRO SCALE(parameter, ipar, dpar);

      proc glm data=scavbe;
      class seq;
      model &ipar =seq/clparm alpha=0.1;
      estimate 'average' intercept 1 seq 0.3333333333 0.3333333333
0.3333333333;
      ods output overallanova=iglm&ipar.1;
      ods output Estimates=iglm&ipar.2;
      ods output NObs=iglm&ipar.3;
      title1 'scaled average BE';
      title2 'intermediate analysis - &ipar glm';
      run;

title "dev iglm&ipar.1";
proc print data=iglm&ipar.1;
run;


      proc glm data=scavbe;
      class seq;
      model &dpar =seq;
      ods output overallanova=dglm&dpar.1;
      ods output NObs=dglm&dpar.3;
      title1 'scaled average BE';
      title2 'intermediate analysis - &dpar  glm';
      run;
```

```
      data unsc&PARAMETER; set unsc&PARAMETER; unscabe_lower=exp(lower);
unscabe_upper=exp(upper);
      keep unscabe_lower unscabe_upper;
      run;


      data iglm&ipar.1; set iglm&ipar.1; if _n_=2; dfi=df; s2i=ms; keep dfi
s2i param;
      param = "&parameter";
    run;

      data iglm&ipar.2; set iglm&ipar.2; pointest=exp(estimate);
x=(estimate**2)-(stderr**2);
      boundx=(max((abs(LowerCL)),(abs(UpperCL))))**2;
      keep pointest x boundx stderr param;
      param = "&parameter";
    run;

      data iglm&ipar.3; set iglm&ipar.3; if _n_ = 2; ni=NobsUsed; keep ni
param;
      param = "&parameter";
   run;

      data dglm&dpar.1; set dglm&dpar.1; if _n_=2; dfd=df; s2wr=ms/2; keep
dfd s2wr param;
      param = "&parameter";
    run;

      data dglm&dpar.3; set dglm&dpar.3; if _n_ = 2; nd=NobsUsed; keep nd
param;
      param = "&parameter";
    run;

      data idallglm&parameter;
        length method_used $15;
      merge unsc&parameter iglm&ipar.1 iglm&ipar.2 iglm&ipar.3 dglm&dpar.1
dglm&dpar.3;

boundy=y*dfd/cinv(0.95,dfd); sWR=sqrt(s2wr);
      critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
      outcome='FAIL';
      if (s2wr < 0.086436) then method_used='Unscaled'; else
method_used='Scaled/PE';
      if ((s2wr < 0.086436) and (unscabe_lower ge 0.8) and (unscabe_upper le
1.25)) then outcome='PASS';
      if ((s2wr ge 0.086436) and (pointest ge 0.8) and (pointest le 1.25) and
(critbound le 0)) then outcome='PASS';
*     else outcome='FAIL';
  run;

      proc print data=idallglm&parameter;
      title1 'output needed for mixed scaled av. BE - using glm';
      run;

      data finalglm; set idallglm&parameter;
      keep param s2wr sWR unscabe_lower unscabe_upper pointest critbound
outcome method_used;
```

```
      run;

      proc print data=finalglm;
      title1 'final output - &parameter - using glm';
      run;

%mend scale;

%scale(LAUCT, ilat, dlat);
%scale(LAUCINF, ilai, dlai);


data all;
  set idallglmLAUCT
      idallglmLAUCINF
        idallglmLCMAX;

       unscabe_lower = round((unscabe_lower*100),.01);
       unscabe_upper = round((unscabe_upper*100),.01);

run;

ods rtf file="&studydir\&ANDA.-ANALYSIS.doc" style=mystyle1 bodytitle;

**** ARITHMETIC MEANS *****;
/*
footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)";
proc report data=pkratio1 nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)";
proc report data=pkratio2 nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
```

```
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)";
proc report data=pkratio3 nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

*/

*** UNSCALED ANALYSIS REPORT *****;
title1 "ANDA: &anda    &drug    STUDY TYPE: &STUDYTYPE";
title2 "SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA";

      proc report
        data=uparams
        headline
        headskip
```

```
        nowd
        split="|" box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

        column parameter ("Geometric Means|" a b) ratio ("90% CI|" lci uci);

        define parameter /display "Parameter" width=20 center;
        define a              /display "Test"       width=15 center
format=8.2;
        define b              /display "Reference" width=15 center
format=8.2;
        define ratio          /display "T/R Ratio" width=15 center
format=8.2;
        define lci            /display "Lower CI" width=20 center format=8.2;
        define uci            /display "Upper CI" width=20 center format=8.2;
      run;


***** SCALED ANALYSIS REPORT *****;
title1 "SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA";

      proc report
        data=all
        headline
        headskip
        nowd
        split='|' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

        column param pointest unscabe_lower unscabe_upper s2wr swr critbound
method_used outcome;


        define param /display "Parameter" width=20 center;
        define pointest   /display "T/R Ratio" width=15 center format=8.2;
        define unscabe_lower /display "Lower|90% CI" width=20 center
format=8.2;
        define unscabe_upper /display "Upper|90% CI" width=20 center
format=8.2;
        define s2wr /display "s2wr" width=15 center;
        define swr /display "sWR" width=15 center;
        define critbound /display "Criteria Bound" width=15 center;
        define method_used /display "Method Used" width=25 center;
        define outcome /display "OUTCOME" width=15 center;

      run;

ods rtf close;
```

4.6.2 Fasting Study Output

Obs	SUBJ	Group	SEQU	PER	TREAT	AUCT	AUCI	Cmax	TMAX	KE	THALF	SEQ	TRT
1	(b)(6) [redacted]	1	R1R2T	1	R1	2815.67	2861.36	614.80	8.00	0.1568	4.42	3	B
2	[redacted]	1	R1R2T	2	R2	967.41	986.30	168.90	11.00	0.0854	8.11	3	B
3	[redacted]	1	R1R2T	3	T	1971.25	1979.92	235.80	7.00	0.1791	3.87	3	A
4	[redacted]	1	TR1R2	1	T	3410.82	3412.28	417.30	24.00	0.6969	0.99	1	A
5	[redacted]	1	TR1R2	2	R1	2380.68	2407.94	209.30	16.00	0.1583	4.38	1	B
6	[redacted]	1	TR1R2	3	R2	4715.11	4779.93	314.70	20.00	0.1420	4.88	1	B
7	[redacted]	1	R1TR2	1	R1	2092.75	2133.80	164.40	14.00	0.0429	16.14	2	B
8	[redacted]	1	R1TR2	2	T	2868.69	2940.27	865.30	7.00	0.0376	18.45	2	A
9	[redacted]	1	R1TR2	3	R2	3168.43	3194.35	480.40	9.00	0.1936	3.58	2	B
10	[redacted]	1	TR1R2	1	T	2960.03	3086.94	261.80	10.00	0.0266	26.02	1	A
11	[redacted]	1	TR1R2	2	R1	2045.07	.	60.40	48.00	.	.	1	B
12	[redacted]	1	TR1R2	3	R2	1678.64	.	120.10	95.00	.	.	1	B
13	[redacted]	1	R1TR2	1	R1	3303.21	.	244.00	32.00	.	.	2	B
14	[redacted]	1	R1TR2	2	T	3005.79	.	139.20	36.00	.	.	2	A
15	[redacted]	1	R1TR2	3	R2	785.37	870.26	88.29	11.00	0.1164	5.96	2	B
16	[redacted]	1	R1R2T	1	R1	510.93	517.33	38.59	28.00	0.3544	1.96	3	B
17	[redacted]	1	R1R2T	2	R2	335.53	.	36.03	28.00	.	.	3	B
18	[redacted]	1	R1R2T	3	T	3723.75	3961.72	288.40	11.00	0.0687	10.09	3	A
19	[redacted]	1	R1R2T	1	R1	1389.28	8575.76	67.93	17.00	0.0050	137.99	3	B
20	[redacted]	1	R1R2T	2	R2	2220.44	.	97.94	36.00	.	.	3	B
21	[redacted]	1	R1R2T	3	T	2035.23	2111.07	150.20	11.00	0.1194	5.80	3	A
22	[redacted]	1	R1TR2	1	R1	5412.22	5489.36	433.30	14.00	0.0698	9.93	2	B
23	[redacted]	1	R1TR2	2	T	6548.05	6565.13	292.70	16.00	0.1108	6.26	2	A
24	[redacted]	1	R1TR2	3	R2	3517.84	3589.57	160.80	13.00	0.0601	11.54	2	B
25	[redacted]	1	TR1R2	1	T	1666.63	1699.00	75.81	28.00	0.0556	12.47	1	A
26	[redacted]	1	TR1R2	2	R1	1089.72	1265.63	56.84	15.00	0.0345	20.11	1	B
27	[redacted]	1	TR1R2	3	R2	1499.22	1549.37	76.84	15.00	0.0283	24.50	1	B
28	[redacted]	1	R1R2T	1	R1	1871.41	1893.12	83.77	28.00	0.0619	11.19	3	B
29	[redacted]	1	R1R2T	2	R2	1627.93	1677.32	141.50	10.00	0.1174	5.91	3	B
30	[redacted]	1	R1R2T	3	T	1297.10	1304.40	221.30	24.00	0.2075	3.34	3	A
31	[redacted]	1	TR1R2	1	T	1572.23	1634.53	53.60	16.00	0.0310	22.35	1	A
32	[redacted]	1	TR1R2	2	R1	1935.83	1950.47	185.70	36.00	0.1203	5.76	1	B
33	[redacted]	1	TR1R2	3	R2	1123.15	1671.63	30.28	34.10	0.0120	57.99	1	B
34	[redacted]	1	R1R2T	1	R1	2229.07	2252.66	95.42	20.00	0.0841	8.25	3	B
35	[redacted]	1	R1R2T	2	R2	3012.29	3543.32	165.90	15.00	0.0652	10.63	3	B
36	[redacted]	1	R1R2T	3	T	2652.43	2661.28	242.30	14.00	0.1494	4.64	3	A
37	[redacted]	1	R1TR2	1	R1	1455.66	1491.35	317.00	13.00	0.0805	8.61	2	B
38	[redacted]	1	R1TR2	2	T	2281.52	2398.22	304.50	13.00	0.1368	5.07	2	A
39	[redacted]	1	R1TR2	3	R2	92.94	.	18.23	28.00	.	.	2	B
40	[redacted]	1	TR1R2	1	T	2095.32	3271.61	131.40	28.00	0.0425	16.31	1	A
41	[redacted]	1	TR1R2	2	R1	1631.86	1671.37	74.86	36.00	0.0861	8.05	1	B
42	[redacted]	1	TR1R2	3	R2	3304.26	3322.99	119.90	47.00	0.0891	7.78	1	B
43	[redacted]	1	R1TR2	1	R1	1876.01	.	62.92	48.00	.	.	2	B
44	[redacted]	1	R1TR2	2	T	1386.19	1939.76	55.07	8.00	0.0418	16.57	2	A
45	[redacted]	1	R1TR2	3	R2	2225.56	.	134.60	47.00	.	.	2	B
46	[redacted]	1	TR1R2	1	T	4086.43	4162.14	591.90	16.00	0.0621	11.16	1	A
47	[redacted]	1	TR1R2	2	R1	5377.23	6006.25	1790.00	9.05	0.0309	22.46	1	B

48	(b) (6)	1	TR1R2	3	R2	4683.08	4789.66	695.10	15.00	0.0509	13.61	1	B
49		1	R1R2T	1	R1	2181.31	2209.60	213.60	14.00	0.3127	2.22	3	B
50		1	R1R2T	2	R2	1045.77	1049.38	92.16	24.00	0.4654	1.49	3	B
51		1	R1R2T	3	T	954.68	970.82	93.07	24.00	0.3502	1.98	3	A
52		1	TR1R2	1	T	7644.54	8166.14	741.60	11.00	0.0449	15.44	1	A
53		1	TR1R2	2	R1	6289.06	6452.15	281.40	6.00	0.0393	17.64	1	B
54		1	TR1R2	3	R2	9774.04	10035.90	3168.00	6.00	0.0398	17.42	1	B
55		1	R1R2T	1	R1	1801.92	1811.72	57.18	11.00	0.1075	6.45	3	B
56		1	R1R2T	2	R2	3196.58	.	190.20	36.00	.	.	3	B
57		1	R1R2T	3	T	1780.94	1800.69	395.60	7.00	0.0718	9.65	3	A

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 10

Obs	SUBJ	Group	SEQU	PER	TREAT	AUC	AUC	Cmax	TMAX	KE	THALF	SEQ	TRT
58	(b) (6)	1	R1TR2	1	R1	4229.94	4528.39	197.200	22.00	0.0879	7.88	2	B
59		1	R1TR2	2	T	3029.99	3122.49	288.900	10.00	0.0999	6.94	2	A
60		1	R1TR2	3	R2	2695.02	2745.60	195.100	11.00	0.0352	19.66	2	B
61		1	R1R2T	1	R1	2940.03	2962.21	297.900	10.00	0.0500	13.85	3	B
62		1	R1R2T	2	R2	1864.63	1932.95	93.780	14.00	0.0361	19.20	3	B
63		1	R1R2T	3	T	5300.30	5323.54	148.100	20.00	0.0512	13.53	3	A
64		1	TR1R2	1	T	2815.59	2853.96	299.400	11.00	0.1015	6.83	1	A
65		1	TR1R2	2	R1	5632.49	5681.43	447.500	20.00	0.1458	4.75	1	B
66		1	TR1R2	3	R2	5197.32	5252.26	468.100	16.00	0.1430	4.85	1	B
67		1	R1TR2	1	R1	3027.03	3037.92	113.200	28.00	0.1017	6.81	2	B
68		1	R1TR2	2	T	3125.27	.	155.900	28.03	.	.	2	A
69		1	R1TR2	3	R2	1756.51	4812.39	143.800	28.00	0.0354	19.56	2	B
70		1	TR1R2	1	T	2603.65	2733.29	170.000	13.00	0.0476	14.55	1	A
71		1	TR1R2	2	R1	1667.07	1682.43	52.850	48.00	0.0787	8.81	1	B
72		1	TR1R2	3	R2	1917.66	2462.76	80.840	8.00	0.0242	28.60	1	B
73		1	R1R2T	1	R1	1408.15	1427.59	256.800	28.00	0.4285	1.62	3	B
74		1	R1R2T	2	R2	663.67	874.12	64.950	11.00	0.0441	15.71	3	B
75		1	R1R2T	3	T	475.84	.	80.700	28.00	.	.	3	A
76		1	R1R2T	1	R1	13.28	.	2.299	20.00	.	.	3	B
77		1	R1R2T	2	R2	279.45	.	45.770	32.00	.	.	3	B
78		1	R1R2T	3	T	54.04	.	9.753	22.00	.	.	3	A
79		1	TR1R2	1	T	6419.48	6421.39	532.500	12.00	0.6519	1.06	1	A
80		1	TR1R2	2	R1	1462.59	1490.52	310.400	6.00	0.2561	2.71	1	B
81		1	TR1R2	3	R2	6151.55	6750.33	725.400	6.00	0.1010	6.86	1	B
82		1	R1TR2	1	R1	786.19	1014.76	19.860	24.00	0.0155	44.68	2	B
83		1	R1TR2	2	T	6214.11	7170.88	121.500	48.00	0.0297	23.35	2	A
84		1	R1TR2	3	R2	1920.96	1943.73	36.610	71.00	0.0664	10.44	2	B
85		1	R1TR2	1	R1	4191.43	4248.62	105.500	28.00	0.0457	15.18	2	B
86		1	R1TR2	2	T	3935.20	4022.54	112.200	32.00	0.0695	9.98	2	A
87		1	R1TR2	3	R2	1928.83	2209.98	184.800	14.00	0.0698	9.93	2	B
88		1	TR1R2	1	T	1096.39	.	77.690	48.00	.	.	1	A
89		1	TR1R2	2	R1	3165.66	3179.06	171.200	24.00	0.1059	6.54	1	B
90		1	TR1R2	3	R2	2573.61	2640.01	177.900	17.00	0.0320	21.64	1	B
91		1	R1R2T	1	R1	2387.58	2455.95	431.000	11.00	0.0524	13.22	3	B
92		1	R1R2T	2	R2	897.49	923.40	105.000	12.00	0.0763	9.09	3	B
93		1	R1R2T	3	T	1775.48	1794.71	216.800	7.00	0.1103	6.28	3	A
94		1	R1R2T	1	R1	2212.96	2220.91	154.200	12.00	0.1282	5.40	3	B
95		1	R1R2T	2	R2	1427.53	1439.31	117.400	18.00	0.1516	4.57	3	B

96	(b) (6)	1	R1R2T	3	T	2306.49	2346.94	261.500	28.00	0.3608	1.92	3	A
97		1	R1TR2	1	R1	1960.24	2055.62	80.580	17.00	0.0303	22.85	2	B
98		1	R1TR2	2	T	4478.87	4650.21	122.200	15.00	0.0638	10.86	2	A
99		1	R1TR2	3	R2	4334.44	4717.32	94.820	47.00	0.0387	17.92	2	B
100		1	TR1R2	1	T	242.61	259.30	27.470	18.03	0.1533	4.52	1	A
101		1	TR1R2	2	R1	2517.01	2672.83	282.700	13.00	0.1065	6.51	1	B
102		1	TR1R2	3	R2	2628.00	2878.92	236.000	22.00	0.1528	4.54	1	B
103		1	R1R2T	1	R1	310.29	.	49.350	28.00	.	.	3	B
104		1	R1R2T	2	R2	1301.61	1322.13	107.100	12.05	0.1309	5.30	3	B
105		1	R1R2T	3	T	2083.67	2121.61	433.500	6.00	0.0282	24.58	3	A
106		1	R1TR2	1	R1	2275.21	2281.92	146.000	18.00	0.2215	3.13	2	B
107		1	R1TR2	2	T	2071.14	3160.82	239.200	24.00	0.0847	8.18	2	A
108		1	R1TR2	3	R2	3138.48	3146.33	456.500	8.00	0.1916	3.62	2	B
109		1	TR1R2	1	T	1669.45	1785.54	65.680	17.00	0.0216	32.10	1	A
110		1	TR1R2	2	R1	3827.58	3966.16	635.000	6.00	0.0205	33.83	1	B
111		1	TR1R2	3	R2	1353.96	1506.02	124.300	24.00	0.0394	17.61	1	B
112		1	TR1R2	1	T	6048.84	6266.22	452.000	13.00	0.0315	21.99	1	A
113		1	TR1R2	2	R1	5466.07	5475.45	422.400	24.10	0.2370	2.93	1	B
114		1	TR1R2	3	R2	4901.88	4967.56	248.200	32.00	0.2063	3.36	1	B

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 11

Obs	SUBJ	GROUP	SEQ	PERIOD	TREAT	AUC	AUCI	Cmax	TMAX	KE	THALF	SEQT
115	(b) (6)	1	R1TR2	1	R1	2274.72	2276.75	241.60	22.00	0.5250	1.32	2 B
116		1	R1TR2	2	T	4121.76	4253.94	290.70	11.00	0.1121	6.18	2 A
117		1	R1TR2	3	R2	3152.28	4999.50	277.90	11.00	0.0475	14.59	2 B
118		1	R1R2T	1	R1	4270.66	4279.98	225.10	16.00	0.1822	3.80	3 B
119		1	R1R2T	2	R2	2418.26	2479.70	150.40	13.00	0.0264	26.26	3 B
120		1	R1R2T	3	T	2007.02	2052.92	100.40	18.00	0.0585	11.84	3 A
121		1	TR1R2	1	T	2510.31	2572.98	71.75	18.00	0.0472	14.70	1 A
122		1	TR1R2	2	R1	4055.61	4085.54	192.10	28.00	0.0915	7.58	1 B
123		1	TR1R2	3	R2	4214.56	4228.34	278.50	14.00	0.0743	9.33	1 B
124		2	R1TR2	1	R1	6395.73	6504.98	1914.00	6.00	0.0458	15.14	2 B
125		2	R1TR2	2	T	2747.12	2813.86	348.90	15.00	0.0748	9.27	2 A
126		2	R1TR2	3	R2	747.52	.	59.88	48.00	.	.	2 B
127		2	R1R2T	1	R1	818.81	1077.28	98.49	6.00	0.0737	9.41	3 B
128		2	R1R2T	2	R2	498.41	.	31.15	32.00	.	.	3 B
129		2	R1R2T	3	T	515.92	.	55.50	28.05	.	.	3 A
130		2	TR1R2	1	T	4008.77	4247.92	300.20	15.00	0.0718	9.65	1 A
131		2	TR1R2	2	R1	1340.57	1344.11	157.40	24.00	0.5491	1.26	1 B
132		2	TR1R2	3	R2	2314.30	2460.88	177.80	28.00	0.0974	7.11	1 B
133		2	R1R2T	1	R1	3987.42	4003.17	220.20	11.00	0.0983	7.05	3 B
134		2	R1R2T	2	R2	4462.43	4922.46	1151.00	4.00	0.0249	27.80	3 B
135		2	R1R2T	3	T	3568.69	3798.06	293.10	24.00	0.0710	9.77	3 A
136		2	R1TR2	1	R1	1239.50	1314.73	137.60	28.00	0.2482	2.79	2 B
137		2	R1TR2	2	T	2561.25	2626.51	168.10	28.00	0.1151	6.02	2 A
138		2	R1TR2	3	R2	1350.40	1361.56	110.40	24.07	0.1622	4.27	2 B
139		2	TR1R2	1	T	1519.98	1685.44	109.60	16.00	0.1272	5.45	1 A
140		2	TR1R2	2	R1	3347.00	3355.84	260.70	22.00	0.4067	1.70	1 B
141		2	TR1R2	3	R2	1563.92	1574.35	280.40	11.00	0.2197	3.16	1 B
142		2	TR1R2	1	T	4660.13	4970.93	403.00	4.00	0.0217	31.92	1 A
143		2	TR1R2	2	R1	2369.94	2381.78	103.20	24.00	0.2251	3.08	1 B

144	(b) (6)	2	TR1R2	3	R2	1304.85	1323.89	86.66	20.00	0.1552	4.47	1	B
145		2	R1R2T	1	R1	1437.59	1512.59	155.90	24.00	0.0943	7.35	3	B
146		2	R1R2T	2	R2	1234.76	1250.80	74.45	10.00	0.1495	4.64	3	B
147		2	R1R2T	3	T	1260.73	1290.16	86.56	15.00	0.1389	4.99	3	A
148		2	R1TR2	1	R1	3017.37	3074.87	147.40	24.00	0.0463	14.98	2	B
149		2	R1TR2	2	T	2885.07	2913.79	157.20	28.00	0.0996	6.96	2	A
150		2	R1TR2	3	R2	4749.15	4783.85	221.70	36.00	0.1162	5.96	2	B
151		2	R1TR2	1	R1	1697.94	2673.34	153.40	12.00	0.0451	15.36	2	B
152		2	R1TR2	2	T	2096.69	2135.98	146.70	15.00	0.2470	2.81	2	A
153		2	R1TR2	3	R2	2475.29	2815.48	127.50	13.00	0.1288	5.38	2	B
154		2	TR1R2	1	T	5393.53	12150.50	340.70	28.00	0.0134	51.65	1	A
155		2	TR1R2	2	R1	1582.05	2854.62	85.57	17.00	0.0262	26.50	1	B
156		2	TR1R2	3	R2	5042.66	9891.59	281.30	11.00	0.0158	43.92	1	B
157		2	R1R2T	1	R1	3277.56	3302.01	261.90	12.00	0.1546	4.48	3	B
158		2	R1R2T	2	R2	806.22	825.06	143.20	22.00	0.2441	2.84	3	B
159		2	R1R2T	3	T	4336.14	4370.71	614.20	24.00	0.1538	4.51	3	A
160		2	R1R2T	1	R1	2638.51	5890.60	284.00	12.00	0.0067	103.93	3	B
161		2	R1R2T	2	R2	2062.17	2073.01	115.70	22.00	0.1956	3.54	3	B
162		2	R1R2T	3	T	827.73	.	73.54	24.00	.	.	3	A
163		2	R1TR2	1	R1	8666.61	8693.32	2459.00	6.00	0.0888	7.81	2	B
164		2	R1TR2	2	T	3948.03	3963.90	301.90	11.00	0.1689	4.10	2	A
165		2	R1TR2	3	R2	4681.43	4694.62	598.20	11.00	0.1805	3.84	2	B
166		2	TR1R2	1	T	2005.15	2039.96	62.36	32.00	0.0377	18.38	1	A
167		2	TR1R2	2	R1	2701.58	2758.29	136.40	14.00	0.0635	10.91	1	B
168		2	TR1R2	3	R2	2310.62	2350.66	101.70	6.00	0.0567	12.23	1	B
169		2	R1R2T	1	R1	1283.27	1376.16	123.10	14.00	0.0228	30.46	3	B
170		2	R1R2T	2	R2	3304.76	3337.52	155.70	20.00	0.1913	3.62	3	B
171		2	R1R2T	3	T	1906.07	2195.65	76.04	24.00	0.0408	16.98	3	A

Obs	SUBJ	Group	SEQU	PER	TREAT	AUC	AUCI	Cmax	TMAX	KE	THALF	SEQ	TRT
172	(b) (6)	2	R1TR2	1	R1	2663.22	.	204.90	48.00	.	.	2	B
173		2	R1TR2	2	T	5941.49	10649.00	300.70	24.00	0.0309	22.43	2	A
174		2	R1TR2	3	R2	6406.82	6431.64	180.10	22.00	0.1152	6.01	2	B
175		2	R1R2T	1	R1	2901.91	3255.25	212.50	13.00	0.0680	10.19	3	B
176		2	R1R2T	2	R2	3564.68	3635.11	217.40	28.00	0.1486	4.66	3	B
177		2	R1R2T	3	T	3057.92	3660.02	197.00	28.00	0.0689	10.06	3	A
178		2	TR1R2	1	T	347.60	397.37	44.82	28.00	0.0756	9.17	1	A
179		2	TR1R2	2	R1	2774.05	2781.49	180.00	16.00	0.3298	2.10	1	B
180		2	TR1R2	3	R2	548.24	.	97.67	28.00	.	.	1	B
181		2	R1TR2	1	R1	2403.99	2408.77	347.20	20.00	0.2197	3.16	2	B
182		2	R1TR2	2	T	3939.21	3947.62	426.30	24.00	0.5625	1.23	2	A
183		2	R1TR2	3	R2	695.39	3718.25	64.43	17.00	0.0160	43.40	2	B
184		2	R1R2T	1	R1	910.10	.	160.30	28.00	.	.	3	B
185		2	R1R2T	2	R2	980.45	995.08	88.71	14.00	0.1431	4.84	3	B
186		2	R1R2T	3	T	1285.98	1631.22	140.70	13.00	0.0689	10.06	3	A
187		2	TR1R2	1	T	4050.04	14503.90	243.60	28.00	0.0138	50.25	1	A
188		2	TR1R2	2	R1	1817.45	1823.34	152.10	28.00	0.2305	3.01	1	B
189		2	TR1R2	3	R2	3222.73	3853.42	177.00	28.00	0.0687	10.09	1	B
190		2	R1TR2	1	R1	1984.03	1996.95	112.10	20.00	0.0932	7.43	2	B
191		2	R1TR2	2	T	169.35	.	27.95	32.00	.	.	2	A

	(b) (6)												
192		2	R1TR2	3	R2	1057.95	1065.32	73.16	28.00	0.1949	3.56	2	B
193		2	R1R2T	1	R1	1866.30	3366.85	56.69	16.03	0.0130	53.48	3	B
194		2	R1R2T	2	R2	1802.09	1823.66	59.29	36.00	0.0684	10.13	3	B
195		2	R1R2T	3	T	1862.32	2618.37	44.39	36.00	0.0176	39.37	3	A
196		2	TR1R2	1	T	1227.69	1275.35	69.76	20.00	0.0520	13.34	1	A
197		2	TR1R2	2	R1	895.10	1181.60	61.68	15.00	0.0361	19.21	1	B
198		2	TR1R2	3	R2	1059.11	.	80.38	36.00	.	.	1	B
199		2	R1TR2	1	R1	154.24	207.03	7.81	36.00	0.0260	26.65	2	B
200		2	R1TR2	2	T	1372.40	1374.03	205.40	24.00	0.6569	1.06	2	A
201		2	R1TR2	3	R2	1894.66	1899.92	150.30	15.00	0.3470	2.00	2	B
202		2	R1TR2	1	R1	314.52	324.20	76.45	11.00	0.1751	3.96	2	B
203		2	R1TR2	2	T	1132.28	1135.15	204.00	18.00	1.0093	0.69	2	A
204		2	R1TR2	3	R2	10.51	.	1.59	28.00	.	.	2	B
205		2	R1R2T	1	R1	1247.66	1327.66	229.40	6.00	0.1126	6.16	3	B
206		2	R1R2T	2	R2	6596.70	6636.48	3183.00	6.00	0.0619	11.20	3	B
207		2	R1R2T	3	T	1346.46	1349.58	191.90	7.00	0.3274	2.12	3	A
208		2	TR1R2	1	T	1497.79	1550.32	51.06	6.00	0.0521	13.29	1	A
209		2	TR1R2	2	R1	2162.48	4595.36	135.60	32.00	0.0312	22.23	1	B
210		2	TR1R2	3	R2	1336.31	2009.04	92.91	17.00	0.0401	17.26	1	B
211		2	R1R2T	1	R1	4006.31	4015.52	167.40	28.00	0.1360	5.10	3	B
212		2	R1R2T	2	R2	2885.88	2915.76	153.80	28.00	0.1926	3.60	3	B
213		2	R1R2T	3	T	5668.30	5701.12	460.30	15.00	0.1534	4.52	3	A
214		2	TR1R2	1	T	2402.59	2449.80	253.20	14.00	0.0223	31.11	1	A
215		2	TR1R2	2	R1	2845.04	3570.51	166.00	11.05	0.0148	46.91	1	B
216		2	TR1R2	3	R2	2175.18	2328.41	282.20	11.00	0.0108	64.33	1	B
217		2	R1TR2	1	R1	809.11	814.73	67.13	28.00	0.2336	2.97	2	B
218		2	R1TR2	2	T	1449.12	1457.69	103.20	11.00	0.1323	5.24	2	A
219		2	R1TR2	3	R2	978.96	1268.10	57.01	17.03	0.0897	7.72	2	B
220		2	R1TR2	1	R1	4428.01	4451.41	329.90	6.00	0.0610	11.35	2	B
221		2	R1TR2	2	T	6296.12	6406.75	2374.00	6.00	0.0340	20.41	2	A
222		2	R1TR2	3	R2	5075.59	5899.77	346.50	2.00	0.0634	10.93	2	B
223		2	TR1R2	1	T	2567.99	2853.91	439.90	8.00	0.0649	10.68	1	A
224		2	TR1R2	2	R1	1751.26	1820.46	172.00	13.00	0.0910	7.61	1	B
225		2	TR1R2	3	R2	1287.36	1468.26	108.50	16.00	0.0496	13.97	1	B
226		2	R1R2T	1	R1	3105.81	3128.62	286.10	14.05	0.0626	11.07	3	B
227		2	R1R2T	2	R2	4739.94	4752.99	229.20	12.00	0.0772	8.98	3	B
228		2	R1R2T	3	T	3062.59	3121.43	232.20	14.05	0.0659	10.51	3	A

		G			T						T		
	S	r	S		R	A	A	C	T		H		
O	U	o	E	P	E	U	U	m	M		A	S	T
b	B	u	Q	E	A	C	C	a	A	K	L	E	R
s	J	p	U	R	T	T	I	x	X	E	F	Q	T
229		(b) (6) 2	TR1R2	1	T	2424.63	2756.77	153.40	15.00	0.0149	46.56	1	A
230		2	TR1R2	2	R1	2603.56	2702.97	101.50	14.00	0.0329	21.06	1	B
231		2	TR1R2	3	R2	2067.68	2478.57	111.40	16.00	0.0181	38.21	1	B
232		2	R1TR2	1	R1	2121.21	2350.93	192.00	20.00	0.0653	10.62	2	B
233		2	R1TR2	2	T	5859.94	6629.37	473.60	24.00	0.0840	8.25	2	A
234		2	R1TR2	3	R2	1798.41	2029.79	173.10	15.00	0.0415	16.69	2	B
235		2	R1TR2	1	R1	1178.06	1333.30	204.30	8.00	0.0202	34.27	2	B
236		2	R1TR2	2	T	2598.10	2675.89	1047.00	7.00	0.0639	10.85	2	A
237		2	R1TR2	3	R2	998.44	1022.96	85.89	11.05	0.0906	7.65	2	B
238		2	TR1R2	1	T	255.13	263.71	40.99	22.00	0.3984	1.74	1	A
239		2	TR1R2	2	R1	1316.74	1400.10	279.10	24.00	0.3011	2.30	1	B

240	(b) (6)	2	TR1R2	3	R2	2873.18	2880.44	207.40	16.00	0.2068	3.35	1 B
241		2	R1R2T	1	R1	6723.98	7841.87	1169.00	8.00	0.0563	12.31	3 B
242		2	R1R2T	2	R2	17015.10	17033.30	3959.00	4.00	0.0665	10.43	3 B
243		2	R1R2T	3	T	7420.71	8826.22	1954.00	8.00	0.0356	19.47	3 A
244		2	R1TR2	1	R1	1648.38	1922.66	202.50	24.00	0.0598	11.60	2 B
245		2	R1TR2	2	T	2902.94	2921.99	167.90	24.00	0.2294	3.02	2 A
246		2	R1TR2	3	R2	2656.81	2669.05	236.80	7.00	0.1945	3.56	2 B
247		2	TR1R2	1	T	4595.59	4748.11	518.00	16.00	0.1143	6.06	1 A
248		2	TR1R2	2	R1	2298.21	2314.29	136.60	24.00	0.2610	2.66	1 B
249		2	TR1R2	3	R2	6.27	14.00	1.90	13.00	0.1739	3.99	1 B

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Obs	SUBJ	Group	SEQU	PER	TREAT	AUCT	AUCI	Cmax	TMAX	KE
1	(b) (6)	1	TR1R2	2	R1	2380.68	2407.94	209.30	16.00	0.1583
2		1	TR1R2	2	R1	2045.07	.	60.40	48.00	.
3		1	TR1R2	2	R1	1089.72	1265.63	56.84	15.00	0.0345
4		1	TR1R2	2	R1	1935.83	1950.47	185.70	36.00	0.1203
5		1	TR1R2	2	R1	1631.86	1671.37	74.86	36.00	0.0861
6		1	TR1R2	2	R1	5377.23	6006.25	1790.00	9.05	0.0309
7		1	TR1R2	2	R1	6289.06	6452.15	281.40	6.00	0.0393
8		1	TR1R2	2	R1	5632.49	5681.43	447.50	20.00	0.1458
9		1	TR1R2	2	R1	1667.07	1682.43	52.85	48.00	0.0787
10		1	TR1R2	2	R1	1462.59	1490.52	310.40	6.00	0.2561
11		1	TR1R2	2	R1	3165.66	3179.06	171.20	24.00	0.1059
12		1	TR1R2	2	R1	2517.01	2672.83	282.70	13.00	0.1065
13		1	TR1R2	2	R1	3827.58	3966.16	635.00	6.00	0.0205
14		1	TR1R2	2	R1	5466.07	5475.45	422.40	24.10	0.2370
15		1	TR1R2	2	R1	4055.61	4085.54	192.10	28.00	0.0915
16		2	TR1R2	2	R1	1340.57	1344.11	157.40	24.00	0.5491
17		2	TR1R2	2	R1	3347.00	3355.84	260.70	22.00	0.4067
18		2	TR1R2	2	R1	2369.94	2381.78	103.20	24.00	0.2251
19		2	TR1R2	2	R1	1582.05	2854.62	85.57	17.00	0.0262
20		2	TR1R2	2	R1	2701.58	2758.29	136.40	14.00	0.0635
21		2	TR1R2	2	R1	2774.05	2781.49	180.00	16.00	0.3298
22		2	TR1R2	2	R1	1817.45	1823.34	152.10	28.00	0.2305
23		2	TR1R2	2	R1	895.10	1181.60	61.68	15.00	0.0361
24		2	TR1R2	2	R1	2162.48	4595.36	135.60	32.00	0.0312
25		2	TR1R2	2	R1	2845.04	3570.51	166.00	11.05	0.0148
26		2	TR1R2	2	R1	1751.26	1820.46	172.00	13.00	0.0910
27		2	TR1R2	2	R1	2603.56	2702.97	101.50	14.00	0.0329
28		2	TR1R2	2	R1	1316.74	1400.10	279.10	24.00	0.3011
29		2	TR1R2	2	R1	2298.21	2314.29	136.60	24.00	0.2610

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
1	4.38	1	B	7.77514	7.78653	5.34377	7.77514	7.78653	5.34377
2	.	1	B	7.62319	.	4.10099	7.62319	.	4.10099
3	20.11	1	B	6.99368	7.14333	4.04024	6.99368	7.14333	4.04024
4	5.76	1	B	7.56829	7.57583	5.22413	7.56829	7.57583	5.22413
5	8.05	1	B	7.39748	7.42140	4.31562	7.39748	7.42140	4.31562
6	22.46	1	B	8.58993	8.70056	7.48997	8.58993	8.70056	7.48997
7	17.64	1	B	8.74657	8.77217	5.63978	8.74657	8.77217	5.63978
8	4.75	1	B	8.63631	8.64496	6.10368	8.63631	8.64496	6.10368
9	8.81	1	B	7.41882	7.42799	3.96746	7.41882	7.42799	3.96746
10	2.71	1	B	7.28796	7.30688	5.73786	7.28796	7.30688	5.73786

11	6.54	1	B	8.06012	8.06434	5.14283	8.06012	8.06434	5.14283
12	6.51	1	B	7.83083	7.89089	5.64439	7.83083	7.89089	5.64439
13	33.83	1	B	8.24999	8.28555	6.45362	8.24999	8.28555	6.45362
14	2.93	1	B	8.60632	8.60803	6.04595	8.60632	8.60803	6.04595
15	7.58	1	B	8.30786	8.31521	5.25802	8.30786	8.31521	5.25802
16	1.26	1	B	7.20085	7.20349	5.05879	7.20085	7.20349	5.05879
17	1.70	1	B	8.11582	8.11846	5.56337	8.11582	8.11846	5.56337
18	3.08	1	B	7.77062	7.77560	4.63667	7.77062	7.77560	4.63667
19	26.50	1	B	7.36648	7.95669	4.44933	7.36648	7.95669	4.44933
20	10.91	1	B	7.90159	7.92237	4.91559	7.90159	7.92237	4.91559
21	2.10	1	B	7.92806	7.93074	5.19296	7.92806	7.93074	5.19296
22	3.01	1	B	7.50519	7.50843	5.02454	7.50519	7.50843	5.02454
23	19.21	1	B	6.79693	7.07462	4.12196	6.79693	7.07462	4.12196
24	22.23	1	B	7.67901	8.43280	4.90971	7.67901	8.43280	4.90971
25	46.91	1	B	7.95333	8.18046	5.11199	7.95333	8.18046	5.11199
26	7.61	1	B	7.46809	7.50684	5.14749	7.46809	7.50684	5.14749
27	21.06	1	B	7.86464	7.90211	4.62006	7.86464	7.90211	4.62006
28	2.30	1	B	7.18291	7.24430	5.63157	7.18291	7.24430	5.63157
29	2.66	1	B	7.73989	7.74686	4.91706	7.73989	7.74686	4.91706

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Obs	SUBJ	Group	SEQU	PER	TREAT	AUCT	AUCI	Cmax	TMAX	KE
30	(b) (6)	1	R1TR2	1	R1	2092.75	2133.80	164.40	14.00	0.0429
31		1	R1TR2	1	R1	3303.21	.	244.00	32.00	.
32		1	R1TR2	1	R1	5412.22	5489.36	433.30	14.00	0.0698
33		1	R1TR2	1	R1	1455.66	1491.35	317.00	13.00	0.0805
34		1	R1TR2	1	R1	1876.01	.	62.92	48.00	.
35		1	R1TR2	1	R1	4229.94	4528.39	197.20	22.00	0.0879
36		1	R1TR2	1	R1	3027.03	3037.92	113.20	28.00	0.1017
37		1	R1TR2	1	R1	786.19	1014.76	19.86	24.00	0.0155
38		1	R1TR2	1	R1	4191.43	4248.62	105.50	28.00	0.0457
39		1	R1TR2	1	R1	1960.24	2055.62	80.58	17.00	0.0303
40		1	R1TR2	1	R1	2275.21	2281.92	146.00	18.00	0.2215
41		1	R1TR2	1	R1	2274.72	2276.75	241.60	22.00	0.5250
42		2	R1TR2	1	R1	6395.73	6504.98	1914.00	6.00	0.0458
43		2	R1TR2	1	R1	1239.50	1314.73	137.60	28.00	0.2482
44		2	R1TR2	1	R1	3017.37	3074.87	147.40	24.00	0.0463
45		2	R1TR2	1	R1	1697.94	2673.34	153.40	12.00	0.0451
46		2	R1TR2	1	R1	8666.61	8693.32	2459.00	6.00	0.0888
47		2	R1TR2	1	R1	2663.22	.	204.90	48.00	.
48		2	R1TR2	1	R1	2403.99	2408.77	347.20	20.00	0.2197
49		2	R1TR2	1	R1	1984.03	1996.95	112.10	20.00	0.0932
50		2	R1TR2	1	R1	154.24	207.03	7.81	36.00	0.0260
51		2	R1TR2	1	R1	314.52	324.20	76.45	11.00	0.1751
52		2	R1TR2	1	R1	809.11	814.73	67.13	28.00	0.2336
53		2	R1TR2	1	R1	4428.01	4451.41	329.90	6.00	0.0610
54		2	R1TR2	1	R1	2121.21	2350.93	192.00	20.00	0.0653
55		2	R1TR2	1	R1	1178.06	1333.30	204.30	8.00	0.0202
56		2	R1TR2	1	R1	1648.38	1922.66	202.50	24.00	0.0598
57		1	R1R2T	1	R1	2815.67	2861.36	614.80	8.00	0.1568
58		1	R1R2T	1	R1	510.93	517.33	38.59	28.00	0.3544

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
30	16.14	2	B	7.64623	7.66566	5.10230	7.64623	7.66566	5.10230

31	.	2	B	8.10265	.	5.49717	8.10265	.	5.49717
32	9.93	2	B	8.59641	8.61057	6.07143	8.59641	8.61057	6.07143
33	8.61	2	B	7.28321	7.30744	5.75890	7.28321	7.30744	5.75890
34	.	2	B	7.53690	.	4.14186	7.53690	.	4.14186
35	7.88	2	B	8.34994	8.41812	5.28422	8.34994	8.41812	5.28422
36	6.81	2	B	8.01534	8.01893	4.72916	8.01534	8.01893	4.72916
37	44.68	2	B	6.66719	6.92241	2.98871	6.66719	6.92241	2.98871
38	15.18	2	B	8.34080	8.35435	4.65871	8.34080	8.35435	4.65871
39	22.85	2	B	7.58082	7.62833	4.38925	7.58082	7.62833	4.38925
40	3.13	2	B	7.72983	7.73277	4.98361	7.72983	7.73277	4.98361
41	1.32	2	B	7.72961	7.73050	5.48728	7.72961	7.73050	5.48728
42	15.14	2	B	8.76339	8.78032	7.55695	8.76339	8.78032	7.55695
43	2.79	2	B	7.12246	7.18139	4.92435	7.12246	7.18139	4.92435
44	14.98	2	B	8.01214	8.03102	4.99315	8.01214	8.03102	4.99315
45	15.36	2	B	7.43717	7.89108	5.03305	7.43717	7.89108	5.03305
46	7.81	2	B	9.06723	9.07031	7.80751	9.06723	9.07031	7.80751
47	.	2	B	7.88729	.	5.32252	7.88729	.	5.32252
48	3.16	2	B	7.78489	7.78687	5.84990	7.78489	7.78687	5.84990
49	7.43	2	B	7.59289	7.59938	4.71939	7.59289	7.59938	4.71939
50	26.65	2	B	5.03852	5.33287	2.05566	5.03852	5.33287	2.05566
51	3.96	2	B	5.75106	5.78136	4.33664	5.75106	5.78136	4.33664
52	2.97	2	B	6.69593	6.70286	4.20663	6.69593	6.70286	4.20663
53	11.35	2	B	8.39571	8.40098	5.79879	8.39571	8.40098	5.79879
54	10.62	2	B	7.65974	7.76257	5.25750	7.65974	7.76257	5.25750
55	34.27	2	B	7.07162	7.19541	5.31959	7.07162	7.19541	5.31959
56	11.60	2	B	7.40755	7.56146	5.31074	7.40755	7.56146	5.31074
57	4.42	3	B	7.94296	7.95905	6.42130	7.94296	7.95905	6.42130
58	1.96	3	B	6.23624	6.24868	3.65299	6.23624	6.24868	3.65299

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Obs	SUBJ	Group	SEQU	PER	TREAT	AUCT	AUCI	Cmax	TMAX	KE
59	(b) (6)	1	R1R2T	1	R1	1389.28	8575.76	67.93	17.00	0.0050
60		1	R1R2T	1	R1	1871.41	1893.12	83.77	28.00	0.0619
61		1	R1R2T	1	R1	2229.07	2252.66	95.42	20.00	0.0841
62		1	R1R2T	1	R1	2181.31	2209.60	213.60	14.00	0.3127
63		1	R1R2T	1	R1	1801.92	1811.72	57.18	11.00	0.1075
64		1	R1R2T	1	R1	2940.03	2962.21	297.90	10.00	0.0500
65		1	R1R2T	1	R1	1408.15	1427.59	256.80	28.00	0.4285
66		1	R1R2T	1	R1	13.28	.	2.30	20.00	.
67		1	R1R2T	1	R1	2387.58	2455.95	431.00	11.00	0.0524
68		1	R1R2T	1	R1	2212.96	2220.91	154.20	12.00	0.1282
69		1	R1R2T	1	R1	310.29	.	49.35	28.00	.
70		1	R1R2T	1	R1	4270.66	4279.98	225.10	16.00	0.1822
71		2	R1R2T	1	R1	818.81	1077.28	98.49	6.00	0.0737
72		2	R1R2T	1	R1	3987.42	4003.17	220.20	11.00	0.0983
73		2	R1R2T	1	R1	1437.59	1512.59	155.90	24.00	0.0943
74		2	R1R2T	1	R1	3277.56	3302.01	261.90	12.00	0.1546
75		2	R1R2T	1	R1	2638.51	5890.60	284.00	12.00	0.0067
76		2	R1R2T	1	R1	1283.27	1376.16	123.10	14.00	0.0228
77		2	R1R2T	1	R1	2901.91	3255.25	212.50	13.00	0.0680
78		2	R1R2T	1	R1	910.10	.	160.30	28.00	.
79		2	R1R2T	1	R1	1866.30	3366.85	56.69	16.03	0.0130
80		2	R1R2T	1	R1	1247.66	1327.66	229.40	6.00	0.1126
81		2	R1R2T	1	R1	4006.31	4015.52	167.40	28.00	0.1360
82		2	R1R2T	1	R1	3105.81	3128.62	286.10	14.05	0.0626

83	87	2	R1R2T	1	R1	6723.98	7841.87	1169.00	8.00	0.0563

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
59	137.99	3	B	7.23654	9.05669	4.21848	7.23654	9.05669	4.21848
60	11.19	3	B	7.53445	7.54598	4.42807	7.53445	7.54598	4.42807
61	8.25	3	B	7.70934	7.71987	4.55829	7.70934	7.71987	4.55829
62	2.22	3	B	7.68768	7.70057	5.36411	7.68768	7.70057	5.36411
63	6.45	3	B	7.49661	7.50203	4.04620	7.49661	7.50203	4.04620
64	13.85	3	B	7.98618	7.99369	5.69676	7.98618	7.99369	5.69676
65	1.62	3	B	7.25003	7.26374	5.54830	7.25003	7.26374	5.54830
66	.	3	B	2.58597	.	0.83247	2.58597	.	0.83247
67	13.22	3	B	7.77804	7.80627	6.06611	7.77804	7.80627	6.06611
68	5.40	3	B	7.70209	7.70567	5.03825	7.70209	7.70567	5.03825
69	.	3	B	5.73751	.	3.89894	5.73751	.	3.89894
70	3.80	3	B	8.35952	8.36170	5.41654	8.35952	8.36170	5.41654
71	9.41	3	B	6.70785	6.98219	4.58996	6.70785	6.98219	4.58996
72	7.05	3	B	8.29090	8.29484	5.39454	8.29090	8.29484	5.39454
73	7.35	3	B	7.27072	7.32158	5.04921	7.27072	7.32158	5.04921
74	4.48	3	B	8.09485	8.10229	5.56796	8.09485	8.10229	5.56796
75	103.93	3	B	7.87797	8.68111	5.64897	7.87797	8.68111	5.64897
76	30.46	3	B	7.15717	7.22705	4.81300	7.15717	7.22705	4.81300
77	10.19	3	B	7.97312	8.08802	5.35894	7.97312	8.08802	5.35894
78	.	3	B	6.81355	.	5.07705	6.81355	.	5.07705
79	53.48	3	B	7.53171	8.12173	4.03760	7.53171	8.12173	4.03760
80	6.16	3	B	7.12903	7.19117	5.43547	7.12903	7.19117	5.43547
81	5.10	3	B	8.29563	8.29792	5.12039	8.29563	8.29792	5.12039
82	11.07	3	B	8.04103	8.04835	5.65634	8.04103	8.04835	5.65634
83	12.31	3	B	8.81344	8.96723	7.06390	8.81344	8.96723	7.06390

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Obs	SUBJ	Group	SEQU	PER	TREAT	AUCT	AUCI	Cmax	TMAX	KE
1	(b) (6)	1	TR1R2	3	R2	4715.11	4779.93	314.70	20.00	0.1420
2		1	TR1R2	3	R2	1678.64	.	120.10	95.00	.
3		1	TR1R2	3	R2	1499.22	1549.37	76.84	15.00	0.0283
4		1	TR1R2	3	R2	1123.15	1671.63	30.28	34.10	0.0120
5		1	TR1R2	3	R2	3304.26	3322.99	119.90	47.00	0.0891
6		1	TR1R2	3	R2	4683.08	4789.66	695.10	15.00	0.0509
7		1	TR1R2	3	R2	9774.04	10035.90	3168.00	6.00	0.0398
8		1	TR1R2	3	R2	5197.32	5252.26	468.10	16.00	0.1430
9		1	TR1R2	3	R2	1917.66	2462.76	80.84	8.00	0.0242
10		1	TR1R2	3	R2	6151.55	6750.33	725.40	6.00	0.1010
11		1	TR1R2	3	R2	2573.61	2640.01	177.90	17.00	0.0320
12		1	TR1R2	3	R2	2628.00	2878.92	236.00	22.00	0.1528
13		1	TR1R2	3	R2	1353.96	1506.02	124.30	24.00	0.0394
14		1	TR1R2	3	R2	4901.88	4967.56	248.20	32.00	0.2063
15		1	TR1R2	3	R2	4214.56	4228.34	278.50	14.00	0.0743
16		2	TR1R2	3	R2	2314.30	2460.88	177.80	28.00	0.0974
17		2	TR1R2	3	R2	1563.92	1574.35	280.40	11.00	0.2197
18		2	TR1R2	3	R2	1304.85	1323.89	86.66	20.00	0.1552
19		2	TR1R2	3	R2	5042.66	9891.59	281.30	11.00	0.0158
20		2	TR1R2	3	R2	2310.62	2350.66	101.70	6.00	0.0567
21		2	TR1R2	3	R2	548.24	.	97.67	28.00	.
22		2	TR1R2	3	R2	3222.73	3853.42	177.00	28.00	0.0687
23		2	TR1R2	3	R2	1059.11	.	80.38	36.00	.

24	(b) (6)	2	TR1R2	3	R2	1336.31	2009.04	92.91	17.00	0.0401
25		2	TR1R2	3	R2	2175.18	2328.41	282.20	11.00	0.0108
26		2	TR1R2	3	R2	1287.36	1468.26	108.50	16.00	0.0496
27		2	TR1R2	3	R2	2067.68	2478.57	111.40	16.00	0.0181
28		2	TR1R2	3	R2	2873.18	2880.44	207.40	16.00	0.2068
29		2	TR1R2	3	R2	6.27	14.00	1.90	13.00	0.1739

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
1	4.88	1	B	8.45853	8.47218	5.75162	8.45853	8.47218	5.75162
2	.	1	B	7.42574	.	4.78832	7.42574	.	4.78832
3	24.50	1	B	7.31270	7.34560	4.34173	7.31270	7.34560	4.34173
4	57.99	1	B	7.02389	7.42155	3.41049	7.02389	7.42155	3.41049
5	7.78	1	B	8.10297	8.10862	4.78666	8.10297	8.10862	4.78666
6	13.61	1	B	8.45171	8.47421	6.54406	8.45171	8.47421	6.54406
7	17.42	1	B	9.18749	9.21392	8.06086	9.18749	9.21392	8.06086
8	4.85	1	B	8.55590	8.56641	6.14868	8.55590	8.56641	6.14868
9	28.60	1	B	7.55886	7.80904	4.39247	7.55886	7.80904	4.39247
10	6.86	1	B	8.72446	8.81735	6.58672	8.72446	8.81735	6.58672
11	21.64	1	B	7.85306	7.87854	5.18122	7.85306	7.87854	5.18122
12	4.54	1	B	7.87398	7.96517	5.46383	7.87398	7.96517	5.46383
13	17.61	1	B	7.21079	7.31723	4.82270	7.21079	7.31723	4.82270
14	3.36	1	B	8.49737	8.51068	5.51423	8.49737	8.51068	5.51423
15	9.33	1	B	8.34630	8.34956	5.62942	8.34630	8.34956	5.62942
16	7.11	1	B	7.74686	7.80827	5.18066	7.74686	7.80827	5.18066
17	3.16	1	B	7.35495	7.36160	5.63622	7.35495	7.36160	5.63622
18	4.47	1	B	7.17384	7.18833	4.46199	7.17384	7.18833	4.46199
19	43.92	1	B	8.52569	9.19944	5.63942	8.52569	9.19944	5.63942
20	12.23	1	B	7.74527	7.76245	4.62203	7.74527	7.76245	4.62203
21	.	1	B	6.30671	.	4.58159	6.30671	.	4.58159
22	10.09	1	B	8.07798	8.25672	5.17615	8.07798	8.25672	5.17615
23	.	1	B	6.96518	.	4.38677	6.96518	.	4.38677
24	17.26	1	B	7.19767	7.60541	4.53163	7.19767	7.60541	4.53163
25	64.33	1	B	7.68487	7.75294	5.64262	7.68487	7.75294	5.64262
26	13.97	1	B	7.16035	7.29183	4.68675	7.16035	7.29183	4.68675
27	38.21	1	B	7.63418	7.81544	4.71313	7.63418	7.81544	4.71313
28	3.35	1	B	7.96317	7.96570	5.33465	7.96317	7.96570	5.33465
29	3.99	1	B	1.83625	2.63920	0.64343	1.83625	2.63920	0.64343

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Obs	SUBJ	Group	SEQU	PER	TREAT	AUCT	AUCI	Cmax	TMAX	KE
30	(b) (6)	1	R1TR2	3	R2	3168.43	3194.35	480.40	9.00	0.1936
31		1	R1TR2	3	R2	785.37	870.26	88.29	11.00	0.1164
32		1	R1TR2	3	R2	3517.84	3589.57	160.80	13.00	0.0601
33		1	R1TR2	3	R2	92.94	.	18.23	28.00	.
34		1	R1TR2	3	R2	2225.56	.	134.60	47.00	.
35		1	R1TR2	3	R2	2695.02	2745.60	195.10	11.00	0.0352
36		1	R1TR2	3	R2	1756.51	4812.39	143.80	28.00	0.0354
37		1	R1TR2	3	R2	1920.96	1943.73	36.61	71.00	0.0664
38		1	R1TR2	3	R2	1928.83	2209.98	184.80	14.00	0.0698
39		1	R1TR2	3	R2	4334.44	4717.32	94.82	47.00	0.0387
40		1	R1TR2	3	R2	3138.48	3146.33	456.50	8.00	0.1916
41		1	R1TR2	3	R2	3152.28	4999.50	277.90	11.00	0.0475
42		2	R1TR2	3	R2	747.52	.	59.88	48.00	.
43		2	R1TR2	3	R2	1350.40	1361.56	110.40	24.07	0.1622

44	(b) (6)	2	R1TR2	3	R2	4749.15	4783.85	221.70	36.00	0.1162
45		2	R1TR2	3	R2	2475.29	2815.48	127.50	13.00	0.1288
46		2	R1TR2	3	R2	4681.43	4694.62	598.20	11.00	0.1805
47		2	R1TR2	3	R2	6406.82	6431.64	180.10	22.00	0.1152
48		2	R1TR2	3	R2	695.39	3718.25	64.43	17.00	0.0160
49		2	R1TR2	3	R2	1057.95	1065.32	73.16	28.00	0.1949
50		2	R1TR2	3	R2	1894.66	1899.92	150.30	15.00	0.3470
51		2	R1TR2	3	R2	10.51	.	1.59	28.00	.
52		2	R1TR2	3	R2	978.96	1268.10	57.01	17.03	0.0897
53		2	R1TR2	3	R2	5075.59	5899.77	346.50	2.00	0.0634
54		2	R1TR2	3	R2	1798.41	2029.79	173.10	15.00	0.0415
55		2	R1TR2	3	R2	998.44	1022.96	85.89	11.05	0.0906
56		2	R1TR2	3	R2	2656.81	2669.05	236.80	7.00	0.1945
57		1	R1R2T	2	R2	967.41	986.30	168.90	11.00	0.0854
58		1	R1R2T	2	R2	335.53	.	36.03	28.00	.

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
30	3.58	2	B	8.06099	8.06914	6.17462	8.06099	8.06914	6.17462
31	5.96	2	B	6.66615	6.76880	4.48063	6.66615	6.76880	4.48063
32	11.54	2	B	8.16560	8.18579	5.08016	8.16560	8.18579	5.08016
33	.	2	B	4.53192	.	2.90307	4.53192	.	2.90307
34	.	2	B	7.70776	.	4.90231	7.70776	.	4.90231
35	19.66	2	B	7.89916	7.91775	5.27351	7.89916	7.91775	5.27351
36	19.56	2	B	7.47108	8.47895	4.96842	7.47108	8.47895	4.96842
37	10.44	2	B	7.56058	7.57236	3.60032	7.56058	7.57236	3.60032
38	9.93	2	B	7.56467	7.70074	5.21927	7.56467	7.70074	5.21927
39	17.92	2	B	8.37435	8.45900	4.55198	8.37435	8.45900	4.55198
40	3.62	2	B	8.05149	8.05399	6.12359	8.05149	8.05399	6.12359
41	14.59	2	B	8.05588	8.51709	5.62726	8.05588	8.51709	5.62726
42	.	2	B	6.61676	.	4.09234	6.61676	.	4.09234
43	4.27	2	B	7.20816	7.21639	4.70411	7.20816	7.21639	4.70411
44	5.96	2	B	8.46572	8.47300	5.40133	8.46572	8.47300	5.40133
45	5.38	2	B	7.81411	7.94289	4.84812	7.81411	7.94289	4.84812
46	3.84	2	B	8.45136	8.45417	6.39393	8.45136	8.45417	6.39393
47	6.01	2	B	8.76512	8.76898	5.19351	8.76512	8.76898	5.19351
48	43.40	2	B	6.54447	8.22101	4.16558	6.54447	8.22101	4.16558
49	3.56	2	B	6.96409	6.97103	4.29265	6.96409	6.97103	4.29265
50	2.00	2	B	7.54679	7.54957	5.01263	7.54679	7.54957	5.01263
51	.	2	B	2.35261	.	0.46058	2.35261	.	0.46058
52	7.72	2	B	6.88649	7.14527	4.04323	6.88649	7.14527	4.04323
53	10.93	2	B	8.53220	8.68267	5.84788	8.53220	8.68267	5.84788
54	16.69	2	B	7.49466	7.61569	5.15387	7.49466	7.61569	5.15387
55	7.65	2	B	6.90620	6.93046	4.45307	6.90620	6.93046	4.45307
56	3.56	2	B	7.88488	7.88948	5.46722	7.88488	7.88948	5.46722
57	8.11	3	B	6.87463	6.89396	5.12931	6.87463	6.89396	5.12931
58	.	3	B	5.81571	.	3.58435	5.81571	.	3.58435

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Obs	SUBJ	Group	SEQU	PER	TREAT	AUCT	AUCI	Cmax	TMAX	KE
59	(b) (6)	1	R1R2T	2	R2	2220.44	.	97.94	36.00	.
60		1	R1R2T	2	R2	1627.93	1677.32	141.50	10.00	0.1174
61		1	R1R2T	2	R2	3012.29	3543.32	165.90	15.00	0.0652
62		1	R1R2T	2	R2	1045.77	1049.38	92.16	24.00	0.4654
63		1	R1R2T	2	R2	3196.58	.	190.20	36.00	.

64	(b) (6)	1	R1R2T	2	R2	1864.63	1932.95	93.78	14.00	0.0361
65		1	R1R2T	2	R2	663.67	874.12	64.95	11.00	0.0441
66		1	R1R2T	2	R2	279.45	.	45.77	32.00	.
67		1	R1R2T	2	R2	897.49	923.40	105.00	12.00	0.0763
68		1	R1R2T	2	R2	1427.53	1439.31	117.40	18.00	0.1516
69		1	R1R2T	2	R2	1301.61	1322.13	107.10	12.05	0.1309
70		1	R1R2T	2	R2	2418.26	2479.70	150.40	13.00	0.0264
71		2	R1R2T	2	R2	498.41	.	31.15	32.00	.
72		2	R1R2T	2	R2	4462.43	4922.46	1151.00	4.00	0.0249
73		2	R1R2T	2	R2	1234.76	1250.80	74.45	10.00	0.1495
74		2	R1R2T	2	R2	806.22	825.06	143.20	22.00	0.2441
75		2	R1R2T	2	R2	2062.17	2073.01	115.70	22.00	0.1956
76		2	R1R2T	2	R2	3304.76	3337.52	155.70	20.00	0.1913
77		2	R1R2T	2	R2	3564.68	3635.11	217.40	28.00	0.1486
78		2	R1R2T	2	R2	980.45	995.08	88.71	14.00	0.1431
79		2	R1R2T	2	R2	1802.09	1823.66	59.29	36.00	0.0684
80		2	R1R2T	2	R2	6596.70	6636.48	3183.00	6.00	0.0619
81		2	R1R2T	2	R2	2885.88	2915.76	153.80	28.00	0.1926
82		2	R1R2T	2	R2	4739.94	4752.99	229.20	12.00	0.0772
83		2	R1R2T	2	R2	17015.10	17033.30	3959.00	4.00	0.0665

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
59	.	3	B	7.70546	.	4.58436	7.70546	.	4.58436
60	5.91	3	B	7.39506	7.42495	4.95230	7.39506	7.42495	4.95230
61	10.63	3	B	8.01046	8.17282	5.11139	8.01046	8.17282	5.11139
62	1.49	3	B	6.95251	6.95595	4.52353	6.95251	6.95595	4.52353
63	.	3	B	8.06984	.	5.24808	8.06984	.	5.24808
64	19.20	3	B	7.53082	7.56680	4.54095	7.53082	7.56680	4.54095
65	15.71	3	B	6.49778	6.77322	4.17362	6.49778	6.77322	4.17362
66	.	3	B	5.63283	.	3.82363	5.63283	.	3.82363
67	9.09	3	B	6.79960	6.82806	4.65396	6.79960	6.82806	4.65396
68	4.57	3	B	7.26370	7.27192	4.76559	7.26370	7.27192	4.76559
69	5.30	3	B	7.17136	7.18700	4.67376	7.17136	7.18700	4.67376
70	26.26	3	B	7.79080	7.81589	5.01330	7.79080	7.81589	5.01330
71	.	3	B	6.21142	.	3.43881	6.21142	.	3.43881
72	27.80	3	B	8.40345	8.50156	7.04839	8.40345	8.50156	7.04839
73	4.64	3	B	7.11863	7.13154	4.31013	7.11863	7.13154	4.31013
74	2.84	3	B	6.69236	6.71546	4.96424	6.69236	6.71546	4.96424
75	3.54	3	B	7.63151	7.63676	4.75100	7.63151	7.63676	4.75100
76	3.62	3	B	8.10312	8.11298	5.04793	8.10312	8.11298	5.04793
77	4.66	3	B	8.17883	8.19839	5.38174	8.17883	8.19839	5.38174
78	4.84	3	B	6.88801	6.90282	4.48537	6.88801	6.90282	4.48537
79	10.13	3	B	7.49670	7.50860	4.08244	7.49670	7.50860	4.08244
80	11.20	3	B	8.79432	8.80034	8.06558	8.79432	8.80034	8.06558
81	3.60	3	B	7.96759	7.97789	5.03565	7.96759	7.97789	5.03565
82	8.98	3	B	8.46378	8.46653	5.43459	8.46378	8.46653	5.43459
83	10.43	3	B	9.74186	9.74293	8.28375	9.74186	9.74293	8.28375

dataset for scaled average BE 20

Obs	SUBJ	PER	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
1	(b) (6)	3	1	B	0.01787	0.00578	0.48611	-0.68339	-0.68565	-0.40785
2		3	1	B	0.46849	.	1.12292	0.19745	.	-0.68734
3		3	1	B	0.26537	0.19333	0.13725	-0.31902	-0.20228	-0.30149
4		3	1	B	0.06416	-0.09958	-0.33576	0.54440	0.15427	1.81365

5	(b) (6)	3	1	B	-0.10276	0.32803	0.32711	-0.70549	-0.68722	-0.47104
6		3	1	B	-0.20539	-0.25360	-0.63368	0.13822	0.22634	0.94592
7		3	1	B	-0.02528	0.01471	-0.24151	-0.44092	-0.44176	-2.42108
8		3	1	B	-0.65318	-0.64922	-0.42440	0.08041	0.07854	-0.04501
9		3	1	B	0.37583	0.29475	0.95583	-0.14004	-0.38104	-0.42501
10		3	1	B	0.76088	0.70528	0.11529	-1.43650	-1.51047	-0.84886
11		3	1	B	-0.95681	.	-0.80930	0.20705	0.18580	-0.03839
12		3	1	B	-2.36096	-2.37004	-2.24101	-0.04315	-0.07428	0.18055
13		3	1	B	-0.31014	-0.31391	-1.45337	1.03920	0.96833	1.63093
14		3	1	B	0.15578	0.18357	0.33359	0.10894	0.09735	0.53172
15		3	1	B	-0.49892	-0.47957	-1.17053	-0.03844	-0.03436	-0.37140
16		3	1	B	0.82238	0.84830	0.58472	-0.54601	-0.60479	-0.12187
17		3	1	B	-0.40893	-0.31025	-0.90296	0.76087	0.75686	-0.07285
18		3	1	B	0.97457	1.02940	1.44961	0.59678	0.58727	0.17468
19		3	1	B	0.64687	0.82706	0.78662	-1.15921	-1.24275	-1.19009
20		3	1	B	-0.21996	-0.22172	-0.63589	0.15632	0.15991	0.29356
21		3	1	B	-1.26635	.	-1.08462	1.62135	.	0.61136
22		3	1	B	0.51490	1.69960	0.39518	-0.57279	-0.74829	-0.15161
23		3	1	B	0.23183	.	-0.00930	-0.16825	.	-0.26481
24		3	1	B	-0.12659	-0.67289	-0.78767	0.48134	0.82739	0.37808
25		3	1	B	-0.03480	-0.16294	0.15688	0.26847	0.42752	-0.53063
26		3	1	B	0.53666	0.55711	1.16943	0.30774	0.21501	0.46074
27		3	1	B	0.04403	0.06304	0.36646	0.23045	0.08667	-0.09307
28		3	1	B	-2.03128	-2.03015	-1.76978	-0.78026	-0.72140	0.29692
29		3	1	B	3.64478	3.27247	3.46973	5.90363	5.10766	4.27363
30		3	2	B	0.10800	0.11886	1.12462	-0.41476	-0.40348	-1.07232
31		3	2	B	0.62390	.	-0.05299	1.43650	.	1.01654
32		3	2	B	0.40591	0.39135	0.10335	0.43081	0.42478	0.99127
33		3	2	B	1.82503	.	1.38769	2.75129	.	2.85583
34		3	2	B	-0.38802	.	-0.51348	-0.17086	.	-0.76044
35		3	2	B	-0.10824	-0.12155	0.38722	0.45078	0.50037	0.01071
36		3	2	B	0.30407	.	0.20042	0.54425	-0.46002	-0.23927
37		3	2	B	1.62069	1.63040	1.50540	-0.89339	-0.64996	-0.61161
38		3	2	B	0.32498	0.27212	-0.21871	0.77613	0.65361	-0.56056
39		3	2	B	0.42954	0.40100	0.33504	-0.79353	-0.83066	-0.16273
40		3	2	B	-0.25481	0.16520	-0.07630	-0.32167	-0.32122	-1.13998
41		3	2	B	0.43129	0.23180	0.11502	-0.32627	-0.78659	-0.13998
42		3	2	B	0.22823	.	0.03014	2.14662	.	3.46461
43		3	2	B	0.68294	0.67452	0.31033	-0.08569	-0.03500	0.22024
44		3	2	B	-0.27163	-0.27480	-0.13972	-0.45358	-0.44198	-0.40818
45		3	2	B	0.02247	-0.25031	0.04781	-0.37694	-0.05180	0.18493
46		3	2	B	-0.47832	-0.47726	-1.39062	0.61587	0.61614	1.41358
47		3	2	B	0.36351	.	0.44810	-0.87783	.	0.12901
48		3	2	B	1.11406	0.27693	1.04740	1.24041	-0.43414	1.68432
49		3	2	B	-2.14651	.	-1.17560	0.62880	0.62835	0.42674
50		3	2	B	0.93166	0.78428	1.79081	-2.50827	-2.21669	-2.95697
51		3	2	B	2.98015	.	2.91951	3.39845	.	3.87605
52		3	2	B	0.48750	0.36054	0.51174	-0.19056	-0.44241	0.16340
53		3	2	B	0.28374	0.22328	1.94900	-0.13649	-0.28169	-0.04909
54		3	2	B	1.09869	1.11014	0.95468	0.16508	0.14688	0.10363
55		3	2	B	0.87362	0.82910	2.06736	0.16543	0.26496	0.86652
56		3	2	B	0.32726	0.25455	-0.26561	-0.47733	-0.32801	-0.15648
57		2	3	B	0.17763	0.16430	-0.31232	1.06833	1.06509	1.29199
58		2	3	B	2.19652	.	2.04568	0.42053	.	0.06864
59		2	3	B	0.14736	.	0.61055	-0.46892	.	-0.36588
60		2	3	B	-0.29687	-0.31197	0.70933	0.13938	0.12103	-0.52422
61		2	3	B	0.02333	-0.05978	0.65534	-0.30112	-0.45295	-0.55310

dataset for scaled average BE 21

Obs	SUBJ	PER	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
62	(b) (6)	2	3	B	-0.45872	-0.45012	-0.41046	0.73517	0.74461	0.84058
63		2	3	B	-0.29833	.	1.33326	-0.57323	.	-1.20187
64		2	3	B	0.81702	0.79965	-0.12097	0.45536	0.42689	1.15581
65		2	3	B	-0.70883	.	-0.47022	0.75225	0.49052	1.37468
66		2	3	B	-0.11968	.	-0.05048	-3.04687	.	-2.99115
67		2	3	B	0.19301	0.17543	0.01894	0.97843	0.97821	1.41215
68		2	3	B	0.26059	0.27207	0.66452	0.43839	0.43375	0.27266
69		2	3	B	1.18745	.	1.78554	-1.43385	.	-0.77483
70		2	3	B	-0.47076	-0.46178	-0.60576	0.56872	0.54581	0.40325
71		2	3	B	-0.21369	.	0.00200	0.49643	.	1.15114
72		2	3	B	-0.16722	-0.15596	-0.54095	-0.11255	-0.20672	-1.65385
73		2	3	B	-0.05523	-0.06404	-0.21883	0.15209	0.19004	0.73909
74		2	3	B	0.98113	0.97381	1.15422	1.40250	1.38683	0.60372
75		2	3	B	-1.03605	.	-0.90216	0.24646	1.04436	0.89797
76		2	3	B	-0.07734	0.02422	-0.59920	-0.94595	-0.88593	-0.23493
77		2	3	B	-0.05049	0.06201	-0.08714	-0.20571	-0.11037	-0.02280
78		2	3	B	0.30850	.	0.16542	-0.07446	.	0.59167
79		2	3	B	0.01537	0.05514	-0.26701	0.03501	0.61313	-0.04484
80		2	3	B	-0.75644	-0.78821	-1.49355	-1.66530	-1.60916	-2.63011
81		2	3	B	0.51104	0.51051	1.05386	0.32804	0.32004	0.08473
82		2	3	B	-0.22539	-0.21139	-0.09787	-0.42275	-0.41818	0.22175
83		2	3	B	-0.36562	-0.26960	-0.09619	-0.92842	-0.77569	-1.21984

unscaled BE 90% CI - guidance version 22

The Mixed Procedure

Model Information

Data Set	WORK.PKN
Dependent Variable	LCMAX
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	SUBJ, SUBJ
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
Group	2	1 2
SEQ	3	1 2 3
SUBJ	83	1 2 3 4 5 6 7 8 9 10 12 13 14 15 16 17 18 19 20 21 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57

		58 59 60 61 63 64 65 66 67 68
		69 70 71 72 73 74 75 76 77 78
		79 80 82 83 84 85 86 87 89 90
PER	3	1 2 3
TRT	2	A B

Dimensions

Covariance Parameters	5
Columns in X	24
Columns in Z Per Subject	2
Subjects	83
Max Obs Per Subject	3

Number of Observations

Number of Observations Read	249
Number of Observations Used	249
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	732.28140459	
1	2	709.32335027	0.12021925
2	1	703.89537215	0.00996137
3	1	702.86138588	0.00000005
4	4	702.86138470	0.00000004
5	1	702.86137966	0.00000000

The Mixed Procedure

Convergence criteria met.

Estimated G Matrix

Row	Effect	TRT	SUBJ	Col1	Col2
1	TRT	A	1	0.8078	0.3833
2	TRT	B	1	0.3833	0.4155

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	SUBJ		0.8988
FA(2,1)	SUBJ		0.4264
FA(2,2)	SUBJ		0.4834
Residual	SUBJ	TRT A	0.1186

Residual	SUBJ	TRT B	0.7539

Fit Statistics

-2 Res Log Likelihood	702.9
AIC (smaller is better)	712.9
AICC (smaller is better)	713.1
BIC (smaller is better)	725.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	29.42	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Group	1	77	0.18	0.6739
SEQ	2	77.6	0.03	0.9742
Group*SEQ	2	77.6	2.50	0.0887
PER(Group)	4	158	2.41	0.0511
TRT	1	78.8	3.36	0.0706
Group*TRT	1	78.8	0.10	0.7582

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T vs. R	0.1967	0.1073	78.8	1.83	0.0706	0.1	0.01807	0.3752

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	5.2064	0.1059	77.6	49.15	<.0001
TRT	B	5.0097	0.09799	77.4	51.13	<.0001

Model Information

Data Set	WORK.PKN
Dependent Variable	LAUCT
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	SUBJ, SUBJ
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
Group	2	1 2
SEQ	3	1 2 3
SUBJ	83	1 2 3 4 5 6 7 8 9 10 12 13 14 15 16 17 18 19 20 21 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 82 83 84 85 86 87 89 90
PER	3	1 2 3
TRT	2	A B

Dimensions

Covariance Parameters	5
Columns in X	24
Columns in Z Per Subject	2
Subjects	83
Max Obs Per Subject	3

Number of Observations

Number of Observations Read	249
Number of Observations Used	249
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	696.41380189	
1	2	667.21756057	0.04815432
2	1	664.01463270	0.30261259
3	1	663.95117818	0.00116396
4	1	663.95091004	0.00000004
5	1	663.95091002	0.00000000

The Mixed Procedure

Convergence criteria met but final hessian is not positive definite.

Estimated G Matrix

Row	Effect	TRT	SUBJ	Col1	Col2
1	TRT	A	1	0.5139	0.3344
2	TRT	B	1	0.3344	0.3770

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	SUBJ		0.7168
FA(2,1)	SUBJ		0.4664
FA(2,2)	SUBJ		0.3992
Residual	SUBJ	TRT A	0.2357
Residual	SUBJ	TRT B	0.6517

Fit Statistics

-2 Res Log Likelihood	664.0
AIC (smaller is better)	674.0
AICC (smaller is better)	674.2
BIC (smaller is better)	686.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	32.46	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Group	1	77	0.21	0.6513
SEQ	2	78.1	0.72	0.4879
Group*SEQ	2	78.1	4.05	0.0212
PER(Group)	4	157	1.74	0.1439
TRT	1	78.6	2.78	0.0997
Group*TRT	1	78.6	0.10	0.7529

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T vs. R	0.1622	0.09733	78.6	1.67	0.0997	0.1	0.000154	0.3242

The Mixed Procedure

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	7.6968	0.09529	77.5	80.77	<.0001
TRT	B	7.5346	0.09228	77.4	81.65	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.PKN
Dependent Variable	LAUCINF
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	SUBJ, SUBJ
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
Group	2	1 2
SEQ	3	1 2 3
SUBJ	83	1 2 3 4 5 6 7 8 9 10 12 13 14 15 16 17 18 19 20 21 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 82 83 84 85 86 87 89 90
PER	3	1 2 3
TRT	2	A B

Dimensions

Covariance Parameters	5
Columns in X	24

Columns in Z Per Subject	2
Subjects	83
Max Obs Per Subject	3

Number of Observations

Number of Observations Read	249
Number of Observations Used	222
Number of Observations Not Used	27

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	522.95375021	
1	2	515.91312817	0.13504295
2	1	512.31120946	0.01422259
3	1	511.58272740	0.00009267
4	1	511.57698263	0.00001072
5	1	511.57698012	0.00000000

The Mixed Procedure

Convergence criteria met.

Estimated G Matrix

Row	Effect	TRT	SUBJ	Col1	Col2
1	TRT	A	1	0.4795	0.1512
2	TRT	B	1	0.1512	0.1545

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	SUBJ		0.6925
FA(2,1)	SUBJ		0.2184
FA(2,2)	SUBJ		0.3268
Residual	SUBJ	TRT A	0.06786
Residual	SUBJ	TRT B	0.4545

Fit Statistics

-2 Res Log Likelihood	511.6
AIC (smaller is better)	521.6
AICC (smaller is better)	521.9
BIC (smaller is better)	533.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	11.38	0.0226

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Group	1	74.4	0.14	0.7140
SEQ	2	72.9	0.30	0.7423
Group*SEQ	2	72.9	3.32	0.0418
PER(Group)	4	140	0.63	0.6454
TRT	1	71.4	2.29	0.1345
Group*TRT	1	71.4	0.60	0.4399

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T vs. R	0.1409	0.09305	71.4	1.51	0.1345	0.1	-0.01421	0.2959

The Mixed Procedure

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	7.9187	0.08559	70.9	92.52	<.0001
TRT	B	7.7778	0.07146	67.5	108.84	<.0001

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read	83
Number of Observations Used	83

The GLM Procedure

Dependent Variable: ilat

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	3.01478172	1.50739086	1.92	0.1527
Error	80	62.67836582	0.78347957		
Corrected Total	82	65.69314754			

R-Square	Coeff Var	Root MSE	ilat Mean
0.045892	537.7830	0.885144	0.164591

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	3.01478172	1.50739086	1.92	0.1527

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	3.01478172	1.50739086	1.92	0.1527

Parameter	Estimate	Standard Error	t Value	Pr > |t|
average	0.16838021	0.09721229	1.73	0.0871

Parameter	90% Confidence Limits	
average	0.00660685	0.33015357

dev iglmilat1 33

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilat	Model	2	3.01478172	1.50739086	1.92	0.1527
2	ilat	Error	80	62.67836582	0.78347957	_	_
3	ilat	Corrected Total	82	65.69314754	_	_	_

scaled average BE 34
intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

```
Number of Observations Read          83
Number of Observations Used          83

scaled average BE                                                      35
intermediate analysis - &dpar  glm

The GLM Procedure

Dependent Variable: dlat

                                   Sum of
Source                     DF       Squares    Mean Square   F Value   Pr > F

Model                       2     1.6059298      0.8029649      0.61   0.5471

Error                      80   105.7041724      1.3213022

Corrected Total            82   107.3101022


R-Square     Coeff Var      Root MSE     dlat Mean

0.014965      919.9929      1.149479      0.124944


Source                     DF      Type I SS    Mean Square   F Value   Pr > F

SEQ                         2     1.60592976     0.80296488      0.61   0.5471


Source                     DF    Type III SS    Mean Square   F Value   Pr > F

SEQ                         2     1.60592976     0.80296488      0.61   0.5471

output needed for mixed scaled av. BE - using glm                      36

       method_    unscabe_   unscabe_
Obs     used        lower      upper    dfi     s2i     param         StdErr

 1    Scaled/PE    1.00015    1.38289    80   0.78348   LAUCT     0.09721229


Obs   pointest        x        boundx    ni    dfd      s2wr     nd     theta

 1     1.18339    0.018902    0.10900    83     80    0.66065    83    0.79669


Obs       y        boundy       sWR      critbound    outcome

 1    -0.52633    -0.41330    0.81280     -0.36288     PASS

final output - &parameter - using glm                                  37

     method_  unscabe_ unscabe_
Obs   used      lower    upper  param pointest   s2wr    sWR   critbound outcome
```

```
 1  Scaled/PE  1.00015  1.38289 LAUCT  1.18339 0.66065 0.81280  -0.36288  PASS

scaled average BE                                                        38
intermediate analysis - &ipar glm

The GLM Procedure

   Class Level Information

Class         Levels    Values

SEQ                3    1 2 3


Number of Observations Read          83
Number of Observations Used          62

scaled average BE                                                        39
intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilai

                                   Sum of
Source                     DF       Squares    Mean Square   F Value   Pr > F

Model                       2    1.13649455     0.56824727      0.93   0.3987

Error                      59   35.89252901     0.60834795

Corrected Total            61   37.02902356


R-Square     Coeff Var      Root MSE     ilai Mean

0.030692      518.6931      0.779967      0.150372


Source                     DF      Type I SS    Mean Square   F Value   Pr > F

SEQ                         2    1.13649455     0.56824727      0.93   0.3987


Source                     DF    Type III SS    Mean Square   F Value   Pr > F

SEQ                         2    1.13649455     0.56824727      0.93   0.3987


                                         Standard
Parameter                 Estimate           Error    t Value    Pr > |t|

average                0.15346786      0.10008293       1.53      0.1305

Parameter              90% Confidence Limits
```

```
average                  -0.01378003   0.32071575

dev iglmilai1                                                                40

Obs Dependent Source              DF           SS           MS  FValue  ProbF

 1    ilai    Model                2   1.13649455   0.56824727    0.93 0.3987
 2    ilai    Error               59  35.89252901   0.60834795     _    _
 3    ilai    Corrected Total     61  37.02902356    _             _    _

scaled average BE                                                            41
intermediate analysis - &dpar  glm

The GLM Procedure

   Class Level Information

Class         Levels    Values

SEQ                3    1 2 3


Number of Observations Read          83
Number of Observations Used          67

scaled average BE                                                            42
intermediate analysis - &dpar  glm

The GLM Procedure

Dependent Variable: dlai

                                    Sum of
Source                      DF        Squares    Mean Square   F Value   Pr > F

Model                        2     1.89288754     0.94644377      1.11   0.3373

Error                       64    54.79119904     0.85611248

Corrected Total             66    56.68408658


R-Square     Coeff Var      Root MSE     dlai Mean

0.033394      3103.733      0.925263      0.029811


Source                      DF      Type I SS    Mean Square   F Value   Pr > F

SEQ                          2     1.89288754     0.94644377      1.11   0.3373


Source                      DF    Type III SS    Mean Square   F Value   Pr > F

SEQ                          2     1.89288754     0.94644377      1.11   0.3373

output needed for mixed scaled av. BE - using glm                            43
```

Obs	method_ used	unscabe_ lower	unscabe_ upper	dfi	s2i	param	StdErr
1	Scaled/PE	0.98590	1.34438	59	0.60835	LAUCINF	0.10008293

Obs	pointest	x	boundx	ni	dfd	s2wr	nd	theta
1	1.16587	0.013536	0.10286	62	64	0.42806	67	0.79669

Obs	y	boundy	sWR	critbound	outcome
1	-0.34103	-0.26084	0.65426	-0.20746	PASS

final output - &parameter - using glm 44

Obs	method_ used	unscabe_ lower	unscabe_ upper	pointest	s2wr	sWR	critbound	outcome
1	Scaled/PE	0.98590	1.34438	LAUCINF	1.16587	0.42806	0.65426	-0.20746 PASS

scaled average BE 45
intermediate analysis - &ipar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 83
Number of Observations Used 83

scaled average BE 46
intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilc

Sum of

```
Source                     DF        Squares    Mean Square   F Value   Pr > F

Model                       2     3.88381429     1.94190714      1.99   0.1440

Error                      80    78.23190645     0.97789883

Corrected Total            82    82.11572073


R-Square     Coeff Var      Root MSE      ilc Mean

0.047297      491.9215      0.988888      0.201025


Source                     DF      Type I SS    Mean Square   F Value   Pr > F

SEQ                         2     3.88381429     1.94190714      1.99   0.1440


Source                     DF    Type III SS    Mean Square   F Value   Pr > F

SEQ                         2     3.88381429     1.94190714      1.99   0.1440


                                        Standard
Parameter                   Estimate           Error    t Value    Pr > |t|

average                  0.20653658      0.10860612       1.90      0.0608

Parameter                90% Confidence Limits

average                  0.02580247   0.38727069

dev iglmilc1                                                              47

Obs Dependent Source              DF           SS           MS  FValue  ProbF

 1     ilc    Model                2   3.88381429   1.94190714    1.99 0.1440
 2     ilc    Error               80  78.23190645   0.97789883     _    _
 3     ilc    Corrected Total     82  82.11572073    _             _    _

scaled average BE                                                         48
intermediate analysis - &dpar  glm

The GLM Procedure

   Class Level Information

Class         Levels    Values

SEQ                3    1 2 3


Number of Observations Read          83
Number of Observations Used          83

scaled average BE                                                         49
```

intermediate analysis - &dpar glm

The GLM Procedure

Dependent Variable: dlc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.9790956	0.9895478	0.65	0.5270
Error	80	122.5959020	1.5324488		
Corrected Total	82	124.5749976			

R-Square	Coeff Var	Root MSE	dlc Mean
0.015887	918.0817	1.237921	0.134838

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	1.97909559	0.98954779	0.65	0.5270

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	1.97909559	0.98954779	0.65	0.5270

output needed for mixed scaled av. BE - using glm 50

Obs	method_ used	unscabe_ lower	unscabe_ upper	dfi	s2i	param	StdErr
1	Scaled/PE	1.01823	1.45534	80	0.97790	LCMAX	0.10860612

Obs	pointest	x	boundx	ni	dfd	s2wr	nd	theta
1	1.22941	0.030862	0.14998	83	80	0.76622	83	0.79669

Obs	y	boundy	sWR	critbound	outcome
1	-0.61044	-0.47934	0.87534	-0.40245	PASS

final output - &parameter - using glm 51

Obs	method_ used	unscabe_ lower	unscabe_ upper	param	pointest	s2wr	sWR	critbound	outcome
1	Scaled/PE	1.01823	1.45534	LCMAX	1.22941	0.76622	0.87534	-0.40245	PASS

ANDA: 203286 Mesalamine Delayed Release Tablets USP STUDY TYPE: Fasting 52
SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Parameter	Geometric Means Test	Reference	T/R Ratio
LAUCT	2201.32	1871.79	1.18
LAUCI	2748.11	2387.03	1.15
LCMAX	182.43	149.86	1.22

ANDA: 203286 Mesalamine Delayed Release Tablets USP STUDY TYPE: Fasting 53
SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

90% CI Lower CI	Upper CI
100.02	138.29
98.59	134.44
101.82	145.53

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 54

Parameter	T/R Ratio	Lower 90% CI
LAUCT	1.18	100.02
LAUCI	1.17	98.59
LCMAX	1.23	101.82

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 55

Upper 90% CI	s2wr	sWR	Criteria Bound
138.29	0.6606511	0.8128045	-0.362881
134.44	0.4280562	0.6542601	-0.207455
145.53	0.7662244	0.8753424	-0.402449

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 56

Method Used	OUTCOME
Scaled/PE	PASS
Scaled/PE	PASS
Scaled/PE	PASS

4.6.3 Fed Study Codes

```
/*=============================================================================
=====
/ Program   : HVScale3Period.SAS
/ SubMacros :
/ Updated   : 15 Aug 2009
/ Purpose   : To analyze three period reference-scaled bioequivalence
studies.
/
/ Notes     : EXCEL DATA FILE MUST BE OPEN WHEN RUNNING THIS PROGRAM.
/                 : OUTPUT FILE (WORD DOCUMENT) CONTAINING SUMMARY TABLES IS
CREATED.
/
/=============================================================================
====
/ PARAMETERS:  THE FOLLOWING COLUMNS SHOULD BE IN THE INPUT DATASET (EXCEL
FILE).
/-------name------- ------------------------description---------------------
----
NAME OF VARIABLE
      SUBJ        SUBJECT NUMBER
      TRT               TREATMENT - CHARACTER (EITHER A OR B) A=TEST; B=REF
      SEQ               SEQUENCE NUMBER - NUMERIC (EITHER 1, 2, OR 3)
      PER               PERIOD NUMBER - NUMERIC (EITHER 1, 2, 3, OR 4)
      AUCT        AREA UNDER CURVE 0-T
      AUCI        AREA UNDER CURVE 0-INF
      CMAX        CMAX
      TMAX        TMAX
      KEL               ELIMINATION RATE CONSTANT
      THALF       HALF LIFE

      sequence 1        T     R     R
      sequence 2        R     T     R
      sequence 3        R     R     T

GROUP EFFECT:
Line 176:  If trt*grp interaction is not significant,
```

```
remove TRT*GROUP term from line 176.

/=============================================================================
====
/ AMENDMENT HISTORY:
/ Init --Date--  ----------------------Description-----------------------
/
/=============================================================================
====*/
options nofmterr nocenter nodate symbolgen mlogic macrogen mprint ps=65
ls=80;

*****STEP 1: ENTER ANDA INFORMATION *****;
%let drug= Mesalamine Delayed Release Tablets USP;
%let anda=203286;
%let studytype=FedALL;

*****STEP 2: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;


***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Documents and Settings\renp\My Documents\203286Mesalamine;

***** STEP 4:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
%let excelfile = &studydir\203286FedSAS.xls;

***** STEP 5:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING STUDY
DATA *****;
%let sheetname = FePK;

proc import datafile="&excelfile"
            out=base
            dbms=excel replace;
                  sheet="&sheetname";
                  getnames=yes;
                  mixed=yes;
run;



libname studylib "&studydir";

***** STEP 5:  PROVIDE NAMES OF THE VARIABLES TO READ IN FROM EXCEL FILE
*****;
***** PROVIDE STANDARD VARIABLE NAMES FROM THE PARAMETER LIST ABOVE *****;
***** VARIABLE NAMES: SUBJ TRT(A,B) SEQ(1,2) PER(1,2,3) AUCT AUCINF CMAX TMAX
KEL THALF ******;


data base;
  set base;
  /*sequence 1          T     R     R
      sequence 2        R     T     R
```

```
      sequence 3        R     R     T
  */

  IF SEQU="TR1R2" THEN SEQ=1;
  ELSE IF SEQU="R1TR2" THEN SEQ=2;
  ELSE IF SEQU="R1R2T" THEN SEQ=3;


  IF TREAT="T" THEN TRT="A";
  ELSE IF TREAT IN("R1","R2") THEN TRT="B";



run;

proc print data=base;
run;


*************************************************************************
;
          ***** DO NOT CHANGE ANYTHING BELOW THIS LINE *****;
*************************************************************************
;

data pk;
  set base;

  LAUCT=log(auct);
  LAUCINF=log(auci);
  LCMAX=log(cmax);

run;




data pkn;
  set pk;
run;

data full;
  set pkn;

run;

proc sort
  data=pkn;
  by seq subj per;



data test; set pkn; if trt='A'; latt=LAUCT; lait=LAUCINF; lct=LCMAX;
run;

data ref; set pkn; if trt='B';
run;
```

```
  /*sequence 1          T     R     R
      sequence 2        R     T     R
      sequence 3        R     R     T
  */
/*** ORIGINAL DON'S CODE ***
data ref1; set ref; if (seq=1 and per=1) or (seq=2 and per=2) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;
***/
data ref1; set ref; if (seq=1 and per=2) or (seq=2 and per=1) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lc1r=LCMAX;
run;

data ref2; set ref; if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and
per=2); lat2r=LAUCT; lai2r=LAUCINF; lc2r=LCMAX;
run;


title "ref1";
proc print data=ref1;
run;

title "ref2";
proc print data=ref2;
run;
title;

data scavbe; merge test ref1 ref2; by seq subj;
ilat=latt-(0.5*(lat1r+lat2r));  *auct;
ilai=lait-(0.5*(lai1r+lai2r));  *auci;
ilc=lct-(0.5*(lc1r+lc2r));      *cmax;

dlat=lat1r-lat2r;  *auct;
dlai=lai1r-lai2r;  *auci;
dlc=lc1r-lc2r;     *cmax;
keep seq subj per trt ilat dlat ilai dlai ilc dlc;
run;

proc print data=scavbe;
title1 'dataset for scaled average BE';
run;

%macro calc(param,no);

      PROC MIXED data=pkn;
      CLASSES GROUP SEQ SUBJ PER TRT;
      MODEL &param = GROUP SEQ GROUP*SEQ PER(GROUP) TRT TRT*GROUP /
DDFM=SATTERTH;
      RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
      REPEATED/GRP=TRT SUB=SUBJ;

      lsmeans trt; /* DEV */
      ods output lsmeans=lsm&param(keep=trt estimate); /* DEV */
      ods output Estimates=unsc&no;
      title1 'unscaled BE 90% CI - guidance version';
      run;
```

```
      DATA UPARAM&NO(KEEP=PARAMETER LCI UCI);
        SET UNSC&NO;

        ESTIMATE = 100 * EXP(ESTIMATE);
        PARAMETER = "&PARAM";
        LCI = 100 * EXP(LOWER);
        UCI = 100 * EXP(UPPER);
      RUN;

   *** for scaled dataset***;
      DATA UNSC&PARAM;
        SET UNSC&NO;
      RUN;

%mend calc;

%calc(LCMAX,1);
%calc(LAUCT,2);


**** ESTIMATES ****;
DATA LSMLAUCT;
  SET LSMLAUCT;
  PARAMETER = "LAUCT";
RUN;

DATA LSMLAUCINF;
  SET LSMLAUCINF;
  PARAMETER = "LAUCI";
RUN;

DATA LSMLCMAX;
  SET LSMLCMAX;
  PARAMETER = "LCMAX";
RUN;

DATA UESTIMATE;
  SET LSMLAUCT LSMLAUCINF LSMLCMAX;
RUN;

DATA UESTIMATE;
  SET UESTIMATE;

  GEOMEAN = EXP(ESTIMATE);
RUN;

PROC SORT
  DATA=UESTIMATE;
  BY PARAMETER;
RUN;

PROC TRANSPOSE
  DATA=UESTIMATE
  OUT=TRANSUEST(DROP=_NAME_);
  VAR GEOMEAN;
  BY PARAMETER;
```

```
  ID TRT;
RUN;

DATA UEST;
  SET TRANSUEST;

  RATIO = ROUND((A/B),.01);
RUN;

DATA UALL;
  SET UPARAM1 UPARAM2 UPARAM3;
RUN;

PROC SORT
  DATA=UALL;
  BY PARAMETER;
RUN;

PROC SORT
  DATA=UEST;
  BY PARAMETER;
RUN;

DATA UPARAMS;
  MERGE UEST
        UALL;
  BY PARAMETER;
RUN;

*** PROPER ORDER AUCT, AUCI, CMAX ***;
DATA UPARAMS;
  SET UPARAMS;

  IF PARAMETER = "LAUCT" THEN ORDER=1;
  ELSE IF PARAMETER = "LAUCI" THEN ORDER=2;
  ELSE IF PARAMETER = "LCMAX" THEN ORDER=3;
RUN;

PROC SORT
  DATA=UPARAMS;
  BY ORDER;
RUN;



proc template;
  define style mystyle1;
  parent = styles.rtf;
    REPLACE fonts /

       'docFont' = ("Arial", 8pt)
     'TitleFont2' = ("Arial",8pt,Bold)
       'TitleFont' = ("Arial",8pt,Bold)
       'StrongFont' = ("Arial",8pt,Bold)
       'EmphasisFont' = ("Arial",8pt)
       'FixedEmphasisFont' = ("Arial",8pt)
```

```
        'FixedStrongFont' = ("Arial",8pt,Bold)
        'FixedHeadingFont' = ("Arial",8pt,Bold)
        'BatchFixedFont' = ("Arial",8pt)
        'FixedFont' = ("Arial",8pt)
        'headingEmphasisFont' = ("Arial",8pt,Bold);

    style SysTitleAndFooterContainer from Container /

      cellpadding = 2
      cellspacing = 2
      borderwidth = 0;

      REPLACE Body from Document /
        bottommargin = 1.0in
        topmargin = 1.0in
        rightmargin = 1in
        leftmargin = 1in;
  END;
run;



/*
data unsc1; set unsc1; unscabe_lower=exp(lower); unscabe_upper=exp(upper);
keep unscabe_lower unscabe_upper; run;
*/


***** SCALED ANALYSIS *****;

%MACRO SCALE(parameter, ipar, dpar);

      proc glm data=scavbe;
      class seq;
      model &ipar =seq/clparm alpha=0.1;
      estimate 'average' intercept 1 seq 0.3333333333 0.3333333333
0.3333333333;
      ods output overallanova=iglm&ipar.1;
      ods output Estimates=iglm&ipar.2;
      ods output NObs=iglm&ipar.3;
      title1 'scaled average BE';
      title2 'intermediate analysis - &ipar glm';
      run;

title "dev iglm&ipar.1";
proc print data=iglm&ipar.1;
run;


      proc glm data=scavbe;
      class seq;
      model &dpar =seq;
      ods output overallanova=dglm&dpar.1;
      ods output NObs=dglm&dpar.3;
      title1 'scaled average BE';
      title2 'intermediate analysis - &dpar  glm';
```

```
      run;

      data unsc&PARAMETER; set unsc&PARAMETER; unscabe_lower=exp(lower);
unscabe_upper=exp(upper);
      keep unscabe_lower unscabe_upper;
      run;


      data iglm&ipar.1; set iglm&ipar.1; if _n_=2; dfi=df; s2i=ms; keep dfi
s2i param;
      param = "&parameter";
    run;

      data iglm&ipar.2; set iglm&ipar.2; pointest=exp(estimate);
x=(estimate**2)-(stderr**2);
      boundx=(max((abs(LowerCL)),(abs(UpperCL))))**2;
      keep pointest x boundx stderr param;
      param = "&parameter";
    run;

      data iglm&ipar.3; set iglm&ipar.3; if _n_ = 2; ni=NobsUsed; keep ni
param;
      param = "&parameter";
   run;

      data dglm&dpar.1; set dglm&dpar.1; if _n_=2; dfd=df; s2wr=ms/2; keep
dfd s2wr param;
      param = "&parameter";
    run;

      data dglm&dpar.3; set dglm&dpar.3; if _n_ = 2; nd=NobsUsed; keep nd
param;
      param = "&parameter";
    run;

      data idallglm&parameter;
        length method_used $15;
      merge unsc&parameter iglm&ipar.1 iglm&ipar.2 iglm&ipar.3 dglm&dpar.1
dglm&dpar.3;

boundy=y*dfd/cinv(0.95,dfd); sWR=sqrt(s2wr);
      critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
      outcome='FAIL';
      if (s2wr < 0.086436) then method_used='Unscaled'; else
method_used='Scaled/PE';
      if ((s2wr < 0.086436) and (unscabe_lower ge 0.8) and (unscabe_upper le
1.25)) then outcome='PASS';
      if ((s2wr ge 0.086436) and (pointest ge 0.8) and (pointest le 1.25) and
(critbound le 0)) then outcome='PASS';
*     else outcome='FAIL';
  run;

      proc print data=idallglm&parameter;
      title1 'output needed for mixed scaled av. BE - using glm';
      run;

      data finalglm; set idallglm&parameter;
```

```
      keep param s2wr sWR unscabe_lower unscabe_upper pointest critbound
outcome method_used;
      run;

      proc print data=finalglm;
      title1 'final output - &parameter - using glm';
      run;

%mend scale;

%scale(LAUCT, ilat, dlat);
%scale(LAUCINF, ilai, dlai);


data all;
  set idallglmLAUCT
      idallglmLAUCINF
        idallglmLCMAX;

       unscabe lower = round((unscabe lower*100),.01);
       unscabe_upper = round((unscabe_upper*100),.01);

run;

ods rtf file="&studydir\&ANDA.-ANALYSIS.doc" style=mystyle1 bodytitle;

**** ARITHMETIC MEANS *****;
/*
footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)";
proc report data=pkratio1 nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)";
proc report data=pkratio2 nowd split='\' box
```

```
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)";
proc report data=pkratio3 nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;
*/


*** UNSCALED ANALYSIS REPORT *****;
title1 "ANDA: &anda    &drug    STUDY TYPE: &STUDYTYPE";
title2 "SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA";

      proc report
        data=uparams
```

```
        headline
        headskip
        nowd
        split="|" box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

        column parameter ("Geometric Means|" a b) ratio ("90% CI|" lci uci);

        define parameter /display "Parameter" width=20 center;
        define a              /display "Test"       width=15 center
format=8.2;
        define b              /display "Reference" width=15 center
format=8.2;
        define ratio          /display "T/R Ratio" width=15 center
format=8.2;
        define lci            /display "Lower CI" width=20 center format=8.2;
        define uci            /display "Upper CI" width=20 center format=8.2;
      run;


***** SCALED ANALYSIS REPORT *****;
title1 "SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA";

      proc report
        data=all
        headline
        headskip
        nowd
        split='|' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

        column param pointest unscabe_lower unscabe_upper s2wr swr critbound
method_used outcome;


        define param /display "Parameter" width=20 center;
        define pointest   /display "T/R Ratio" width=15 center format=8.2;
        define unscabe_lower /display "Lower|90% CI" width=20 center
format=8.2;
        define unscabe_upper /display "Upper|90% CI" width=20 center
format=8.2;
        define s2wr /display "s2wr" width=15 center;
        define swr /display "sWR" width=15 center;
        define critbound /display "Criteria Bound" width=15 center;
        define method used /display "Method Used" width=25 center;
        define outcome /display "OUTCOME" width=15 center;

      run;

ods rtf close;
```

4.6.4 Fed Study Output

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 48

Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE	THALF	SEQ	TRT
1	(b) (6)	1	R1R2T	1	R1	3834.63	3916.77	408.00	28	0.3365	2.06	3	B
2		1	R1R2T	2	R2	3330.45	3575.4	212.30	28	0.1199	5.78	3	B
3		1	R1R2T	3	T	1928.01	1959.09	679.60	12	0.1304	5.32	3	A
4		1	R1TR2	1	R1	258.81	.	58.93	24	.	.	2	B
5		1	R1TR2	2	T	1530.85	1554.76	94.44	24	0.0965	7.18	2	A
6		1	R1TR2	3	R2	649.59	.	73.95	36	.	.	2	B
7		1	TR1R2	1	T	5633.45	5661.88	286.70	13	0.1077	6.43	1	A
8		1	TR1R2	2	R1	1658.20	1716.9	86.84	24	0.0738	9.39	1	B
9		1	TR1R2	3	R2	2768.72	2795.33	67.17	36	0.0578	11.98	1	B
10		2	R1R2T	1	R1	1375.01	1520.78	90.53	24	0.0799	8.67	3	B
11		2	R1R2T	2	R2	3650.62	3680.96	612.40	8	0.274	2.53	3	B
12		2	R1R2T	3	T	1847.50	1881.34	108.90	7	0.1553	4.46	3	A
13		1	R1TR2	1	R1	8281.60	8304.09	2078.00	24	0.1	6.93	2	B
14		1	R1TR2	2	T	9047.96	9061.58	1909.00	24	0.1033	6.71	2	A
15		1	R1TR2	3	R2	13678.70	13698.8	4115.00	24	0.0541	12.82	2	B
16		1	TR1R2	1	T	3655.38	3684.93	273.30	32	0.1093	6.34	1	A
17		1	TR1R2	2	R1	16333.60	16355.7	3343.00	28	0.0632	10.97	1	B
18		1	TR1R2	3	R2	3458.51	3497.5	241.00	24	0.0938	7.39	1	B
19		1	R1TR2	1	R1	2224.95	2368.49	244.50	24	0.2173	3.19	2	B
20		1	R1TR2	2	T	2216.61	2302.15	226.80	12	0.243	2.85	2	A
21		1	R1TR2	3	R2	1819.58	1853.96	138.90	24	0.2603	2.66	2	B
22		1	R1R2T	1	R1	3871.22	3899.59	554.60	28	0.062	11.19	3	B
23		1	R1R2T	2	R2	3381.44	3552.28	89.33	48	0.0383	18.11	3	B
24		1	R1R2T	3	T	1786.82	1873.29	75.49	36	0.0386	17.96	3	A
25		1	TR1R2	1	T	2761.86	4137.02	143.70	9	0.0348	19.92	1	A
26		1	TR1R2	2	R1	2325.32	2433.67	141.60	28	0.136	5.1	1	B
27		1	TR1R2	3	R2	4568.59	5839.97	226.30	24	0.0539	12.87	1	B
28		1	R1TR2	1	R1	6075.91	6104.88	2577.00	9	0.0766	9.04	2	B
29		1	R1TR2	2	T	8418.24	8431.81	3189.00	13	0.1701	4.07	2	A
30		1	R1TR2	3	R2	3060.05	.	249.00	28	.	.	2	B
31		1	R1R2T	1	R1	3051.10	9426.52	160.40	22	0.0152	45.74	3	B
32		1	R1R2T	2	R2	2801.21	.	273.50	32	.	.	3	B
33		1	R1R2T	3	T	2334.31	2352.56	171.90	18	0.1196	5.79	3	A
34		1	R1TR2	1	R1	1737.63	2603.65	355.50	24	0.0561	12.35	2	B
35		1	R1TR2	2	T	92.38	.	6.86	48	.	.	2	A
36		1	R1TR2	3	R2	6017.88	6111.11	1040.00	24	0.0975	7.11	2	B
37		1	TR1R2	1	T	1104.47	1287.57	71.16	28	0.0676	10.26	1	A
38		1	TR1R2	2	R1	1275.21	1462.72	75.76	13	0.0708	9.79	1	B
39		1	TR1R2	3	R2	1346.93	1573.32	94.76	28	0.082	8.45	1	B
40		1	R1TR2	1	R1	4438.02	4501.25	1083.00	22	0.0843	8.22	2	B
41		1	R1TR2	2	T	828.79	.	72.69	48	.	.	2	A
42		1	R1TR2	3	R2	1166.44	.	90.95	36	.	.	2	B
43		1	R1R2T	1	R1	9309.60	11377.3	1738.00	24	0.052	13.32	3	B

44	(b) (6)	1	R1R2T	2	R2	4455.87	4578.06	197.10	36	0.0844	8.22	3	B
45		1	R1R2T	3	T	2101.36	2119.13	82.62	48	0.0837	8.28	3	A
46		1	TR1R2	1	T	1659.50	3459.14	130.20	13	0.0384	18.04	1	A
47		1	TR1R2	2	R1	1538.95	1560.7	138.10	22	0.2042	3.39	1	B
48		1	TR1R2	3	R2	2028.64	2505.33	176.30	22	0.0908	7.64	1	B
49		1	R1R2T	1	R1	2803.98	.	191.70	36	.	.	3	B
50		1	R1R2T	2	R2	7040.32	7625.05	928.00	24	0.0617	11.23	3	B
51		1	R1R2T	3	T	2160.63	2177.51	156.60	36	0.1212	5.72	3	A
52		1	TR1R2	1	T	5933.88	6641.65	2428.00	11	0.0392	17.7	1	A
53		1	TR1R2	2	R1	2175.01	2273.33	101.60	18	0.0935	7.41	1	B
54		1	TR1R2	3	R2	1783.48	1801.97	170.80	32	0.091	7.62	1	B
55		1	R1TR2	1	R1	8454.90	8627.25	2364.00	24	0.069	10.05	2	B
56		1	R1TR2	2	T	16047.80	16102.5	4692.00	24	0.0884	7.84	2	A
57		1	R1TR2	3	R2	10262.60	10495.5	3181.00	24	0.042	16.52	2	B

Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE	THALF	SEQ	TRT
58	(b) (6)	1	TR1R2	1	T	8057.66	11530.8	2013.00	24.00	0.0171	40.5	1	A
59		1	TR1R2	2	R1	8028.52	8049.42	1960.00	22.00	0.095	7.29	1	B
60		1	TR1R2	3	R2	8250.24	8922.43	2035.00	24.00	0.0323	21.49	1	B
61		1	TR1R2	1	T	6566.37	6596.2	1809.00	22.00	0.1423	4.87	1	A
62		1	TR1R2	2	R1	2246.72	2278.53	703.70	22.00	0.1369	5.06	1	B
63		1	TR1R2	3	R2	1165.49	1192.25	169.90	22.03	0.0655	10.58	1	B
64		1	R1TR2	1	R1	4269.53	4281.5	256.30	11.00	0.1246	5.56	2	B
65		1	R1TR2	2	T	6123.77	6202.55	389.90	28.00	0.0863	8.03	2	A
66		1	R1TR2	3	R2	6010.40	6849.49	238.80	22.00	0.0432	16.06	2	B
67		1	R1TR2	1	R1	363.80	.	88.78	24.00	.	.	2	B
68		1	R1TR2	2	T	15.19	.	4.19	22.00	.	.	2	A
69		1	R1TR2	3	R2	78.37	.	16.95	24.00	.	.	2	B
70		1	R1R2T	1	R1	4432.67	4511.17	662.10	24.00	0.1476	4.69	3	B
71		1	R1R2T	2	R2	5247.50	5257.84	364.40	9.00	0.4911	1.41	3	B
72		1	R1R2T	3	T	1509.17	1524.34	133.80	32.00	0.2238	3.1	3	A
73		1	R1R2T	1	R1	2003.30	2013.53	103.50	22.00	0.2276	3.04	3	B
74		1	R1R2T	2	R2	2143.35	2205.53	95.90	24.00	0.1482	4.68	3	B
75		1	R1R2T	3	T	1355.75	.	175.20	32.00	.	.	3	A
76		1	TR1R2	1	T	4576.13	4615.35	436.50	24.00	0.0487	14.24	1	A
77		1	TR1R2	2	R1	766.13	1847.93	48.78	32.00	0.0258	26.88	1	B
78		1	TR1R2	3	R2	1020.95	.	83.74	36.00	.	.	1	B
79		1	R1TR2	1	R1	142.63	.	38.01	28.00	.	.	2	B
80		1	R1TR2	2	T	2306.11	6052.88	182.40	11.00	0.0151	45.89	2	A
81		1	R1TR2	3	R2	1701.26	1806.09	111.70	28.00	0.1157	5.99	2	B
82		1	TR1R2	1	T	3431.00	3918.57	200.20	32.00	0.0426	16.27	1	A
83		1	TR1R2	2	R1	48.62	.	16.14	22.00	.	.	1	B
84		1	TR1R2	3	R2	985.96	.	109.60	36.00	.	.	1	B
85		1	R1TR2	1	R1	1846.87	2201.01	196.20	24.00	0.0152	45.66	2	B
86		1	R1TR2	2	T	5707.98	5813.12	918.80	24.00	0.0418	16.6	2	A
87		1	R1TR2	3	R2	3249.96	3392.24	443.90	22.00	0.0334	20.76	2	B
88		1	R1R2T	1	R1	113.91	248.43	6.07	9.00	0.0121	57.24	3	B
89		1	R1R2T	2	R2	93.42	134.489	5.90	8.00	0.046	15.06	3	B
90		1	R1R2T	3	T	2901.11	.	159.90	48.17	.	.	3	A
91		1	R1TR2	1	R1	787.36	792.674	122.40	28.00	0.4831	1.43	2	B

Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE	THALF	SEQ	TRT
92	(b) (6)	1	R1TR2	2	T	1626.91	1632.73	607.30	9.00	0.2042	3.39	2	A
93		1	R1TR2	3	R2	3283.14	3616.73	1099.00	11.00	0.0336	20.65	2	B
94		2	TR1R2	1	T	1489.55	1530.62	419.00	9.05	0.0291	23.83	1	A
95		2	TR1R2	2	R1	1315.30	1354.81	216.00	10.00	0.0266	26.05	1	B
96		2	TR1R2	3	R2	1538.74	1580.5	119.30	14.00	0.0548	12.65	1	B
97		1	R1R2T	1	R1	5011.73	5033.85	816.90	24.00	0.0778	8.91	3	B
98		1	R1R2T	2	R2	10553.70	10689	2942.00	24.03	0.0288	24.08	3	B
99		1	R1R2T	3	T	6149.41	6195.63	1548.00	24.00	0.036	19.26	3	A
100		1	TR1R2	1	T	149.62	263.219	15.89	32.00	0.0485	14.29	1	A
101		1	TR1R2	2	R1	1499.04	.	127.30	32.00	.	.	1	B
102		1	TR1R2	3	R2	1868.14	1971.05	110.30	28.00	0.2061	3.36	1	B
103		2	R1R2T	1	R1	3077.79	.	210.70	36.00	.	.	3	B
104		2	R1R2T	2	R2	2633.66	2673.03	415.70	24.00	0.1648	4.21	3	B
105		2	R1R2T	3	T	2779.09	2784.82	214.60	32.00	0.3138	2.21	3	A
106		2	TR1R2	1	T	2718.56	2795.01	147.00	36.00	0.0858	8.08	1	A
107		2	TR1R2	2	R1	3011.82	3219.94	154.00	32.00	0.0443	15.66	1	B
108		2	TR1R2	3	R2	2347.91	2396.73	171.10	32.00	0.0379	18.27	1	B
109		2	R1TR2	1	R1	2376.31	3053.53	288.70	28.00	0.1396	4.97	2	B
110		2	R1TR2	2	T	5073.49	.	444.30	36.00	.	.	2	A
111		2	R1TR2	3	R2	5893.15	8170.91	247.20	18.00	0.0372	18.61	2	B
112		2	R1R2T	1	R1	1110.19	1232.37	138.20	24.00	0.1615	4.29	3	B
113		2	R1R2T	2	R2	1812.56	1978.82	415.60	11.00	0.1034	6.7	3	B
114		2	R1R2T	3	T	520.57	551.357	147.40	22.00	0.1566	4.43	3	A

Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE	THALF	SEQ	TRT
115	(b) (6)	2	R1TR2	1	R1	2871.51	3294.97	727.50	9.00	0.0783	8.86	2	B
116		2	R1TR2	2	T	4588.80	4608.36	739.00	9.00	0.1437	4.82	2	A
117		2	R1TR2	3	R2	7553.40	7613.46	2949.00	12.00	0.1505	4.61	2	B
118		2	TR1R2	1	T	3505.41	3621.38	400.90	24.00	0.2527	2.74	1	A
119		2	TR1R2	2	R1	2136.54	2150.48	293.60	12.00	0.0801	8.66	1	B
120		2	TR1R2	3	R2	64.02	72.4269	20.20	8.00	0.1256	5.52	1	B
121		2	R1R2T	1	R1	1663.63	1726.37	353.10	22.00	0.1266	5.48	3	B
122		2	R1R2T	2	R2	2041.29	2092.77	564.30	22.00	0.1142	6.07	3	B
123		2	R1R2T	3	T	827.66	829.973	200.00	28.00	0.6178	1.12	3	A
124		2	R1TR2	1	R1	14765.10	14865.9	2573.00	24.00	0.1021	6.79	2	B
125		2	R1TR2	2	T	3793.76	5791.66	522.70	24.00	0.0421	16.47	2	A
126		2	R1TR2	3	R2	13262.60	13299	2538.00	24.00	0.2044	3.39	2	B
127		2	TR1R2	1	T	1113.69	.	94.83	36.00	.	.	1	A
128		2	TR1R2	2	R1	2641.73	2856.12	196.10	32.00	0.125	5.55	1	B
129		2	TR1R2	3	R2	7423.42	7432.25	1727.00	24.00	0.2011	3.45	1	B
130		2	R1R2T	1	R1	6550.04	6936.29	346.40	28.00	0.0527	13.14	3	B
131		2	R1R2T	2	R2	800.85	850.919	431.60	14.00	0.0306	22.68	3	B
132		2	R1R2T	3	T	5701.72	5711.32	671.30	24.00	0.2851	2.43	3	A
133		2	R1TR2	1	R1	3695.27	5434.75	1802.00	10.00	0.0093	74.75	2	B
134		2	R1TR2	2	T	11088.20	11120.8	3586.00	22.00	0.0323	21.49	2	A
135		2	R1TR2	3	R2	3607.57	3637.83	949.00	8.00	0.0475	14.61	2	B
136		2	R1R2T	1	R1	1918.11	.	58.91	48.00	.	.	3	B
137		2	R1R2T	2	R2	2303.82	2887.53	495.10	24.00	0.0657	10.55	3	B
138		2	R1R2T	3	T	946.07	.	72.27	48.00	.	.	3	A
139		2	R1TR2	1	R1	7933.51	8012.48	298.90	28.00	0.0476	14.56	2	B

140	(b) (6)	2	R1TR2	2	T	2430.23	2444.71	295.40	20.00	0.1228	5.64	2	A
141		2	R1TR2	3	R2	6037.90	6061.26	287.30	28.00	0.0817	8.49	2	B
142		2	TR1R2	1	T	3898.93	3927.25	1075.00	16.00	0.1771	3.91	1	A
143		2	TR1R2	2	R1	3718.90	4001.71	258.30	24.00	0.1084	6.39	1	B
144		2	TR1R2	3	R2	4553.82	4569.42	308.60	24.12	0.2425	2.86	1	B
145		2	TR1R2	1	T	3278.74	3370.46	919.70	12.00	0.025	27.69	1	A
146		2	TR1R2	2	R1	2904.10	4540.12	166.10	24.00	0.0392	17.67	1	B
147		2	TR1R2	3	R2	6797.01	6849.38	3470.00	11.00	0.0236	29.39	1	B
148		2	R1TR2	1	R1	7751.51	7780.96	2820.00	9.00	0.0764	9.07	2	B
149		2	R1TR2	2	T	3283.46	3290.73	968.20	9.00	0.407	1.7	2	A
150		2	R1TR2	3	R2	637.62	643.129	63.95	24.00	0.1926	3.6	2	B
151		2	TR1R2	1	T	3061.59	3121.43	116.90	36.00	0.0449	15.44	1	A
152		2	TR1R2	2	R1	2551.11	2586.53	107.20	36.00	0.0519	13.36	1	B
153		2	TR1R2	3	R2	4499.02	4908.76	342.30	22.00	0.0308	22.52	1	B
154		2	R1TR2	1	R1	1279.51	1491.05	64.83	36.00	0.0243	28.54	2	B
155		2	R1TR2	2	T	4333.79	4437.6	201.40	24.00	0.0513	13.51	2	A
156		2	R1TR2	3	R2	5420.99	6078.85	1436.00	13.05	0.0363	19.07	2	B
157		2	TR1R2	1	T	3022.92	3070.81	633.80	9.00	0.0693	10	1	A
158		2	TR1R2	2	R1	3571.20	3603.28	1143.00	10.00	0.1101	6.29	1	B
159		2	TR1R2	3	R2	465.48	480.591	63.75	24.00	0.2502	2.77	1	B
160		2	R1TR2	1	R1	2146.19	2158.76	117.60	32.00	0.1185	5.85	2	B
161		2	R1TR2	2	T	5655.68	5670.06	1489.00	17.00	0.1128	6.15	2	A
162		2	R1TR2	3	R2	1442.28	1669.48	90.98	22.00	0.0775	8.95	2	B
163		2	R1R2T	1	R1	3489.98	3505.59	624.00	8.00	0.0708	9.79	3	B
164		2	R1R2T	2	R2	8885.70	8903.41	2557.00	8.00	0.0588	11.79	3	B
165		2	R1R2T	3	T	5731.30	6323	1011.00	9.00	0.0249	27.82	3	A
166		2	TR1R2	1	T	7948.12	10452.6	177.50	48.00	0.0232	29.83	1	A
167		2	TR1R2	2	R1	5434.97	5441.2	1374.00	13.00	0.5036	1.38	1	B
168		2	TR1R2	3	R2	1412.80	1989.56	28.03	36.00	0.0142	48.95	1	B
169		2	R1TR2	1	R1	2119.26	2138.31	102.90	36.00	0.1096	6.32	2	B
170		2	R1TR2	2	T	3103.14	.	354.00	36.00	.	.	2	A
171		2	R1TR2	3	R2	3136.38	3289.99	830.80	11.00	0.096	7.22	2	B

Obs	SUBJ	Group	SEQU	PER	Treat	AUC	AUCI	CMAX	TMAX	KE	THALF	SEQT
172	(b) (6)	2	TR1R2	1	T	8.99	71.5999	1.51	15.00	0.0214	32.32	1 A
173		2	TR1R2	2	R1	2858.70	2884.6	756.60	10.00	0.1493	4.64	1 B
174		2	TR1R2	3	R2	11422.00	11447.8	3689.00	13.00	0.2365	2.93	1 B
175		2	R1R2T	1	R1	3085.80	3188.74	230.70	32.00	0.0831	8.34	3 B
176		2	R1R2T	2	R2	5344.55	17470.1	280.90	24.00	0.0127	54.51	3 B
177		2	R1R2T	3	T	5568.16	5902.5	233.50	36.00	0.0456	15.2	3 A
178		2	R1TR2	1	R1	1600.45	2275.23	113.30	32.00	0.0653	10.61	2 B
179		2	R1TR2	2	T	5357.90	5837.54	881.80	22.00	0.1052	6.59	2 A
180		2	R1TR2	3	R2	1273.07	.	275.70	22.00	.	.	2 B
181		2	R1R2T	1	R1	1661.92	1680.85	526.20	22.00	0.1739	3.99	3 B
182		2	R1R2T	2	R2	1709.58	1731.74	135.70	12.00	0.1763	3.93	3 B
183		2	R1R2T	3	T	726.70	763.802	85.68	32.00	0.1631	4.25	3 A
184		2	TR1R2	1	T	10307.20	10354.1	2890.00	22.00	0.1427	4.86	1 A
185		2	TR1R2	2	R1	144.64	151.693	35.67	22.00	0.2013	3.44	1 B
186		2	TR1R2	3	R2	2715.30	.	217.90	36.00	.	.	1 B
187		2	R1R2T	1	R1	3242.60	3250.07	211.10	24.00	0.282	2.46	3 B

	(b) (6)												
188		2	R1R2T	2	R2	2097.78	2117.28	81.97	10.00	0.0767	9.04	3	B
189		2	R1R2T	3	T	1136.86	1284.57	174.00	9.00	0.0551	12.59	3	A
190		2	R1TR2	1	R1	4212.26	4225.54	1396.00	10.17	0.2199	3.15	2	B
191		2	R1TR2	2	T	1315.24	1323.35	124.60	24.00	0.4265	1.63	2	A
192		2	R1TR2	3	R2	1717.40	1728.3	434.50	13.00	0.1426	4.86	2	B
193		2	R1R2T	1	R1	3390.43	3399.17	1444.00	11.00	0.3039	2.28	3	B
194		2	R1R2T	2	R2	63.77	70.3547	17.75	22.00	0.3407	2.03	3	B
195		2	R1R2T	3	T	513.05	522.257	73.85	20.00	0.286	2.42	3	A
196		2	TR1R2	1	T	1225.40	1238.15	156.80	10.00	0.1355	5.12	1	A
197		2	TR1R2	2	R1	950.14	986.789	73.71	28.00	0.2571	2.7	1	B
198		2	TR1R2	3	R2	1561.27	1572.04	151.50	20.00	0.4289	1.62	1	B
199		2	R1TR2	1	R1	4147.04	4301.32	110.60	28.00	0.035	19.79	2	B
200		2	R1TR2	2	T	5995.94	6167.76	1100.00	15.00	0.022	31.57	2	A
201		2	R1TR2	3	R2	8710.68	8930.34	2424.00	14.00	0.0185	37.54	2	B
202		2	R1R2T	1	R1	2144.74	2164.4	139.20	28.00	0.2156	3.22	3	B
203		2	R1R2T	2	R2	1080.29	1182.77	324.20	7.00	0.0708	9.8	3	B
204		2	R1R2T	3	T	3749.69	3785.66	543.20	15.00	0.2097	3.31	3	A
205		2	R1TR2	1	R1	3650.57	4116.52	220.40	32.00	0.1011	6.86	2	B
206		2	R1TR2	2	T	2749.29	.	142.50	36.00	.	.	2	A
207		2	R1TR2	3	R2	3363.01	3561.33	232.90	28.00	0.1289	5.38	2	B
208		2	TR1R2	1	T	3641.42	3649.14	1332.00	10.00	0.2732	2.54	1	A
209		2	TR1R2	2	R1	3726.99	4001.95	457.00	24.00	0.1338	5.18	1	B
210		2	TR1R2	3	R2	1974.27	2075.49	258.00	24.00	0.1959	3.54	1	B

Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE
1	(b) (6)	1	TR1R2	2	R1	1658.20	1716.9	86.84	24.00	0.0738
2		1	TR1R2	2	R1	16333.60	16355.7	3343.00	28.00	0.0632
3		1	TR1R2	2	R1	2325.32	2433.67	141.60	28.00	0.136
4		1	TR1R2	2	R1	1275.21	1462.72	75.76	13.00	0.0708
5		1	TR1R2	2	R1	1538.95	1560.7	138.10	22.00	0.2042
6		1	TR1R2	2	R1	2175.01	2273.33	101.60	18.00	0.0935
7		1	TR1R2	2	R1	8028.52	8049.42	1960.00	22.00	0.095
8		1	TR1R2	2	R1	2246.72	2278.53	703.70	22.00	0.1369
9		1	TR1R2	2	R1	766.13	1847.93	48.78	32.00	0.0258
10		1	TR1R2	2	R1	48.62	.	16.14	22.00	.
11		2	TR1R2	2	R1	1315.30	1354.81	216.00	10.00	0.0266
12		1	TR1R2	2	R1	1499.04	.	127.30	32.00	.
13		2	TR1R2	2	R1	3011.82	3219.94	154.00	32.00	0.0443
14		2	TR1R2	2	R1	2136.54	2150.48	293.60	12.00	0.0801
15		2	TR1R2	2	R1	2641.73	2856.12	196.10	32.00	0.125
16		2	TR1R2	2	R1	3718.90	4001.71	258.30	24.00	0.1084
17		2	TR1R2	2	R1	2904.10	4540.12	166.10	24.00	0.0392
18		2	TR1R2	2	R1	2551.11	2586.53	107.20	36.00	0.0519
19		2	TR1R2	2	R1	3571.20	3603.28	1143.00	10.00	0.1101
20		2	TR1R2	2	R1	5434.97	5441.2	1374.00	13.00	0.5036
21		2	TR1R2	2	R1	2858.70	2884.6	756.60	10.00	0.1493
22		2	TR1R2	2	R1	144.64	151.693	35.67	22.00	0.2013
23		2	TR1R2	2	R1	950.14	986.789	73.71	28.00	0.2571
24		2	TR1R2	2	R1	3726.99	4001.95	457.00	24.00	0.1338
25		1	R1TR2	1	R1	258.81	.	58.93	24.00	.
26		1	R1TR2	1	R1	8281.60	8304.09	2078.00	24.00	0.1
27		1	R1TR2	1	R1	2224.95	2368.49	244.50	24.00	0.2173
28		1	R1TR2	1	R1	6075.91	6104.88	2577.00	9.00	0.0766
29		1	R1TR2	1	R1	1737.63	2603.65	355.50	24.00	0.0561

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
1	9.39	1	B	7.41349	7.44828	4.46407	7.41349	7.44828	4.46407
2	10.97	1	B	9.70098	9.70233	8.11462	9.70098	9.70233	8.11462
3	5.1	1	B	7.75161	7.79716	4.95301	7.75161	7.79716	4.95301
4	9.79	1	B	7.15087	7.28805	4.32757	7.15087	7.28805	4.32757
5	3.39	1	B	7.33886	7.35289	4.92798	7.33886	7.35289	4.92798
6	7.41	1	B	7.68479	7.72900	4.62104	7.68479	7.72900	4.62104
7	7.29	1	B	8.99076	8.99336	7.58070	8.99076	8.99336	7.58070
8	5.06	1	B	7.71723	7.73129	6.55635	7.71723	7.73129	6.55635
9	26.88	1	B	6.64135	7.52182	3.88732	6.64135	7.52182	3.88732
10	.	1	B	3.88402	.	2.78130	3.88402	.	2.78130
11	26.05	1	B	7.18182	7.21142	5.37528	7.18182	7.21142	5.37528
12	.	1	B	7.31258	.	4.84655	7.31258	.	4.84655
13	15.66	1	B	8.01030	8.07712	5.03695	8.01030	8.07712	5.03695
14	8.66	1	B	7.66694	7.67345	5.68222	7.66694	7.67345	5.68222
15	5.55	1	B	7.87919	7.95722	5.27862	7.87919	7.95722	5.27862
16	6.39	1	B	8.22118	8.29448	5.55412	8.22118	8.29448	5.55412
17	17.67	1	B	7.97388	8.42071	5.11259	7.97388	8.42071	5.11259
18	13.36	1	B	7.84428	7.85807	4.67470	7.84428	7.85807	4.67470
19	6.29	1	B	8.18066	8.18960	7.04141	8.18066	8.18960	7.04141
20	1.38	1	B	8.60061	8.60175	7.22548	8.60061	8.60175	7.22548

21	4.64	1	B	7.95812	7.96714	6.62883	7.95812	7.96714	6.62883
22	3.44	1	B	4.97425	5.02186	3.57431	4.97425	5.02186	3.57431
23	2.7	1	B	6.85661	6.89446	4.30014	6.85661	6.89446	4.30014
24	5.18	1	B	8.22336	8.29454	6.12468	8.22336	8.29454	6.12468
25	.	2	B	5.55609	.	4.07635	5.55609	.	4.07635
26	6.93	2	B	9.02179	9.02450	7.63916	9.02179	9.02450	7.63916
27	3.19	2	B	7.70749	7.77001	5.49922	7.70749	7.77001	5.49922
28	9.04	2	B	8.71209	8.71684	7.85438	8.71209	8.71684	7.85438
29	12.35	2	B	7.46028	7.86467	5.87353	7.46028	7.86467	5.87353

Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE
30	(b) (6)	1	R1TR2	1	R1	4438.02	4501.25	1083.00	22.00	0.0843
31		1	R1TR2	1	R1	8454.90	8627.25	2364.00	24.00	0.069
32		1	R1TR2	1	R1	4269.53	4281.5	256.30	11.00	0.1246
33		1	R1TR2	1	R1	363.80	.	88.78	24.00	.
34		1	R1TR2	1	R1	142.63	.	38.01	28.00	.
35		1	R1TR2	1	R1	1846.87	2201.01	196.20	24.00	0.0152
36		1	R1TR2	1	R1	787.36	792.674	122.40	28.00	0.4831
37		2	R1TR2	1	R1	2376.31	3053.53	288.70	28.00	0.1396
38		2	R1TR2	1	R1	2871.51	3294.97	727.50	9.00	0.0783
39		2	R1TR2	1	R1	14765.10	14865.9	2573.00	24.00	0.1021
40		2	R1TR2	1	R1	3695.27	5434.75	1802.00	10.00	0.0093
41		2	R1TR2	1	R1	7933.51	8012.48	298.90	28.00	0.0476
42		2	R1TR2	1	R1	7751.51	7780.96	2820.00	9.00	0.0764
43		2	R1TR2	1	R1	1279.51	1491.05	64.83	36.00	0.0243
44		2	R1TR2	1	R1	2146.19	2158.76	117.60	32.00	0.1185
45		2	R1TR2	1	R1	2119.26	2138.31	102.90	36.00	0.1096
46		2	R1TR2	1	R1	1600.45	2275.23	113.30	32.00	0.0653
47		2	R1TR2	1	R1	4212.26	4225.54	1396.00	10.17	0.2199
48		2	R1TR2	1	R1	4147.04	4301.32	110.60	28.00	0.035
49		2	R1TR2	1	R1	3650.57	4116.52	220.40	32.00	0.1011
50		1	R1R2T	1	R1	3834.63	3916.77	408.00	28.00	0.3365
51		2	R1R2T	1	R1	1375.01	1520.78	90.53	24.00	0.0799
52		1	R1R2T	1	R1	3871.22	3899.59	554.60	28.00	0.062
53		1	R1R2T	1	R1	3051.10	9426.52	160.40	22.00	0.0152
54		1	R1R2T	1	R1	9309.60	11377.3	1738.00	24.00	0.052
55		1	R1R2T	1	R1	2803.98	.	191.70	36.00	.
56		1	R1R2T	1	R1	4432.67	4511.17	662.10	24.00	0.1476
57		1	R1R2T	1	R1	2003.30	2013.53	103.50	22.00	0.2276
58		1	R1R2T	1	R1	113.91	248.43	6.07	9.00	0.0121

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
30	8.22	2	B	8.39796	8.41211	6.98749	8.39796	8.41211	6.98749
31	10.05	2	B	9.04250	9.06268	7.76811	9.04250	9.06268	7.76811
32	5.56	2	B	8.35926	8.36206	5.54635	8.35926	8.36206	5.54635
33	.	2	B	5.89661	.	4.48616	5.89661	.	4.48616
34	.	2	B	4.96022	.	3.63785	4.96022	.	3.63785
35	45.66	2	B	7.52125	7.69667	5.27913	7.52125	7.69667	5.27913
36	1.43	2	B	6.66869	6.67541	4.80729	6.66869	6.67541	4.80729
37	4.97	2	B	7.77330	8.02405	5.66539	7.77330	8.02405	5.66539
38	8.86	2	B	7.96259	8.10015	6.58961	7.96259	8.10015	6.58961
39	6.79	2	B	9.60002	9.60683	7.85283	9.60002	9.60683	7.85283
40	74.75	2	B	8.21481	8.60057	7.49665	8.21481	8.60057	7.49665

41	14.56	2	B	8.97885	8.98876	5.70011	8.97885	8.98876	5.70011
42	9.07	2	B	8.95564	8.95944	7.94449	8.95564	8.95944	7.94449
43	28.54	2	B	7.15423	7.30724	4.17177	7.15423	7.30724	4.17177
44	5.85	2	B	7.67145	7.67729	4.76729	7.67145	7.67729	4.76729
45	6.32	2	B	7.65882	7.66777	4.63376	7.65882	7.66777	4.63376
46	10.61	2	B	7.37804	7.72984	4.73004	7.37804	7.72984	4.73004
47	3.15	2	B	8.34575	8.34890	7.24137	8.34575	8.34890	7.24137
48	19.79	2	B	8.33015	8.36668	4.70592	8.33015	8.36668	4.70592
49	6.86	2	B	8.20264	8.32276	5.39544	8.20264	8.32276	5.39544
50	2.06	3	B	8.25183	8.27302	6.01127	8.25183	8.27302	6.01127
51	8.67	3	B	7.22622	7.32698	4.50568	7.22622	7.32698	4.50568
52	11.19	3	B	8.26132	8.26863	6.31825	8.26132	8.26863	6.31825
53	45.74	3	B	8.02326	9.15128	5.07767	8.02326	9.15128	5.07767
54	13.32	3	B	9.13880	9.33938	7.46049	9.13880	9.33938	7.46049
55	.	3	B	7.93880	.	5.25593	7.93880	.	5.25593
56	4.69	3	B	8.39676	8.41431	6.49542	8.39676	8.41431	6.49542
57	3.04	3	B	7.60255	7.60764	4.63957	7.60255	7.60764	4.63957
58	57.24	3	B	4.73536	5.51516	1.80352	4.73536	5.51516	1.80352

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Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE
59	(b) (6)	1	R1R2T	1	R1	5011.73	5033.85	816.90	24.00	0.0778
60		2	R1R2T	1	R1	3077.79	.	210.70	36.00	.
61		2	R1R2T	1	R1	1110.19	1232.37	138.20	24.00	0.1615
62		2	R1R2T	1	R1	1663.63	1726.37	353.10	22.00	0.1266
63		2	R1R2T	1	R1	6550.04	6936.29	346.40	28.00	0.0527
64		2	R1R2T	1	R1	1918.11	.	58.91	48.00	.
65		2	R1R2T	1	R1	3489.98	3505.59	624.00	8.00	0.0708
66		2	R1R2T	1	R1	3085.80	3188.74	230.70	32.00	0.0831
67		2	R1R2T	1	R1	1661.92	1680.85	526.20	22.00	0.1739
68		2	R1R2T	1	R1	3242.60	3250.07	211.10	24.00	0.282
69		2	R1R2T	1	R1	3390.43	3399.17	1444.00	11.00	0.3039
70		2	R1R2T	1	R1	2144.74	2164.4	139.20	28.00	0.2156

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat1r	lai1r	lc1r
59	8.91	3	B	8.51954	8.52394	6.70552	8.51954	8.52394	6.70552
60	.	3	B	8.03197	.	5.35044	8.03197	.	5.35044
61	4.29	3	B	7.01229	7.11669	4.92870	7.01229	7.11669	4.92870
62	5.48	3	B	7.41676	7.45378	5.86675	7.41676	7.45378	5.86675
63	13.14	3	B	8.78723	8.84452	5.84759	8.78723	8.84452	5.84759
64	.	3	B	7.55910	.	4.07601	7.55910	.	4.07601
65	9.79	3	B	8.15765	8.16211	6.43615	8.15765	8.16211	6.43615
66	8.34	3	B	8.03457	8.06738	5.44112	8.03457	8.06738	5.44112
67	3.99	3	B	7.41573	7.42705	6.26568	7.41573	7.42705	6.26568
68	2.46	3	B	8.08413	8.08643	5.35233	8.08413	8.08643	5.35233
69	2.28	3	B	8.12871	8.13129	7.27517	8.12871	8.13129	7.27517
70	3.22	3	B	7.67077	7.67990	4.93591	7.67077	7.67990	4.93591

Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE
1	(b) (6)	1	TR1R2	3	R2	2768.72	2795.33	67.17	36.00	0.0578
2		1	TR1R2	3	R2	3458.51	3497.5	241.00	24.00	0.0938
3		1	TR1R2	3	R2	4568.59	5839.97	226.30	24.00	0.0539
4		1	TR1R2	3	R2	1346.93	1573.32	94.76	28.00	0.082
5		1	TR1R2	3	R2	2028.64	2505.33	176.30	22.00	0.0908
6		1	TR1R2	3	R2	1783.48	1801.97	170.80	32.00	0.091
7		1	TR1R2	3	R2	8250.24	8922.43	2035.00	24.00	0.0323
8		1	TR1R2	3	R2	1165.49	1192.25	169.90	22.03	0.0655
9		1	TR1R2	3	R2	1020.95	.	83.74	36.00	.
10		1	TR1R2	3	R2	985.96	.	109.60	36.00	.
11		2	TR1R2	3	R2	1538.74	1580.5	119.30	14.00	0.0548
12		1	TR1R2	3	R2	1868.14	1971.05	110.30	28.00	0.2061
13		2	TR1R2	3	R2	2347.91	2396.73	171.10	32.00	0.0379
14		2	TR1R2	3	R2	64.02	72.4269	20.20	8.00	0.1256
15		2	TR1R2	3	R2	7423.42	7432.25	1727.00	24.00	0.2011
16		2	TR1R2	3	R2	4553.82	4569.42	308.60	24.12	0.2425
17		2	TR1R2	3	R2	6797.01	6849.38	3470.00	11.00	0.0236
18		2	TR1R2	3	R2	4499.02	4908.76	342.30	22.00	0.0308
19		2	TR1R2	3	R2	465.48	480.591	63.75	24.00	0.2502
20		2	TR1R2	3	R2	1412.80	1989.56	28.03	36.00	0.0142
21		2	TR1R2	3	R2	11422.00	11447.8	3689.00	13.00	0.2365
22		2	TR1R2	3	R2	2715.30	.	217.90	36.00	.
23		2	TR1R2	3	R2	1561.27	1572.04	151.50	20.00	0.4289
24		2	TR1R2	3	R2	1974.27	2075.49	258.00	24.00	0.1959
25		1	R1TR2	3	R2	649.59	.	73.95	36.00	.
26		1	R1TR2	3	R2	13678.70	13698.8	4115.00	24.00	0.0541
27		1	R1TR2	3	R2	1819.58	1853.96	138.90	24.00	0.2603
28		1	R1TR2	3	R2	3060.05	.	249.00	28.00	.
29		1	R1TR2	3	R2	6017.88	6111.11	1040.00	24.00	0.0975

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
1	11.98	1	B	7.92614	7.93571	4.20723	7.92614	7.93571	4.20723
2	7.39	1	B	8.14859	8.15980	5.48480	8.14859	8.15980	5.48480
3	12.87	1	B	8.42696	8.67248	5.42186	8.42696	8.67248	5.42186
4	8.45	1	B	7.20558	7.36094	4.55135	7.20558	7.36094	4.55135
5	7.64	1	B	7.61512	7.82618	5.17219	7.61512	7.82618	5.17219
6	7.62	1	B	7.48632	7.49664	5.14049	7.48632	7.49664	5.14049
7	21.49	1	B	9.01800	9.09632	7.61825	9.01800	9.09632	7.61825
8	10.58	1	B	7.06090	7.08360	5.13521	7.06090	7.08360	5.13521
9	.	1	B	6.92849	.	4.42772	6.92849	.	4.42772
10	.	1	B	6.89362	.	4.69684	6.89362	.	4.69684
11	12.65	1	B	7.33872	7.36550	4.78164	7.33872	7.36550	4.78164
12	3.36	1	B	7.53270	7.58632	4.70320	7.53270	7.58632	4.70320
13	18.27	1	B	7.76128	7.78186	5.14225	7.76128	7.78186	5.14225
14	5.52	1	B	4.15913	4.28258	3.00568	4.15913	4.28258	3.00568
15	3.45	1	B	8.91240	8.91358	7.45414	8.91240	8.91358	7.45414
16	2.86	1	B	8.42372	8.42714	5.73205	8.42372	8.42714	5.73205
17	29.39	1	B	8.82424	8.83191	8.15191	8.82424	8.83191	8.15191
18	22.52	1	B	8.41161	8.49878	5.83569	8.41161	8.49878	5.83569
19	2.77	1	B	6.14306	6.17502	4.15497	6.14306	6.17502	4.15497
20	48.95	1	B	7.25333	7.59567	3.33328	7.25333	7.59567	3.33328

21	2.93	1	B	9.34330	9.34555	8.21311	9.34330	9.34555	8.21311
22	.	1	B	7.90666	.	5.38404	7.90666	.	5.38404
23	1.62	1	B	7.35325	7.36013	5.02059	7.35325	7.36013	5.02059
24	3.54	1	B	7.58795	7.63795	5.55296	7.58795	7.63795	5.55296
25	.	2	B	6.47635	.	4.30339	6.47635	.	4.30339
26	12.82	2	B	9.52360	9.52506	8.32239	9.52360	9.52506	8.32239
27	2.66	2	B	7.50636	7.52508	4.93375	7.50636	7.52508	4.93375
28	.	2	B	8.02619	.	5.51745	8.02619	.	5.51745
29	7.11	2	B	8.70249	8.71786	6.94698	8.70249	8.71786	6.94698

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Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE
	(b) (6)									
30		1	R1TR2	3	R2	1166.44	.	90.95	36.00	.
31		1	R1TR2	3	R2	10262.60	10495.5	3181.00	24.00	0.042
32		1	R1TR2	3	R2	6010.40	6849.49	238.80	22.00	0.0432
33		1	R1TR2	3	R2	78.37	.	16.95	24.00	.
34		1	R1TR2	3	R2	1701.26	1806.09	111.70	28.00	0.1157
35		1	R1TR2	3	R2	3249.96	3392.24	443.90	22.00	0.0334
36		1	R1TR2	3	R2	3283.14	3616.73	1099.00	11.00	0.0336
37		2	R1TR2	3	R2	5893.15	8170.91	247.20	18.00	0.0372
38		2	R1TR2	3	R2	7553.40	7613.46	2949.00	12.00	0.1505
39		2	R1TR2	3	R2	13262.60	13299	2538.00	24.00	0.2044
40		2	R1TR2	3	R2	3607.57	3637.83	949.00	8.00	0.0475
41		2	R1TR2	3	R2	6037.90	6061.26	287.30	28.00	0.0817
42		2	R1TR2	3	R2	637.62	643.129	63.95	24.00	0.1926
43		2	R1TR2	3	R2	5420.99	6078.85	1436.00	13.05	0.0363
44		2	R1TR2	3	R2	1442.28	1669.48	90.98	22.00	0.0775
45		2	R1TR2	3	R2	3136.38	3289.99	830.80	11.00	0.096
46		2	R1TR2	3	R2	1273.07	.	275.70	22.00	.
47		2	R1TR2	3	R2	1717.40	1728.3	434.50	13.00	0.1426
48		2	R1TR2	3	R2	8710.68	8930.34	2424.00	14.00	0.0185
49		2	R1TR2	3	R2	3363.01	3561.33	232.90	28.00	0.1289
50		1	R1R2T	2	R2	3330.45	3575.4	212.30	28.00	0.1199
51		2	R1R2T	2	R2	3650.62	3680.96	612.40	8.00	0.274
52		1	R1R2T	2	R2	3381.44	3552.28	89.33	48.00	0.0383
53		1	R1R2T	2	R2	2801.21	.	273.50	32.00	.
54		1	R1R2T	2	R2	4455.87	4578.06	197.10	36.00	0.0844
55		1	R1R2T	2	R2	7040.32	7625.05	928.00	24.00	0.0617
56		1	R1R2T	2	R2	5247.50	5257.84	364.40	9.00	0.4911
57		1	R1R2T	2	R2	2143.35	2205.53	95.90	24.00	0.1482
58		1	R1R2T	2	R2	93.42	134.489	5.90	8.00	0.046

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
30	.	2	B	7.06171	.	4.51031	7.06171	.	4.51031
31	16.52	2	B	9.23626	9.25870	8.06495	9.23626	9.25870	8.06495
32	16.06	2	B	8.70125	8.83193	5.47563	8.70125	8.83193	5.47563
33	.	2	B	4.36142	.	2.83027	4.36142	.	2.83027
34	5.99	2	B	7.43912	7.49892	4.71582	7.43912	7.49892	4.71582
35	20.76	2	B	8.08640	8.12925	6.09560	8.08640	8.12925	6.09560
36	20.65	2	B	8.09656	8.19333	7.00216	8.09656	8.19333	7.00216
37	18.61	2	B	8.68155	9.00834	5.51020	8.68155	9.00834	5.51020
38	4.61	2	B	8.92975	8.93767	7.98922	8.92975	8.93767	7.98922
39	3.39	2	B	9.49270	9.49544	7.83913	9.49270	9.49544	7.83913
40	14.61	2	B	8.19079	8.19914	6.85541	8.19079	8.19914	6.85541

41	8.49	2	B	8.70581	8.70967	5.66053	8.70581	8.70967	5.66053
42	3.6	2	B	6.45774	6.46635	4.15810	6.45774	6.46635	4.15810
43	19.07	2	B	8.59803	8.71257	7.26962	8.59803	8.71257	7.26962
44	8.95	2	B	7.27398	7.42027	4.51064	7.27398	7.42027	4.51064
45	7.22	2	B	8.05082	8.09864	6.72239	8.05082	8.09864	6.72239
46	.	2	B	7.14919	.	5.61931	7.14919	.	5.61931
47	4.86	2	B	7.44857	7.45489	6.07420	7.44857	7.45489	6.07420
48	37.54	2	B	9.07231	9.09721	7.79317	9.07231	9.09721	7.79317
49	5.38	2	B	8.12059	8.17789	5.45061	8.12059	8.17789	5.45061
50	5.78	3	B	8.11086	8.18183	5.35800	8.11086	8.18183	5.35800
51	2.53	3	B	8.20265	8.21093	6.41739	8.20265	8.21093	6.41739
52	18.11	3	B	8.12606	8.17534	4.49234	8.12606	8.17534	4.49234
53	.	3	B	7.93781	.	5.61130	7.93781	.	5.61130
54	8.22	3	B	8.40198	8.42903	5.28371	8.40198	8.42903	5.28371
55	11.23	3	B	8.85941	8.93919	6.83303	8.85941	8.93919	6.83303
56	1.41	3	B	8.56551	8.56748	5.89825	8.56551	8.56748	5.89825
57	4.68	3	B	7.67013	7.69872	4.56331	7.67013	7.69872	4.56331
58	15.06	3	B	4.53711	4.90148	1.77427	4.53711	4.90148	1.77427

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Obs	SUBJ	Group	SEQU	PER	Treat	AUCT	AUCI	CMAX	TMAX	KE
59	(b) (6)	1	R1R2T	2	R2	10553.70	10689	2942.00	24.03	0.0288
60		2	R1R2T	2	R2	2633.66	2673.03	415.70	24.00	0.1648
61		2	R1R2T	2	R2	1812.56	1978.82	415.60	11.00	0.1034
62		2	R1R2T	2	R2	2041.29	2092.77	564.30	22.00	0.1142
63		2	R1R2T	2	R2	800.85	850.919	431.60	14.00	0.0306
64		2	R1R2T	2	R2	2303.82	2887.53	495.10	24.00	0.0657
65		2	R1R2T	2	R2	8885.70	8903.41	2557.00	8.00	0.0588
66		2	R1R2T	2	R2	5344.55	17470.1	280.90	24.00	0.0127
67		2	R1R2T	2	R2	1709.58	1731.74	135.70	12.00	0.1763
68		2	R1R2T	2	R2	2097.78	2117.28	81.97	10.00	0.0767
69		2	R1R2T	2	R2	63.77	70.3547	17.75	22.00	0.3407
70		2	R1R2T	2	R2	1080.29	1182.77	324.20	7.00	0.0708

Obs	THALF	SEQ	TRT	LAUCT	LAUCINF	LCMAX	lat2r	lai2r	lc2r
59	24.08	3	B	9.26423	9.27697	7.98684	9.26423	9.27697	7.98684
60	4.21	3	B	7.87613	7.89097	6.02996	7.87613	7.89097	6.02996
61	6.7	3	B	7.50250	7.59026	6.02972	7.50250	7.59026	6.02972
62	6.07	3	B	7.62134	7.64624	6.33559	7.62134	7.64624	6.33559
63	22.68	3	B	6.68567	6.74632	6.06750	6.68567	6.74632	6.06750
64	10.55	3	B	7.74232	7.96816	6.20476	7.74232	7.96816	6.20476
65	11.79	3	B	9.09220	9.09419	7.84659	9.09220	9.09419	7.84659
66	54.51	3	B	8.58383	9.76825	5.63800	8.58383	9.76825	5.63800
67	3.93	3	B	7.44400	7.45688	4.91045	7.44400	7.45688	4.91045
68	9.04	3	B	7.64863	7.65789	4.40635	7.64863	7.65789	4.40635
69	2.03	3	B	4.15535	4.25355	2.87639	4.15535	4.25355	2.87639
70	9.8	3	B	6.98498	7.07561	5.78136	6.98498	7.07561	5.78136

Obs	SUBJ	PER	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
1	(b) (6)	3	1	B	0.96666	0.94952	1.32279	-0.51265	-0.48743	0.25684
2		3	1	B	-0.72083	-0.71906	-1.18914	1.55239	1.54253	2.62983
3		3	1	B	-0.16563	0.09291	-0.21971	-0.67535	-0.87533	-0.46886
4		3	1	B	-0.17110	-0.16399	-0.17453	-0.05472	-0.07289	-0.22378
5		3	1	B	-0.06272	0.55924	-0.18101	-0.27627	-0.47329	-0.24421
6		3	1	B	1.10288	1.18830	2.91405	0.19847	0.23237	-0.51945
7		3	1	B	-0.01000	0.30794	0.00791	-0.02724	-0.10297	-0.03755
8		3	1	B	1.40065	1.38681	1.65475	0.65633	0.64769	1.42114
9		3	1	B	1.64369	.	1.92127	-0.28714	.	-0.54040
10		3	1	B	2.75179	.	1.56025	-3.00959	.	-1.91554
11		3	1	B	0.04596	0.04497	0.95941	-0.15690	-0.15408	0.59364
12		3	1	B	-2.41451	.	-2.00919	-0.22012	.	0.14334
13		3	1	B	0.02207	0.00610	-0.09917	0.24902	0.29526	-0.10530
14		3	1	B	2.24902	2.21660	1.64976	3.50781	3.39087	2.67654
15		3	1	B	-1.38036	.	-1.81430	-1.03321	-0.95636	-2.17552
16		3	1	B	-0.05400	-0.08511	1.33699	-0.20254	-0.13266	-0.17792
17		3	1	B	-0.30384	-0.50351	0.19180	-0.85036	-0.41120	-3.03932
18		3	1	B	-0.10126	-0.13238	-0.49387	-0.56733	-0.64070	-1.16099
19		3	1	B	0.85212	0.84739	0.85354	2.03760	2.01458	2.88644
20		3	1	B	1.05372	1.15589	-0.10041	1.34728	1.00609	3.89221
21		3	1	B	-6.45482	-4.38525	-7.01019	-1.38517	-1.37841	-1.58428
22		3	1	B	2.80015	.	3.48984	-2.93241	.	-1.80973
23		3	1	B	0.00609	-0.00592	0.39461	-0.49664	-0.46567	-0.72045
24		3	1	B	0.29447	0.23600	1.35562	0.63540	0.65658	0.57172
25		3	2	B	1.31736	.	0.35809	-0.92025	.	-0.22704
26		3	2	B	-0.16240	-0.16298	-0.42644	-0.50180	-0.50056	-0.68323
27		3	2	B	0.09681	0.09406	0.20758	0.20113	0.24493	0.56546
28		3	2	B	0.66902	.	1.38155	0.68590	.	2.33693
29		3	2	B	-3.55551	.	-4.48425	-1.24221	-0.85319	-1.07345
30		3	2	B	-1.00987	.	-1.46270	1.33625	.	2.47718
31		3	2	B	0.54395	0.52604	0.53708	-0.19376	-0.19602	-0.29684
32		3	2	B	0.18968	0.13572	0.45490	-0.34199	-0.46987	0.07072
33		3	2	B	-2.40864	.	-2.22575	1.53519	.	1.65589
34		3	2	B	1.54365	.	1.02937	-2.47891	.	-1.07797
35		3	2	B	0.84580	0.75491	1.13570	-0.56515	-0.43257	-0.81646
36		3	2	B	0.01182	-0.03636	0.50430	-1.42787	-1.51791	-2.19486
37		3	2	B	0.30436	.	0.50871	-0.90824	-0.98428	0.15519
38		3	2	B	-0.01480	-0.08329	-0.68412	-0.96716	-0.83752	-1.39961
39		3	2	B	-1.30525	-0.88696	-1.58697	0.10732	0.11138	0.01370
40		3	2	B	1.11084	0.91672	1.00876	0.02402	0.40143	0.64124
41		3	2	B	-1.04659	-1.04753	0.00801	0.27304	0.27908	0.03958
42		3	2	B	0.38996	0.38597	0.82414	2.49790	2.49309	3.78639
43		3	2	B	0.49806	0.38797	-0.41540	-1.44380	-1.40533	-3.09785
44		3	2	B	1.16770	1.09418	2.66690	0.39747	0.25702	0.25665
45		3	2	B	0.18535	.	0.19122	-0.39200	-0.43087	-2.08863
46		3	2	B	1.32271	.	1.60729	0.22885	.	-0.88927
47		3	2	B	-0.71539	-0.71398	-1.83267	0.89719	0.89401	1.16717
48		3	2	B	-0.00239	-0.00485	0.75352	-0.74216	-0.73053	-3.08725
49		3	2	B	-0.24252	.	-0.46368	0.08205	0.14487	-0.05517
50		2	3	B	-0.61710	-0.64719	0.83687	0.14097	0.09119	0.65327
51		2	3	B	-0.19285	-0.22921	-0.77110	-0.97644	-0.88395	-1.91170
52		2	3	B	-0.70550	-0.68653	-1.08129	0.13527	0.09328	1.82591

53	(b) (6)	2	3	B	-0.22506	.	-0.19757	0.08545	.	-0.53363
54		2	3	B	-1.12005	-1.22544	-1.95785	0.73682	0.91034	2.17678
55		2	3	B	-0.72095	.	-0.99079	-0.92061	.	-1.57710
56		2	3	B	-1.16182	-1.16158	-1.30049	-0.16875	-0.15316	0.59716
57		2	3	B	-0.42423	.	0.56449	-0.06757	-0.09108	0.07627
58		2	3	B	3.33661	.	3.28565	0.19826	0.61368	0.02925
59		2	3	B	-0.16777	-0.16886	-0.00146	-0.74470	-0.75303	-1.28133
60		2	3	B	-0.02417	.	-0.32142	0.15584	.	-0.67953
61		2	3	B	-1.00247	-1.04109	-0.48606	-0.49021	-0.47356	-1.10102

dataset for scaled average BE 59

Obs	SUBJ	PER	SEQ	TRT	ilat	ilai	ilc	dlat	dlai	dlc
62	(b) (6)	2	3	B	-0.80044	-0.82862	-0.80285	-0.20458	-0.19247	-0.46883
63		2	3	B	0.91207	0.85479	0.55167	2.10156	2.09821	-0.21991
64		2	3	B	-0.79839	.	-0.85998	-0.18323	.	-2.12875
65		2	3	B	0.02877	0.12380	-0.22267	-0.93455	-0.93208	-1.41044
66		2	3	B	0.31562	-0.23468	-0.08638	-0.54927	-1.70086	-0.19688
67		2	3	B	-0.84135	-0.80366	-1.13744	-0.02827	-0.02983	1.35523
68		2	3	B	-0.83036	-0.71398	0.27971	0.43550	0.42854	0.94598
69		2	3	B	0.09834	0.06574	-0.77374	3.97337	3.87774	4.39879
70		2	3	B	0.90155	0.86122	0.93884	0.68579	0.60428	-0.84545

unscaled BE 90% CI - guidance version 60

The Mixed Procedure

Model Information

Data Set	WORK.PKN
Dependent Variable	LCMAX
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	SUBJ, SUBJ
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
Group	2	1 2
SEQ	3	1 2 3
SUBJ	70	1 2 3 4 6 7 9 10 11 12 13 14 15 16 17 18 19 20 22 24 25 27 28 29 31 32 33 34 35 36 38 39 40 41 43 44 45 46 47 48 50 51 54 55 58 60 62 63 64 66 67 68 70 71 72 74 76 77 78 79 80 82 83 84 85 86 87 88 89 90
PER	3	1 2 3
TRT	2	A B

Dimensions

Covariance Parameters	5
Columns in X	24
Columns in Z Per Subject	2
Subjects	70
Max Obs Per Subject	3

Number of Observations

Number of Observations Read	210
Number of Observations Used	210
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	737.00818740	
1	2	729.89478925	0.05269775
2	1	726.89264855	0.01118891
3	1	725.88479755	0.00280006
4	1	725.58141197	0.00075115
5	1	725.49441106	0.00021791
6	1	725.46936538	0.00007143
7	1	725.46177802	0.00002807
8	1	725.45926101	0.00001385

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
9	1	725.45832720	0.00000861
10	1	725.45794217	0.00000645
11	1	725.45777024	0.00000549
12	1	725.45768941	0.00000504
13	1	725.45765033	0.00000482
14	1	725.45763070	0.00000470
15	1	725.45761708	0.00067698
16	1	725.45761677	0.00000462
17	1	725.45757972	0.00064668
18	1	725.45757960	0.00064664
19	1	725.45757541	0.00000439
20	1	725.45752651	0.00060357
21	1	725.45752570	0.00060296
22	1	725.45752384	0.00000410
23	1	725.45696832	0.00000101
24	1	725.45678546	0.00000000

Convergence criteria met.

Estimated G Matrix

Row	Effect	TRT	SUBJ	Col1	Col2
1	TRT	A	1	2.2689	0.4447
2	TRT	B	1	0.4447	0.5379

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	SUBJ		1.5063
FA(2,1)	SUBJ		0.2952
FA(2,2)	SUBJ		0.6714
Residual	SUBJ	TRT A	7.002E-6
Residual	SUBJ	TRT B	1.3257

Fit Statistics

-2 Res Log Likelihood	725.5
AIC (smaller is better)	735.5
AICC (smaller is better)	735.8
BIC (smaller is better)	746.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	11.55	0.0210

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Group	1	64.4	1.05	0.3088
SEQ	2	64.1	1.84	0.1667
Group*SEQ	2	64.1	0.20	0.8217
PER(Group)	4	132	0.38	0.8202
TRT	1	66.8	0.01	0.9070
Group*TRT	1	66.8	0.03	0.8631

Estimates

Standard

Label	Estimate	Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T vs. R	0.02264	0.1930	66.8	0.12	0.9070	0.1	-0.2993	0.3446

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	5.6156	0.1812	65.8	30.99	<.0001
TRT	B	5.5930	0.1320	64.6	42.39	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.PKN
Dependent Variable	LAUCT
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	SUBJ, SUBJ
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
Group	2	1 2
SEQ	3	1 2 3
SUBJ	70	1 2 3 4 6 7 9 10 11 12 13 14 15 16 17 18 19 20 22 24 25 27 28 29 31 32 33 34 35 36 38 39 40 41 43 44 45 46 47 48 50 51 54 55 58 60 62 63 64 66 67 68 70 71 72 74 76 77 78 79 80 82 83 84 85 86 87 88 89 90
PER	3	1 2 3
TRT	2	A B

Dimensions

Covariance Parameters	5
Columns in X	24
Columns in Z Per Subject	2
Subjects	70
Max Obs Per Subject	3

Number of Observations

Number of Observations Read	210
Number of Observations Used	210
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	665.53720148	
1	2	650.29969893	0.05406058
2	1	647.66672296	0.01191577
3	1	646.79828708	0.00301027
4	1	646.53951817	0.00081184
5	1	646.46562641	0.00023707
6	1	646.44434780	0.00007849
7	1	646.43787605	0.00003127
8	1	646.43571526	0.00001567

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
9	1	646.43490791	0.00000987
10	1	646.43457303	0.00000747
11	1	646.43442290	0.00000640
12	1	646.43435217	0.00000589
13	1	646.43431767	0.00000564
14	1	646.43430866	0.00000558
15	1	646.43430125	0.00000553
16	1	646.43429511	0.00107237
17	1	646.43428688	0.00000541
18	1	646.43426724	0.00000527
19	1	646.43424914	0.00000514
20	1	646.43422906	0.00000500
21	1	646.43416197	0.00088765
22	1	646.43415840	0.00000449
23	1	646.43387336	0.00048672
24	1	646.43387321	0.00000247
25	1	646.43372068	0.00000138
26	1	646.43352539	0.00000000

Convergence criteria met.

Estimated G Matrix

Row	Effect	TRT	SUBJ	Col1	Col2
1	TRT	A	1	1.6869	0.2839

2	TRT	B	1	0.2839	0.5356

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	SUBJ		1.2988
FA(2,1)	SUBJ		0.2186
FA(2,2)	SUBJ		0.6985
Residual	SUBJ	TRT A	2.369E-6
Residual	SUBJ	TRT B	0.7143

Fit Statistics

-2 Res Log Likelihood	646.4
AIC (smaller is better)	656.4
AICC (smaller is better)	656.7
BIC (smaller is better)	667.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	19.10	0.0007

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Group	1	64.2	0.23	0.6348
SEQ	2	64.1	0.50	0.6074
Group*SEQ	2	64.1	1.92	0.1554
PER(Group)	4	123	0.20	0.9399
TRT	1	66.6	0.00	0.9744
Group*TRT	1	66.6	0.05	0.8299

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T vs. R	-0.00549	0.1704	66.6	-0.03	0.9744	0.1	-0.2897	0.2787

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|

TRT	A	7.7412	0.1562	65.4	49.55	<.0001
TRT	B	7.7467	0.1138	64.5	68.09	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.PKN
Dependent Variable	LAUCINF
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	SUBJ, SUBJ
Group Effect	TRT
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
Group	2	1 2
SEQ	3	1 2 3
SUBJ	70	1 2 3 4 6 7 9 10 11 12 13 14 15 16 17 18 19 20 22 24 25 27 28 29 31 32 33 34 35 36 38 39 40 41 43 44 45 46 47 48 50 51 54 55 58 60 62 63 64 66 67 68 70 71 72 74 76 77 78 79 80 82 83 84 85 86 87 88 89 90
PER	3	1 2 3
TRT	2	A B

Dimensions

Covariance Parameters	5
Columns in X	24
Columns in Z Per Subject	2
Subjects	70
Max Obs Per Subject	3

Number of Observations

Number of Observations Read	210
Number of Observations Used	183
Number of Observations Not Used	27

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	507.36048559	
1	2	501.37409921	0.03051303
2	1	499.59117012	0.00036309
3	1	499.55919941	0.00051355
4	1	499.55903031	0.00000002
5	1	499.55903030	0.00000000

The Mixed Procedure

Convergence criteria met but final hessian is not positive definite.

Estimated G Matrix

Row	Effect	TRT	SUBJ	Col1	Col2
1	TRT	A	1	0.6723	0.1417
2	TRT	B	1	0.1417	0.3041

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	SUBJ		0.8199
FA(2,1)	SUBJ		0.1729
FA(2,2)	SUBJ		0.5237
Residual	SUBJ	TRT A	0.1972
Residual	SUBJ	TRT B	0.6384

Fit Statistics

-2 Res Log Likelihood	499.6
AIC (smaller is better)	509.6
AICC (smaller is better)	509.9
BIC (smaller is better)	520.8

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	7.80	0.0991

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Group	1	57.7	1.41	0.2405

SEQ	2	60.2	4.08	0.0218
Group*SEQ	2	60.2	0.24	0.7911
PER(Group)	4	115	0.20	0.9380
TRT	1	53.3	0.04	0.8469
Group*TRT	1	53.3	0.00	0.9968

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T vs. R	0.02791	0.1438	53.3	0.19	0.8469	0.1	-0.2128	0.2687

The Mixed Procedure

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|
TRT	A	8.0256	0.1216	56	66.02	<.0001
TRT	B	7.9977	0.1005	60.9	79.54	<.0001

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 70
Number of Observations Used 70

The GLM Procedure

Dependent Variable: ilat

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.2344905	0.6172452	0.31	0.7326
Error	67	132.2730200	1.9742242		
Corrected Total	69	133.5075105			

```
R-Square     Coeff Var      Root MSE     ilat Mean

0.009247     -10292.38      1.405071     -0.013652


Source                     DF      Type I SS    Mean Square   F Value   Pr > F

SEQ                         2     1.23449048     0.61724524      0.31   0.7326


Source                     DF    Type III SS    Mean Square   F Value   Pr > F

SEQ                         2     1.23449048     0.61724524      0.31   0.7326


                                        Standard
Parameter                   Estimate           Error    t Value    Pr > |t|

average                 -0.02113934      0.16840394      -0.13      0.9005

Parameter                90% Confidence Limits

average                 -0.30202299   0.25974430

dev iglmilat1                                                              71

Obs Dependent Source              DF           SS           MS  FValue  ProbF

 1    ilat    Model                2    1.2344905    0.6172452    0.31 0.7326
 2    ilat    Error               67  132.2730200    1.9742242     _    _
 3    ilat    Corrected Total     69  133.5075105     _            _    _

scaled average BE                                                          72
intermediate analysis - &dpar  glm

The GLM Procedure

   Class Level Information

Class         Levels    Values

SEQ                3    1 2 3


Number of Observations Read          70
Number of Observations Used          70

scaled average BE                                                          73
intermediate analysis - &dpar  glm

The GLM Procedure

Dependent Variable: dlat

                                    Sum of
Source                     DF       Squares    Mean Square   F Value   Pr > F
```

```
Model                        2     1.27400317     0.63700158      0.44    0.6441

Error                       67    96.39308011     1.43870269

Corrected Total             69    97.66708328


R-Square     Coeff Var      Root MSE     dlat Mean

0.013044     -2815.908      1.199459     -0.042596


Source                      DF      Type I SS    Mean Square   F Value   Pr > F

SEQ                          2     1.27400317     0.63700158      0.44    0.6441


Source                      DF    Type III SS    Mean Square   F Value   Pr > F

SEQ                          2     1.27400317     0.63700158      0.44    0.6441

output needed for mixed scaled av. BE - using glm                              74

       method_    unscabe_   unscabe_
Obs     used        lower      upper    dfi     s2i     param         StdErr

 1    Scaled/PE    0.74848    1.32147    67   1.97422   LAUCT     0.16840394


Obs   pointest       x        boundx    ni   dfd     s2wr    nd    theta

 1     0.97908   -0.027913   0.091218   70    67   0.71935   70   0.79669


Obs       y        boundy       sWR      critbound    outcome

 1    -0.57310    -0.44080    0.84815     -0.42298     PASS

final output - &parameter - using glm                                          75

     method_  unscabe_ unscabe_
Obs   used      lower    upper  param pointest   s2wr    sWR   critbound outcome

 1  Scaled/PE  0.74848  1.32147 LAUCT  0.97908 0.71935 0.84815  -0.42298  PASS

scaled average BE                                                              76
intermediate analysis - &ipar glm

The GLM Procedure

   Class Level Information

Class         Levels    Values

SEQ                3    1 2 3
```

Number of Observations Read 70
Number of Observations Used 49

scaled average BE 77
intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilai

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	2.82119709	1.41059854	1.52	0.2303
Error	46	42.80016721	0.93043842		
Corrected Total	48	45.62136430			

R-Square	Coeff Var	Root MSE	ilai Mean
0.061839	-3195.229	0.964592	-0.030189

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	2.82119709	1.41059854	1.52	0.2303

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	2.82119709	1.41059854	1.52	0.2303

Parameter	Estimate	Standard Error	t Value	Pr > |t|
average	-0.04689045	0.13865581	-0.34	0.7368

Parameter	90% Confidence Limits	
average	-0.27964646	0.18586557

dev iglmilai1 78

Obs	Dependent	Source	DF	SS	MS	FValue	ProbF
1	ilai	Model	2	2.82119709	1.41059854	1.52	0.2303
2	ilai	Error	46	42.80016721	0.93043842	_	_
3	ilai	Corrected Total	48	45.62136430	_	_	_

scaled average BE 79
intermediate analysis - &dpar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 70
Number of Observations Used 56

scaled average BE 80
intermediate analysis - &dpar glm

The GLM Procedure

Dependent Variable: dlai

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.80848962	0.90424481	0.74	0.4828
Error	53	64.91611536	1.22483237		
Corrected Total	55	66.72460498			

R-Square	Coeff Var	Root MSE	dlai Mean
0.027104	1717.109	1.106721	0.064453

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	1.80848962	0.90424481	0.74	0.4828

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	1.80848962	0.90424481	0.74	0.4828

output needed for mixed scaled av. BE - using glm 81

Obs	method_ used	unscabe_ lower	unscabe_ upper	dfi	s2i	param	StdErr
1	Scaled/PE	0.80828	1.30822	46	0.93044	LAUCINF	0.13865581

Obs	pointest	x	boundx	ni	dfd	s2wr	nd	theta
1	0.95419	-0.017027	0.078202	49	53	0.61242	56	0.79669

Obs	y	boundy	sWR	critbound	outcome
1	-0.48791	-0.36424	0.78257	-0.34885	PASS

final output - &parameter - using glm 82

Obs	method used	unscabe_ lower	unscabe_ upper	param	pointest	s2wr	critbound	outcome
1	Scaled/PE	0.80828	1.30822	LAUCINF	0.95419	0.61242	0.78257	-0.34885 PASS

scaled average BE 83
intermediate analysis - &ipar glm

The GLM Procedure

Class Level Information

Class	Levels	Values
SEQ	3	1 2 3

Number of Observations Read 70
Number of Observations Used 70

scaled average BE 84
intermediate analysis - &ipar glm

The GLM Procedure

Dependent Variable: ilc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F

```
Model                        2      2.6229516      1.3114758      0.51   0.6018

Error                       67    171.6952443      2.5626156

Corrected Total             69    174.3181958


R-Square     Coeff Var      Root MSE      ilc Mean

0.015047      8106.324      1.600817      0.019748


Source                      DF      Type I SS    Mean Square   F Value   Pr > F

SEQ                          2     2.62295158     1.31147579      0.51   0.6018


Source                      DF    Type III SS    Mean Square   F Value   Pr > F

SEQ                          2     2.62295158     1.31147579      0.51   0.6018


                                                 Standard
Parameter                    Estimate           Error    t Value    Pr > |t|

average                   0.01042835      0.19186499       0.05      0.9568

Parameter                 90% Confidence Limits

average                  -0.30958637   0.33044307

dev iglmilc1                                                                85

Obs Dependent Source              DF           SS           MS  FValue  ProbF

 1     ilc    Model                2    2.6229516    1.3114758    0.51 0.6018
 2     ilc    Error               67  171.6952443    2.5626156     _    _
 3     ilc    Corrected Total     69  174.3181958     _            _    _

scaled average BE                                                           86
intermediate analysis - &dpar  glm

The GLM Procedure

   Class Level Information

Class         Levels    Values

SEQ                3    1 2 3


Number of Observations Read          70
Number of Observations Used          70

scaled average BE                                                           87
intermediate analysis - &dpar  glm
```

The GLM Procedure

Dependent Variable: dlc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.3904541	0.1952271	0.07	0.9299
Error	67	179.7221818	2.6824206		
Corrected Total	69	180.1126359			

R-Square	Coeff Var	Root MSE	dlc Mean
0.002168	-3041.800	1.637810	-0.053843

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.39045415	0.19522707	0.07	0.9299

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.39045415	0.19522707	0.07	0.9299

output needed for mixed scaled av. BE - using glm 88

Obs	method_ used	unscabe_ lower	unscabe_ upper	dfi	s2i	param	StdErr
1	Scaled/PE	0.74131	1.41146	67	2.56262	LCMAX	0.19186499

Obs	pointest	x	boundx	ni	dfd	s2wr	nd	theta
1	1.01048	-0.036703	0.10919	70	67	1.34121	70	0.79669

Obs	y	boundy	sWR	critbound	outcome
1	-1.06853	-0.82187	1.15811	-0.81865	PASS

final output - &parameter - using glm 89

Obs	method_ used	unscabe_ lower	unscabe_ upper	param	pointest	s2wr	sWR	critbound	outcome
1	Scaled/PE	0.74131	1.41146	LCMAX	1.01048	1.34121	1.15811	-0.81865	PASS

Parameter	Geometric Means Test	Reference	T/R Ratio
LAUCT	2301.26	2313.92	0.99
LAUCI	3058.24	2974.08	1.03
LCMAX	274.69	268.54	1.02

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SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

90% CI Lower CI	Upper CI
74.85	132.15
80.83	130.82
74.13	141.15

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 92

Parameter	T/R Ratio	Lower 90% CI
LAUCT	0.98	74.85
LAUCI	0.95	80.83
LCMAX	1.01	74.13

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA 93

Upper 90% CI	s2wr	sWR	Criteria Bound
132.15	0.7193513	0.8481458	-0.422984
130.82	0.6124162	0.7825702	-0.348853
141.15	1.3412103	1.1581063	-0.818653

Method Used	OUTCOME
Scaled/PE	PASS
Scaled/PE	PASS
Scaled/PE	PASS

4.7 Additional Attachments

4.7.1 Attachment I

Background for Reference Scaled Average BE Approach[20]

In the analysis of a bioequivalence study, the measurements of both Cmax and AUC are subject to the procedure described below. The measurement for each subject is log-transformed and the averages, μT and μR, of the test and reference products are calculated. The within subject variability of the reference product, σ2 WR, is also calculated.

There are two parts to the proposed bioequivalence criteria, a scaled average bioequivalence evaluation and a point estimate (geometric mean ratio) constraint of 80-125%. An additional requirement of a point-estimate constraint will impose a limit on the difference between the test and reference means, thereby eliminating the potential that a test product would enter the market based on a bioequivalence study with a large mean difference.

In order to demonstrate bioequivalence both parts must pass.

Scaled Average Bioequivalence
Scaled average bioequivalence (BE) for both AUC and C_{max} is evaluated by testing the following null hypothesis

$$H_0 : \frac{\left(\mu_T - \mu_R\right)^2}{\sigma^2_{WR}} > \theta$$

(for given $\theta > 0$) versus the alternative hypothesis

$$H_1 : \frac{\left(\mu_T - \mu_R\right)^2}{\sigma^2_{WR}} \leq \theta \ ,$$

where μ_T and μ_R are the averages of the log-transformed measure (C_{max}, AUC) for the test and reference products, respectively; usually testing is done at level $\alpha = 0.05$; and θ is the scaled average BE limit. Furthermore,

$$\theta = \frac{\left(\ln \Delta\right)^2}{\sigma^2_{W0}}$$

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where Δ is 1.25, the usual average BE upper limit for the untransformed Test/Reference ratio of geometric means, and $\sigma_{W0} = 0.25$. Note that rejection of the null hypothesis H_0 supports the conclusion of equivalence.

A 95% upper confidence bound for $\frac{\left(\overline{Y}_T - \overline{Y}_R\right)^2}{s_{WR}^2}$ determined in a BE study must be ≤ θ, or

equivalently, a 95% upper confidence bound for $\left(\overline{Y}_T - \overline{Y}_R\right)^2 - \theta s_{WR}^2$ must be ≤ 0.

Where S_{WR} is within reference standard deviation determined in the BE study.

Additionally, the point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25]. The test drug must pass both conditions before it is judged bioequivalent to the reference product.

The overall analysis is a mixed scaling approach. If the estimated intrasubject reference variability (s_{WR}) is less than the pre-specified value set by the Agency (0.294), then the non-scaled average bioequivalence approach is used. If s_{WR} is greater than or equal to 0.294, then the bioequivalence limits will scale to the variability of the reference product and an additional acceptance criteria for the point-estimate of 80 to 125% will be applied.

4.7.2 Attachment II (Study of two Group Design)

Control document #98-392 that discusses the Group-by-Treatment interaction

Bio Control Document No: 98-392
Barbara M. Davit
v:\ firmsnz\ppd\controls\98-392a.doc

Firm: (b) (4) Reviewer: (b) (4)

Submission date: 10/30/98
Date finalized: 8/6/99

Addendum to the Review

Introduction:

The firm is requesting that the Division of Bioequivalence (DBE) comment on the appropriateness of the following dosing schemes to be used when bioequivalence study subjects are not recruited as a single group. Two proposed dosing schemes are shown below, for a drug with a one week washout period:

Dosing Scheme	11/1	11/8	11/15	11/22
1	Group 1 Period 1	Group 1 Period 2	Group 2 Period 1	Group 2 Period 2
2	Group 1 Period 1	Group 1 Period 2 Group 2 Period 1	Group 2 Period 2	

The firm is also requesting comment on the appropriate of the statistical model to be used in data analysis for the above bioequivalence study designs.

Comments:

CDER Quantitative Methods and Research Staff (QMRS) provided a written review commenting on the firm's proposals. The review is attached. The review written by the DBE primary reviewer is also attached.

Both Dosing Schemes are acceptable to QMRS. Dosing Scheme 1 is the classic two group design.

For both dosing schemes, the DBE recommends the following statistical model:

Group
Sequence
Treatment
Subject (nested within Group*Sequence)
Period (nested within Group)
Group-by-Sequence Interaction
Group-by-Treatment Interaction

Subject (nested within Group*Sequence) is a random effect and all other factors are fixed effects. QMRS states that if SAS PROC GLM or equivalent software is used to analyze the study, including or not including this interaction will not change the confidence intervals. If SAS PROC MIXED is used, including this interaction might change the confidence intervals. By nesting the Period effect within Group, the model allows for the possibility that the effects of Period 1 and Period 2 in Group 1 may not be the same as the effects of Period 1 and Period 2 in Group 2.

An alternate model for Dosing Scheme 2 would include the following factors:

Group
Sequence
Treatment
Subject (nested within Group*Sequence)
Week
Group-by-Sequence Interaction
Group-by-Treatment Interaction

The factor Week reflects which of the three weeks (11/1, 11/8, 11/15) the observations came from. If SAS PROC GLM or equivalent software is used to analyze the study, this model should produce the same confidence intervals as the model with Period (nested within Group).

For both models, if the Group-by-Treatment interaction test is not statistically significant ($p \exists 0.1$), the Group-by-Treatment term can be dropped from the statistical model.

If the Group-by-Treatment interaction is statistically significant ($p < 0.1$), DBE recommends that equivalence be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence study. This is similar to the recommendation presented by QMRS as option #3 (see attached QMRS review). The firm should be cautioned that statistical analysis for bioequivalence studies dosed in more than one group should commence only after all subjects have been dosed and all pharmacokinetic parameters have been calculated. Statistical analysis to determine bioequivalence within each dosing group should never be initiated prior to dosing the next group; otherwise the study becomes one of sequential design.

With both Dosing Schemes, if all of the following criteria are met, it may not be necessary to test for group effects in the model:

- the clinical study takes place at one site;
- all study subjects have been recruited from the same enrollment pool;
- all of the subjects have similar demographics;
- all enrolled subjects are randomly assigned to treatment groups at study outset.

In this latter case, the appropriate statistical model would include only the factors Sequence, Period, Treatment, and Subject (nested within Sequence).
Recommendations:

The following comments should be conveyed to the sponsor:

1. Both Dosing Schemes are acceptable to the Division of Bioequivalence.

2. The following statistical model can be applied to both Dosing Schemes.

    Group
    Sequence
    Treatment
    Subject (nested within Group*Sequence)
    Period (nested within Group)
    Group-by-Sequence Interaction
    Group-by-Treatment Interaction

3. Subject (nested within Group*Sequence) is a random effect and all other factors are fixed effects. If SAS PROC GLM or equivalent software is used to analyze the study, including or not including this interaction will not change the confidence intervals. If SAS PROC MIXED is used, including this interaction might change the confidence intervals. By nesting the Period effect within Group, the model allows for the possibility that the effects of Period 1 and Period 2 in Group 1 may not be the same as the effects of Period 1 and Period 2 in Group 2.

4. An alternate model for Dosing Scheme 2 would include the following factors:

Group
Sequence
Treatment
Subject (nested within Group*Sequence)
Week
Group-by-Sequence Interaction
Group-by-Treatment Interaction

5. The factor Week in the statistical model for Dosing Scheme 2 reflects which of the three weeks the observations came from. If SAS PROC GLM or equivalent software is used to analyze the study, this model should produce the same confidence intervals as the model with Period (nested within Group).

6. If the Group-by-Treatment interaction test is not statistically significant ($p \exists 0.1$), only the Group-by-Treatment term can be dropped from the statistical model.

7. **If the Group-by-Treatment interaction is statistically significant ($p < 0.1$), DBE requests that equivalence be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence study.**

8. **DBE cautions the firm that statistical analysis for bioequivalence studies dosed in more than one group should commence only after all subjects have been dosed and all pharmacokinetic parameters have been calculated. Statistical analysis to determine bioequivalence within each dosing group should never be initiated prior to dosing the next group; otherwise the study becomes one of sequential design.**

9. **If <u>ALL</u> of the following criteria are met, it may not be necessary to include Group-by-Treatment in the statistical model:**

    - the clinical study takes place at one site;
    - all study subjects have been recruited from the same enrollment pool;
    - all of the subjects have similar demographics;
    - all enrolled subjects are randomly assigned to treatment groups at study outset.

    In this latter case, the appropriate statistical model need include only the factors Sequence, Period, Treatment, and Subject (nested within Sequence).

10. **Please be advised that the above comments are subject to revision by the Division of Bioequivalence.**

Barbara M. Davit, Ph.D.
Team Leader
Review Branch III
Division of Bioequivalence

Rabinandra Patnaik, Ph.D.

Deputy Division Director
Division of Bioequivalence

Concur:_____Date:
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

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cc: HFD-630, HFD-650 (Director), HFD-658 (Davit), Drug File, Division File

(b) (4)

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BIOEQUIVALENCE DEFICIENCY

ANDA: 203286

APPLICANT: Zydus Pharmaceuticals (USA) Inc.

DRUG PRODUCT: Mesalamine Delayed Release Tablets USP, 800 mg

The Division of Bioequivalence II (DB II) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. We can not locate the individual data for comparative dissolution testing in 0.1 N HCl followed by pH 4.5 Acetate buffer.

2. Due to the high variability of your submitted dissolution data conducted in multimedia, an f2 test using mean profiles of test vs. reference listed drug ("RLD") is not sufficient as per the CDER Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms ("Dissolution Guidance"). Therefore, we calculated the f2 metric (an f2 confidence interval) using a bootstrapping method for the dissolution profile comparison. For general information on this approach, please refer to Shah et al. In Vitro Dissolution Profile Comparison-Statistics and Analysis of the Similarity Factor, f2. Pharmaceutical Research (1998) Vol. 15, No.6, page 889-896.

   For the test products, the mean values (f2) in pH 6.8 and pH 7.5 phosphate buffer are lower than 50 and the lower bound of 90% confidence interval ("CI") for the f2 test comparing test vs. RLD in pH 6.8, pH 7.2, and pH 7.5 phosphate buffer is lower than those comparing the RLD against itself under the same conditions. These values suggest that the dissolution profiles of the test product are significantly different from those of the corresponding reference under these conditions. Your dissolution data in pH 6.8, 7.2 and 7.5 are not acceptable.

3. To address why the test product is different from the RLD product, please repeat comparative dissolution testing on your **fresh test product** using a **larger sample** of tablets to provide a better estimate of the mean difference, or take other appropriated steps as necessary to reduce the variability for the purpose of achieving accurate f2 calculation.

   The dissolution testing should be conducted on at least 24 tablets (more if necessary) of the test product and at least two lots of unexpired RLD product (using 12 tablets per lot) using the following method as specified in the FDA Guidance on Mesalamine (800 mg):

   Apparatus: USP Apparatus II (paddle)
   Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
   Evaluation Stage:
   Each of
   (1) pH 4.5 Acetate buffer at 50 rpm
   (2) pH 6.8 Phosphate buffer at 50 rpm
   (3) pH 7.2 Phosphate buffer at 50 rpm
   (4) pH 7.5 Phosphate buffer at 50 rpm

   Volume: 900 mL
   Temperature: 37°C
   Sample times: 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes or as needed for profile comparison

   Please submit individual dissolution data as well as the mean, range, %coefficient of variation (CV) at each time point for the total numbers of tablets tested including dates of dissolution testing, manufacture date and expiration date as applicable.

   The DB II will perform an f2 test on your submitted dissolution data. If the variability of the dissolution data is such that mean data cannot be used for the f2 test, as per the Dissolution Guidance, we will use the above-referenced bootstrapping approach.

   For the bootstrapping method, sampling with replacement is used for creating 10,000 replicates of test and reference products. The means of the test

and reference units at each time point for each replicate are obtained and used for f2 calculation. The 90% confidence intervals of the f2 values are calculated using the percentile approach as described in the Shah et al. reference. Similar procedure can be followed for comparing reference vs. reference products.

Please note only one measurement after 85% dissolution of both the products should be included in the f2 calculation.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 203286

Reviewer: Ren, Ping **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Mesalamine Delayed Release Tablets USP, 800 mg

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***		
20919	7/12/2011	Bioequivalence Study (REGULAR)	Fasting Study	1	1	Edit	Delete
20919	7/12/2011	Bioequivalence Study (REGULAR)	Fed Study	1	1	Edit	Delete
20919	7/12/2011	Bioequivalence Study (REGULAR)	In Vitro Study (other dosage forms, each study type)	1	1	Edit	Delete
20919	7/12/2011	Bioequivalence Study (REGULAR)	In Vitro Study (other dosage forms, each study type)	1	1	Edit	Delete
20919	7/12/2011	Bioequivalence Study (REGULAR)	In Vitro Study (other dosage forms, each study type)	1	1	Edit	Delete
20919	7/12/2011	Bioequivalence Study (REGULAR)	In Vitro Study (other dosage forms, each study type)	1	1	Edit	Delete
20919	7/12/2011	Bioequivalence Study (REGULAR)	In Vitro Study (other dosage forms, each study type)	1	1	Edit	Delete
				Total:	7		

Enter Review Productivity and Generate Report

Typical BE Study Applications

BE Study Fasting and Fed	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fasting Study Total	*3*
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fed Study Total	*3*
In vitro Dissolution	
Multi media Dissolution	5
Dissolution waiver	0
Others	
Study Summary Total	*11*

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/s/

PING REN
11/12/2013

MINGLEI CUI
11/12/2013

ETHAN M STIER
11/15/2013

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	203286		
Drug Product Name	Mesalamine Delayed Release Tablets USP		
Strength (s)	800 mg		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Address	73, Route 31 North, Pennington, NJ 08534		
Applicant's Point of Contact	G. Srinivas Zydus Pharmaceuticals USA Inc., 73, Route 31 North, Pennington, NJ 08534		
Contact's Phone Number	609-730-1900		
Contact's Fax Number	609-730-1999		
Submission Date(s)	07/12/2011		
First Generic	Yes		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	# MSN-P0-732	# MSN-P0-733	
Study Type (s)	Fasting	Fed	
Strength(s)	800 mg	800 mg	
Clinical Site	Algorithme Pharma Inc.		
Clinical Site Address	Algorithme Pharma Inc. 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1		
Analytical Site	(b) (4)		
Analytical Address			
OVERALL REVIEW RESULT	INADEQUATE		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Fasting	800 mg	**PENDING**
1	Fed	800 mg	**PENDING**
1	DISSOLUTION	800 mg	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is a USP method for this product. The firm's dissolution testing data with the USP method are acceptable. The DB II acknowledges that the firm will follow the USP method and specifications.

The firm has conducted acceptable dissolution method validation for Mesalamine.

The submitted Long Term Storage Stability (LTSS) data is not sufficient to cover the maximum storage period of the fasting (#MSN-P0-732) and fed (#MSN-P0-733) bioequivalence (BE) studies. The firm is requested to submit sufficient LTSS to cover at least the maximum storage period (116 days) of the BE studies samples for Mesalamine.

The firm submitted all the requested summary bio-tables in MSWord format.

The DB II will review the fasted and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☐	☒
Did the firm use the USP dissolution method			☒	☐	☐
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	☒
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☐	☒	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

II. DISSOLUTION METHOD VALIDATION

Information Requested	
Bioanalytical method validation report location	Analytical method validation is attached in section 3.2.P.5.3 (Validation of analytical procedures) of Module 3
Analyte:	Mesalamine
Study Report Number	(b) (4)
Method description	Analytical method validation for Dissolution by UV of Mesalamine Delayed Release Tablets USP for strength 800 mg
Standard curve concentrations (units/mL)	**Linearity Results** **Table 4 (for 0.1 N HCl)** Linearity Level | Concentration of Mesalamine in µg/mL | Absorbance at 302 nm 10% | 1.5980 | 0.044 40% | 6.3920 | 0.160 60% | 9.5880 | 0.243 80% | 12.7840 | 0.322 100% | 15.9800 | 0.376 120% | 19.1760 | 0.448 The plot was found to be linear with a correlation co-efficient of 0.99820. **Table 5 (for pH 6.0 Phosphate Buffer)** Linearity Level | Concentration of Mesalamine in µg/mL | Absorbance at 330 nm 10% | 0.9980 | 0.013 40% | 3.9920 | 0.067 60% | 5.9880 | 0.099 80% | 7.9840 | 0.132 100% | 9.9840 | 0.167 120% | 11.9760 | 0.192 The plot was found to be linear with a correlation co-efficient of 0.99895. **Table 6 (for pH 7.2 Phosphate Buffer)** Linearity Level | Concentration of Mesalamine in µg/mL | Absorbance at 332 nm 20% | 5.4000 | 0.117 40% | 10.8000 | 0.217 60% | 16.2000 | 0.333 80% | 21.6000 | 0.446 100% | 27.0000 | 0.557 120% | 32.4000 | 0.653
System Suitability and Precision	Reading No. | Absorbance: 0.1 N HCl (at 302 nm) | pH 6.0 Buffer (at 330 nm) | pH 7.2 Buffer (at 332 nm) 1 | 0.383 | 0.162 | 0.554 2 | 0.382 | 0.162 | 0.555 3 | 0.383 | 0.163 | 0.557 4 | 0.383 | 0.163 | 0.557 5 | 0.383 | 0.161 | 0.558 **Average** | **0.383** | **0.162** | **0.556** **% RSD** | **0.1** | **0.5** | **0.3**
Method Validation for Dissolution by UV	Placebo Preparation No. | % Interference from the placebo: 0.1 N HCl (at 2 Hours) | pH 6.0 Phosphate Buffer (at 1 Hour) | pH 7.2 Phosphate Buffer (at 90 minutes) 1 | 0.0 | 0.0 | 0.0 2 | 0.0 | 0.0 | 0.0 3 | 0.0 | 0.0 | 0.7 4 | 0.0 | 0.0 | 0.0 5 | 0.0 | 0.0 | 0.2 6 | 0.0 | 0.0 | 0.2 **Mean** | **0.0** | **0.0** | **0.2**

Method Recovery

Recovery for Mesalamine

Table 14
Recovery at LOQ level

Sample No.	Amount Spiked (mg)	Amount Recovered (mg)	% Recovery
1	0.0501	0.0490	97.8
2		0.0477	95.2
3		0.0492	98.2
Average			**97.1**
% RSD			1.7

Table 15
Recovery at 50 % level

Sample No.	Amount Spiked (mg)	Amount Recovered (mg)	% Recovery
1	0.1003	0.1010	100.7
2		0.1003	100.0
3		0.1013	101.0
Average			**100.6**
% RSD			**0.5**

Table 16
Recovery at 100 % level

Sample No.	Amount Spiked (mg)	Amount Recovered (mg)	% Recovery
1	0.2005	0.2009	100.2
2		0.2004	100.0
3		0.2048	102.1
Average			**100.8**
% RSD			**1.1**

Table 17
Recovery at 150 % level

Sample No.	Amount Spiked (mg)	Amount Recovered (mg)	% Recovery
1	0.3008	0.3044	101.2
2		0.3063	101.8
3		0.3044	101.2
Average			**101.4**
% RSD			**0.3**

Method Ruggedness

The ruggedness of test method was demonstrated for analyte by carrying out precision at LOQ level (in terms of Mesalamine) using second HPLC systems of different make. The precision of the results obtained using the second HPLC system was evaluated by computing the percentage relative standard deviation for Mesalamine. The response for Mesalamine obtained on the second system is tabulated below.

Precision at LOQ Level

Injection No.	Peak Area of Mesalamine
1	12.374
2	14.213
3	14.032
4	13.698
5	11.930
6	15.597
Mean	**13.641**
%RSD	**9.7**

Comments on the Dissolution Method Validation:

The dissolution method validation is **acceptable.**

RLD information (Current Orange Book)

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021830		Yes	MESALAMINE	TABLET, DELAYED RELEASE; ORAL	800MG	ASACOL HD	WARNER CHILCOTT LLC

USP Dissolution Method

***Source of Method (USP, FDA or Firm)**	USP
Medium	Acid Stage: 0.1N HCl Buffer Stage I: pH 6.0 Phosphate Buffer Buffer Stage II: pH 7.2 Phosphate Buffer
Volume (mL)	Acid Stage: 500 mL Buffer Stage : 900 mL
USP Apparatus type	USP 2 (Paddle)
Rotation (rpm)	Acid Stage: 100 RPM 2 hours Buffer Stage I: 100 RPM 1 hour Buffer Stage II: 50 RPM 90 minutes
USP-recommended specifications	Acid Stage: NMT 1% in 2 hours Buffer Stage I: NMT 1% in 1 hour Buffer Stage II: NLT 80% (Q) in 90 minutes

*Note: Also per DARRTS ANDA [redacted] (b) (4)

Firm's summary Dissolution testing conditions (provided by the firm)

		Rationale
Apparatus	USP-II (Paddle)	The dissolution method, limit and parameter are based on USP monograph of this drug product.
Medium	pH 1.2, 0.1N HCl (Acid Stage) followed by pH 6.0 Phosphate buffer (Buffer Stage I) followed by pH 7.2 Phosphate buffer (Buffer Stage II)	
Volume	500 mL for Acid Stage, 900 mL (Buffer Stage I) 900 mL (Buffer Stage II)	
Speed	100 RPM (Acid stage and Buffer Stage I), 50 RPM (Buffer Stage II)	
Time	2 Hours (Acid Stage), 1 Hour (Buffer Stage I) 90 Minutes (Buffer Stage II)	
Temperature	37°C ± 0.5°C	

Specification**:** Acceptance criteria for dissolution as per given below:

Acid Stage (2 hour): Not more than 1.0 %

Buffer Stage I (1 hour): Not more than 1.0 %

Buffer Stage II (90 Minutes): Not less than 80% (Q) of the labeled amount of Mesalamine is dissolved in 90 Minutes.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	Apparatus:	USP-II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1N HCl (b) (4) (for 2 hours) followed by pH 6.0 Phosphate buffer (for 1 hours) followed by pH 7.2 Phosphate buffer
	Volume:	900 mL
	Temperature:	37 C ± 0.5 C
Firm's Proposed Specifications	Acid Stage: Not more that 1% dissolved in 2 hours. Buffer Stage I: Not more that 1% dissolved in 1 hours. Buffer Stage II: Not less than 80 % (Q) of the labeled amount of Mesalamine is dissolved in 90 minutes.	
Dissolution Testing Site (Name, Address)	Cadila Healthcare Ltd., Sarkhej-Bavla, N. H. No. 8A, Moraiya, Tal.: Sanand, Dist, Ahmedabad – 382 210	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test-Manufacture Date) (Reference–Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (Minutes) 2 hour	1 hour	15	30	45	60	90	Study Report Location
Study Report #:	June 27, 2011	Mesalamine Delayed Release Tablets USP, 800 mg Lot No.: EMK150 Mfg Date: March, 2010	800 mg Tablet	12	Mean	0.0	0.1	18.4	46.4	73.5	85.9	100.6	Refer Module 5.3.1.3
					Range	(b) (4)							
					%CV	233.5	159.5	82.1	60.0	41.9	31.7	6.2	
Study Report #:	June 27, 2011	ASACOL® HD (Mesalamine) Delayed Release Tablets USP, 800 mg Lot No: 442661S3 Expiry : 03/2013	800 mg Tablet	12	Mean	0.0	0.1	14.1	30.7	60.8	82.0	99.6	
					Range	(b) (4)							
					%CV	233.5	184.6	142.8	104.0	45.2	18.4	1.2	

F2: 51.20
Dissolution Conditions:
Medium : 900 mL, Phosphate buffer pH 7.2
Apparatus : USP-II (Paddle)
RPM : 50
Temperature : 37 C ± 0.5 C
Acceptance Criteria: Acid Stage: Not more that 1% dissolved in 2 hours.
Buffer Stage I: Not more that 1% dissolved in 1 hour.
Buffer Stage II: Not less than 80 % (Q) of the labeled amount of Mesalamine is dissolved in 90 minutes.

III. COMMENTS:

1. There is a USP method for this product. The firm's dissolution testing data with the USP method are acceptable. The DB II acknowledges that the firm will follow the USP method and specifications.

2. The firm has conducted acceptable dissolution method validation for Mesalamine.

3. The submitted Long Term Storage Stability (LTSS) data is not sufficient to cover the maximum storage period of the fasting (#MSN-P0-732) and fed (#MSN-P0-733) bioequivalence (BE) studies. The firm is requested to submit sufficient LTSS to cover at least the maximum storage period (116 days) of the BE studies samples for Mesalamine.

4. The firm submitted all the requested summary bio-tables in MSWord format.

5. The DB II will review the fasted and fed BE studies and the waiver request at a later date.

IV. DEFICIENCY COMMENTS:

1. The submitted Long Term Storage Stability (LTSS) data is not sufficient to cover the maximum storage period of the fasting (#MSN-P0-732) and fed (#MSN-P0-733) bioequivalence (BE) studies. The firm is requested to submit sufficient LTSS to cover at least the maximum storage period (116 days) of the BE studies samples for Mesalamine.

V. RECOMMENDATIONS:

The in vitro dissolution testing conducted by Zydus Pharmaceuticals (USA) Inc. on its test product, Mesalamine Delayed Release Tablets USP, 800 mg is acceptable. The test product meets the USP following dissolution specifications.

Acid Stage: NMT 1% in 2 hours
Buffer Stage I: NMT 1% in 1 hour
Buffer Stage II: NLT 80% (Q) in 90 minutes

BIOEQUIVALENCE DEFICIENCIES

ANDA:	203286
APPLICANT:	Zydus Pharmaceuticals (USA) Inc.
DRUG PRODUCT:	Mesalamine Delayed Release Tablets USP, 800 mg

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

The submitted Long Term Storage Stability (LTSS) data is not sufficient to cover the maximum storage period of the fasting (#MSN-P0-732) and fed (#MSN-P0-733) bioequivalence (BE) studies. Please submit sufficient LTSS to cover at least the maximum storage period (116 days) of the BE studies samples for Mesalamine.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 203286

Completed Assignment for 203286 ID: 16035

Reviewer: Wahba, Zakaria Date Completed:
Verifier: , Date Verified:
Division: Division of Bioequivalence
Description:

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
16035	7/12/2011	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY ANDA 203286

Dissolution Review	
Dissolution Review	1
Dissolution Review Total	*1*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZAKARIA Z WAHBA
02/16/2012

MOHEB H MAKARY
02/16/2012

ETHAN M STIER on behalf of BARBARA M DAVIT
02/16/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

OTHER REVIEWS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 30, 2014

TO: Ethan M. Stier, Ph.D., R.Ph
Director (Acting)
Division of Bioequivalence-II
Office of Generic Drugs

FROM: Sripal R. Mada, Ph.D.
BE Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, BE Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering studies (ANDA 204-299 and ANDA 203-286), inspection utilizing bioequivalence surveillance approach (b) (4) (b) (4)

Table of Contents

1. Summary

At the request of Division of Bioequivalence-II (DBE-II), Office of Generic Drugs (OGD), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected both clinical and analytical portions of the above applications utilizing a bioequivalence surveillance approach. A summary of the inspected studies is provided below.

Review Div.	Application	Studies	Facility	Drug Product	Sponsor	Recommend
DBE-II Ethan M. Stier	ANDA 204-299	BA11133427-01 and BA11133428-01	Clinical and Analytical	Zolpidem Tartrate Sublingual Tablets, 1.75 and 3.5 mg	Novel Laboratories, Inc.	Acceptable
DBE-II Ethan M. Stier	ANDA 203-286	MSN-P0-732 and MSN-P0-733	Analytical	Mesalamine Delayed Release Tablets, USP, 800 mg	Zydus Pharmaceuticals, USA Inc.	Acceptable

The FDA inspectors planned and included the following studies for the audit (b) (4)

BA11133427-01: "An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Zolpidem Tartrate Sublingual Tablets 3.5 mg of Novel Laboratories Inc., USA and INTERMEZZO® (Zolpidem Tartrate) Sublingual Tablets 3.5 mg of Transcept Pharmaceuticals, Inc., CA 94084 in healthy adult human subjects under fasting conditions"

BA11133428-01: "An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Zolpidem Tartrate Sublingual Tablets 3.5 mg of Novel Laboratories Inc., USA and INTERMEZZO® (Zolpidem Tartrate) Sublingual Tablets 3.5 mg of Transcept Pharmaceuticals, Inc., CA 94084 in healthy adult human subjects under fed conditions"

MSN-P0-732: "Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 800 mg Delayed-Release Tablets in Healthy Male and Female Volunteers under Fasting State"

MSN-P0-733: "Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 800 mg Delayed-Release Tablets in Healthy Male and Female Volunteers under Fed State"

The FDA inspectors covered clinical portion of study #BA11133427-01, and analytical portions of studies #MSN-P0-732 and #BA11133427-01. The selection of studies for this BE surveillance inspection was based on pre-set, risk-based criteria.

2. Recommendation

ANDA 204-299:

The clinical data from study BA11133427-01, and analytical data from studies BA11133427-01 and BA11133428-01 are acceptable for review.

ANDA 203-286:

The analytical data from studies MSN-P0-732 and MSN-P0-733 are acceptable for review.

3. Inspectional Findings

Following the inspection by Gopa Biswas, Ph.D (OSI) and Scott B. Laufenberg (ORA, OIP, India Office) [redacted], there were no significant observations at the clinical site and no Form FDA-483 was issued.

4. Final Site Classification

[redacted]

cc:
OSI/Kassim
OSI/DBGLPC/Taylor/Dejernett/Johnson/Fenty-Stewart/Nkah
OSI/DBGLPC/GLPB/Bonapace/Dasgupta
OSI/DBGLPC/BB/Biswas/Mada/Choi/Skelly/Haidar
OPS/OGD/DBEII/Stier/Kreger/Mahadevan
ORA/OIP, India Office/Laufenberg
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Inspections/BE Program/Analytical sites/ [redacted]

Draft: SRM 07/17/2014
Edits: YMC 07/29/2014; SHH 07/29/2014

OSI FILE# BE6575; O:\Bioequiv\EIRCover\204299 nov zol.doc
FACTS: 8737064

OSI FILE# BE6322; O:\Bioequiv\EIRCover\203286 zyd mes.doc
FACTS: 1391158

5. Attachments none

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIPAL R MADA
07/30/2014

SAM H HAIDAR
07/30/2014

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 09, 2010

TO: Johnny Young, R.Ph.
Office of Generic Drugs (OGD)
DLPS/RSS

FROM: Sushanta K. Chakder, Ph.D.
Supervisory Pharmacologist
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Through: Andrew Mulberg, M.D.
Deputy Division Director
Division of Gastroenterology and Inborn Errors Products (DGIEP)

SUBJECT: Consult Request from the OGD for assessment of safety of the proposed level of Eudragit S (b) (4) in Mesalamine Delayed Release Tablets USP, 800 mg (Zydus Pharma USA Inc.) (ANDA 203286; Consult No. 2011-0543).

Attached, please find the review of the consult request (#2011-0543) for safety assessment of the proposed level of Eudragit S (b) (4) in Mesalamine Delayed Release Tablets USP, 800 mg.

Sushanta K. Chakder, Ph.D.
Supervisory Pharmacologist, DGIEP

CC:
DGP
DGIEP/WIshihara
DGIEP/BStrongin
OGD/JYoung
OGD/TTran
DGP/AMulberg
DGP/SChakder

Safety Assessment of the Proposed Eudragit S [(b) (4)] (Methacrylic Acid Copolymer, Type B) Levels in Mesalamine Delayed Release Tablets.
(ANDA 203286; Consult No: 2011-0543)

Background: Zydus Pharmaceuticals USA Inc. submitted an ANDA (ANDA # 203286) application for Mesalamine Delayed Release Tablets (800 mg). Each Mesalamine Delayed Release Tablet contains [(b) (4)] of Eudragit S [(b) (4)] The proposed daily dose of the Mesalamine Delayed Release Tablets is 6 tablets a day (2 tablets 3 times a day). Thus, the maximum daily Eudragit S [(b) (4)] intake from Mesalamine Delayed Release Tablets would be [(b) (4)] x 6 = [(b) (4)] The proposed amount of Eudragit S [(b) (4)] in the existing approved Drug Products Database (IIG). The Office of Generic Drugs has sent a consult to DGIEP for nonclinical safety assessment of the level of Eudragit S [(b) (4)] in the proposed formulation of Mesalamine Delayed Release Tablets.

The composition of Mesalamine Delayed Release Tablets (800 mg) is provided in the Sponsor's Table below.

▪ **Quantitaive composition of Mesalamine Delayed Release Tablets USP, 800 mg:**

Name of Ingredient	Quantity/ Tablet (mg)	Quantity (% w/w)/Tablet[$]
(b) (4)		
Mesalamine, USP	800.000	(b) (4)
Sodium Starch Glycolate, NF (b) (4)	(b) (4)	
Colloidal Silicon Dioxide, NF (b) (4)		
Magnesium Stearate, NF		
(b) (4)		
Microcrystalline Cellulose, NF (b) (4)		
Povidone (b) (4) USP (b) (4)		
(b) (4)		
(b) (4)		
Sodium Starch GlycolateNF, (b) (4)		
Talc, USP (b) (4)		
Colloidal Silicon Dioxide, NF (b) (4)		
Magnesium Stearate, NF		
(b) (4)		
Methacrylic Acid Copolymer, NF - Type B (Eudragit S (b) (4)		
Talc, USP		
Acetyltributyl Citrate, NF		
Titanium Dioxide, USP (b) (4)		
Ferric Oxide Red, NF		
Isopropyl Alcohol, USP*		
(b) (4)		
(b) (4)		
Opacode Black (b) (4)		
Isopropyl Alcohol, USP*		
Total	**1102.400**	**100.000**
(b) (4)		

NONCLINICAL STUDY REPORTS SUBMITTED:

The sponsor submitted full reports of two 6-month oral toxicity studies in rats, a 6-week oral toxicity study in male mice and a 6-week oral toxicity study in rabbits with Eudragit S (b) (4) In addition, summary report of a non-GLP feeding study of Eudragit L (b) (4) and Eudragit S (b) (4) in rats, a bacterial reverse mutation assay (Ames test) and an embryofetal development study in rats were submitted.

General Toxicology:

Feeding Experiments with Eudragit L and Eudragit S in Rats:

The sponsor submitted a summarized report of a feeding study of Eudragit L and Eudragit S in rats. Three groups (30 animals/group) of rats were fed pan-coated (two groups) or uncoated (one group) barley for about one month. However, the animals de-husked the barley and ate the grains, and it was not possible to determine how much lacquer was taken by the animals. The animals were then given a granulated standard rat feed to with a mixture of lactose and pan coating lacquers containing a 5% mixture of Eudragit L and Eudragit S in equal ratios were added. Group 1 and Group 2 animals consumed approximately 3.1 mg and 15.5 mg of lacquer solid/animal/day. Group 3 (control) animals received a standard diet. All animals gained normal body weight during the study. Macroscopic examination of all tissues and microscopic examination of the liver did not reveal any adverse effects related to Eudragit.
This was not a standard toxicology study and is not useful in assessing the safety of Eudragit S (b) (4)

Six-Month Oral Toxicity Studies in Rats:

Two 6-month repeat dose oral (gavage) toxicity studies with Eudragit S (b) (4) in rats were submitted in this submission.

In the first 6-month oral toxicity study of Eudragit S (b) (4) in rats, 0, 200, 600 and 1500 mg/kg/day doses were administered once daily to four groups (25 animals/sex/group for the main study) of Wistar rats. Subgroups of 10 animals/sex/group from the control and high dose groups were assigned to a 4-week treatment-free recovery period. In this study, the NOAEL was not established, because an activation of the thyroid epithelium was observed at all doses. The severity and the incidence of the effect on the thyroid gland was dose related and was not reversible at the end of the 4-week recovery period. In addition, a decrease in the liver weight was observed at all doses, and an increased incidence of peripheral fatty degeneration pattern of liver cells was observed at the high dose.

The second study was conducted to determine whether oral administration of Eudragit S (b) (4) at doses lower than 200 mg/kg/day produces morphological changes in the thyroid glands of rats. The previous study in rats showed an activation of thyroid epithelium in rats at 200 mg/kg and higher doses of Eudragit S (b) (4).
In this 6-month oral toxicity study (Project No. 3-4-120-89; GLP compliant), groups of male and female Wistar rats (15 males and 15 females in each group; 6 weeks of age at the beginning of dosing; body wt. 132-169 g for males, 111-142 g for females) were administered Eudragit S (b) (4) at dose levels of 0, 10, 30, 100 mg/kg/day once daily by oral gavage for 6 months. Control animals received the vehicle (purified water). No treatment-related clinical signs were observed in any group. There were no treatment related mortalities; one animal from the 10 mg/kg group died after 15 weeks of dosing due to a gavage error. No significant changes in food consumption, body weight, hematology, gross pathology or organ weight were observed in any group. Histopathological examination of the thyroid gland did not show any test article related changes. Thus, the 100 mg/kg/day dose was the NOAEL for Eudragit S (b) (4) in this study.

Six-Week Oral Subchronic Toxicity Study in Male Mice (IBR Project No. 2-1-772-87)

In a 6-week oral toxicity study of Eudragit S (b) (4) in male NMRI (SPF Han) mice, 0, 100, 600 and 1500 mg/kg QD doses were orally administered to groups of animals (12 animals/group). Thyroids were slightly activated at the 1500 mg/kg dose, and a tendency towards activation was observed at the 600 mg/kg dose. No effect on the thyroid gland was observed at the low dose of 100 mg/kg/day. Thus, the 100 mg/kg/day dose was the NOAEL in this study.

Six-Week Oral Toxicity Study in Rabbits:

In a 6-week oral toxicity study in New Zealand white rabbits (6 males and 6 females/group), Eudragit S (b) (4) was administered by oral gavage at 0, 100, 600 and 1500 mg/kg/day doses. There were no mortalities in any group. No treatment-related effects on clinical signs, body weight, food consumption, hematology, or organ weights were observed. Histopathology examinations showed dose-related activation of the thyroid epithelium in the mid- and high-dose groups. The NOAEL was 100 mg/kg/day in this study, and the thyroid gland was the target organ of toxicity.

Genetic Toxicology: EUDRAGIT S (b) (4) was not mutagenic in the bacterial reverse mutation (Ames test) assay in the presence or absence of metabolic activation.

Experiments to Determine the Effect of 2577 G and 2697 on Pregnant Rats and Their Fetuses

Twenty pregnant Wistar rats were administered 1000 mg/kg/day doses of 2577 G and 2697 from gestation day 6 through gestation day 16. No adverse effects on maternal animals or fetuses were reported. However, the compounds used in this study were identified by their code names, and it is not known whether Eudragit S (b) (4) was one of them used in the study.
In another study, Eudragit S (b) (4) and Eudragit L (b) (4) did not show any teratogenic potential in rats at an oral dose of 500 mg/kg/day.

SUMMARY AND EVALUATION:

Eudragit S (b) (4) formulations to deliver drugs in the intestine. Zydus Pharmaceuticals, USA Inc. submitted ANDA 203286 in the OGD for Mesalamine Delayed Release Tablets. Each Mesalamine Delayed Release Tablet contains (b) (4) of Eudragit S (b) (4). The proposed daily dose of the Mesalamine Delayed Release Tablets is 6 tablets/day (2 tablets 3 times a day). Thus, the maximum daily amount of Eudragit S (b) (4) intake from the Mesalamine Delayed Release Tablets would be (b) (4) x 6 = (b) (4). The proposed amount of Eudragit S (b) (4) in the existing approved Drug Products Database (IIG). The

Office of Generic Drugs has sent a consult request to DGIEP for nonclinical safety assessment of the proposed level of Eudragit S [(b) (4)] in Mesalamine Delayed Release Tablets.

In support of the safety of the proposed Eudragit S [(b) (4)] levels in the Mesalamine Delayed Release Tablet formulation, the sponsor submitted full reports of two 6-month oral toxicity studies in rats, a 6-week oral toxicity study in male mice and a 6-week oral toxicity study in rabbits with Eudragit S [(b) (4)]. In addition, summary report of a non-GLP feeding study of Eudragit L [(b) (4)] and Eudragit S [(b) (4)] in rats, a bacterial reverse mutation assay (Ames test) and an embryofetal development study in rats were submitted.

Eudragit S [(b) (4)] is present in a number of FDA approved products as an enteric coating agent. However, the level proposed in the mesalamine delayed release tablet formulation is [(b) (4)] Eudragit S [(b) (4)] is considered to be relatively safe as an enteric coating agent. [(b) (4)]. In a 6-month oral toxicity study of Eudragit S [(b) (4)] in rats, thyroid was the target organ of toxicity, and the NOAEL was identified as 100 mg/kg/day. The 100 mg/kg/day dose was also identified as the NOAEL in a 6-week oral toxicity study in male mice and a 6-week oral toxicity study in rabbits. The NOAEL of 100 mg/kg/day provides about 24 times safety margin for the anticipated daily intake of [(b) (4)] Eudragit S [(b) (4)] from the maximum daily recommended dose of mesalamine (4.8 g/day). Eudragit S [(b) (4)] showed no genotoxic potential in the Ames test, and was not teratogenic in rats.

Thus, from a nonclinical standpoint, there are no safety concerns for the sponsor's proposed amount of Eudragit S [(b) (4)] in Mesalamine Delayed Release Tablets (800 mg), and the proposed amount of Eudragit S [(b) (4)] per tablet [(b) (4)] is acceptable.

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/s/

SUSHANTA K CHAKDER
09/09/2011

ANDREW E MULBERG
09/11/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203286

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: EA Taylor Team Leader: Taylor

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

ANDA #: 203286 Applicant: Zydus Pharmaceuticals (USA) Inc.
Established Product Name: Mesalamine Delayed-Release Tablets USP, 800 mg

Basis of Submission (RLD): 021830/Asacol HD
Basis Of Submission Discontinued? Yes ☐ No ☒
If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?
Yes ☐ FR Notice dated _____; Vol. _____; No. _____
No ☐ Consult completed but not yet published in FR

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

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

Regulatory Project Manager Evaluation: **Date: 7/7/2017**

☒ Date (Received) Acceptable for Filing -- Date 7/13/2011
☒ Date last Complete Response (CR) letter was issued -- Date 2/3/2017
☐ Previously reviewed and tentatively approved (if applicable) --- Date _____

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Bioequivalence 12/11/2015 • Date of BE Guidance (if any) 6/1/2016 Date of Acceptable Labeling 6/22/2017 • Date of last RLD labeling update 5/5/2016 Date of Acceptable Quality 6/23/2017 • DMF No(s). 22999 Date(s) Acceptable 7/29/2016 • No outstanding DMF review amendments ☒ • Date of Acceptable Overall Manufacturing Inspection 6/16/2017	If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review N/A Date of Acceptable Dissolution 2/16/2012 Date of Acceptable REMS N/A
☒	☐	**MMA:** All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).	
☐	☒	Are consults pending for any discipline?	
☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable	
☐	☒	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed ☐; Memo uploaded (if applicable) ☐	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☐	
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed 6/23/2017	

Review Discipline/Division and RPM TL Endorsements

☒	☐	Applicable review discipline/division endorsements completed
☒	☐	RPM Team Leader endorsement completed

Additional Notes (if applicable)

For DMF 22999 There is a DARRTS NAI dated 3/24/2017 after receipt of an annual report on 8/2/2016
Email from BioPM stating Bio is still adequate after guidance revision uploaded to Quality Check . . . task

(b) (4)

[redacted]

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 7/11/2017
Name: IM for MHS

Patent/Exclusivity Certification:

☐ **PI** ☒ **PII** ☐ **PIII** ☒ **PIV** ☐ **section viii**

If Paragraph IV Certification- did applicant:

Notify patent holder/NDA holder: Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☒ No ☐
Applicant addressed all listed exclusivities Yes ☒ No ☐

Do the patent and exclusivity certifications align? Yes ☒ No ☐
Have there been any revisions to the use code since the original submission? Yes ☐ No ☒

RLD = Asacol HD NDA# 21830 ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#**:** 7/11/2017

Type of Letter:
☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)

LETTER RECOMMENDED FOR DRUGS@FDA Yes ☒ No ☐

Forfeiture Information
Is a forfeiture memo needed for the first applicant: Yes ☐ No ☒
If yes, the date forfeiture memo was completed
Date_____ ANDA number _____

180 Day Exclusivity Information
Is applicant eligible for 180 day exclusivity Yes ☒ No ☐
☒ Sole
☐ Shared
ANDA Exclusivity for each strength: Yes ☐ No ☐
Which strength(s) eligible _____

Comments: BOS = Asacol HD (NDA 21830) Application submission 7/13/2011 with PIII certifications to the '170 and '171 patents and a PIV certification to the '662 patent. Acknowledgment letter signed 9/9/2011.
Amendment 10/11/2011 with copies of PIV return receipts sent via USPS to Warner Chilcott LLC (NJ) x2 and Fitzpatrick Cella Harper & Scinto (NY) and received 9/27/201, 9/27/2011, 9/28/2011. PIV filing notice also sent via (b) (4) 9/26/2011 to Warner Chilcott LLC (NJ) x2, Fitzpatrick Cella Harper & Scinto (NY) and an unknown location in Ireland and received 9/27/2011, 9/27/2011, 9/27/2011 and 9/28/2011.
Amendment 10/12/2011 Zydus provided an additional PIV return not included in the 10/11/2011 amendment sent via USPS to Warner Chilcott Company (PR) and received 10/7/2011.
Amendment 12/5/2011 with a copy of a complaint filed 11/8/2011 in USDC for the District of Delaware, CA# 1:11-cv-01105-UNA, for infringement of the '662 patent. The 30-month stay associated with this complaint would expire 4/7/2014.
Amendment 7/15/2014 Zydus addressed the newly listed '302 patent with a PIV certification, as well as revising their certification to the '170 and '171 patents from PIII to PII (exp. 7/30/2013).
Amendment 7/22/2014 with copies of PIV return receipts for the '302 patent sent 7/15/2014 via (b) (4) Warner Chilcott LLC (NJ), Fitzpatrick Cella Harper & Scinto (NY), Warner Chiclott PLC (Ireland) and Warner Chilcott Company LLC (PR) and received 7/16/2014, 7/16/2014, 7/17/2014 and 7/16/2014.
Amendment 5/1/2015 Zydus submitted a Stipulation and Order of Dismissal issued 6/9/2014 by the USDC for the District of Delaware, CA# 1:11-cv-01105, which states the parties have agreed to the terms of a negotiated settlement agreement, and all claims and counterclaims are dismissed without prejudice. Also included is a press release from Actavis dated 6/9/2014 which announces the settlement agreement with Zydus for Asacol HD which would allow Zydus to begin marketingtheir generic product 11/15/2015, or Zydus may commence commercial marketing an AG 7/1/2016 if FDA approval of the ANDA has not been granted by that date.
Amendment 1/13/2016 addressing the newly listed '492 patent with a PIV certification.
Amendment 2/25/2016 with submission of (b) (4) PIV return receipts sent 2/18/2016 to Warner Chiclott (PR), Warner Chilcott LLC (NJ), Fitzpatrick Cella Harper & Scinto (NY), Allergan Inc. (CA) and Warner Chilcott (Ireland) and received 2/19/2016, 2/19/2016, 2/19/2016, 2/19/2016 and 2/22/2016.

Amendment 8/5/2016 respons to an OGD request regarding marketing with Zydus stating they launched an AG 8/1/2016.
There are no additional unexpired patents and no unexpired exclusivities listed in the OB for the NDA. There is no pending CP for the drug product.
With respect to 180-day, Zydus is the first ANDA received with a PIV certification to the NDA and would be eligible for 180-day exclusivity. However, the ANDA has not received a tentative approval within 30 months of the original submission date and may have forfeited the exclusivity based upon this issue. Since Zydus commenced commercial marketing of an AG 8/1/2016, this action triggered their exclusivity and it began to run as of that date and expired 1/28/2017.
This ANDA is eligible for immediate Full Approval and the letter will acknowledge the 180-day exclusivity has expired.

Justification for Full/Tentative Approval: Litigation dismissed and no 30-month stay on the two later listed patents

180 Day Exclusivity Status/Landscape: triggered by marketing of an AG by Zydus

Citizen Petitions Impact: N/A

First Legally Approvable Date: 5/1/2015 when Zydus provided a copy of the dismissal

If Tentative Approval, anticipated full approval date: N/A

2. Final Decision

Date: _____
Name/Title: _____

ANDA received on _____ for the _____ strengths
RTR'd? Yes ☐ No ☐ If yes, RTR'd on _____ and subsequently resubmitted on _____
Priority Status? Yes ☐ No ☐ If yes, prioritization factor is _____
Basis of Submission
Drug Name _____
NDA/ANDA# _____
Applicant Name _____

Patent/Exclusivity Certifications:
As of _____, there are no applicable changes in patents/exclusivities for the RLD listed in the Orange Book since Division of Legal and Regulatory Support Endorsement dated _____.

On Policy Alert List?
Yes ☐ Pending POLICY ALERT BASIS for CLASS/DRUG/ETC (DOCKET NUMBER).
☐ Memo dated _____ from OGDP, SIGNATURE AUTHORITY, states OGD determined LIST DETERMINATION
☐ Memo not needed
No ☐ There are no issues noted on the OGD Policy Alert List as of _____

☐ All relevant disciplines are adequate and endorsements and checklists have been completed.
Additional Comments: _____

Are there visible alerts in the platform?
☐ Yes, comment on why alert does not affect OMIR _____
☐ No
The overall manufacturing inspection recommendation is approve (see screen shot below)

This ANDA is ready for FULL/TENTATIVE APPROVAL.

INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL

REFERENCES / ASSOCIATED DOCUMENTS

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

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02		Kevin Denny	Reviser	• Update form to reflect revisions to SOP (b) (4) 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

BACKLOG & COHORT YEAR 1-2 COMPLETE RESPONSE CHECKLIST**

RPM: EA Taylor **Action Type: CR**

☒ **RX or** ☐ **OTC ANDA #: 203286 Applicant: Zydus Pharmaceuticals (USA), Inc. Cohort Year: Backlog/FY2011**

ANDA Drug Name and Strength: Mesalamine Delayed-Release Tablets USP, 800 mg

Basis of Submission (RLD): NDA021830/Asacol HD Delayed-release Tablets **MAPP 5240.3 Priority ANDA:** ☒
(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☐ **Yes** ☒ **No** *(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)*

Regulatory Project Manager Evaluation:		**Date: 1/30/2017**
Yes/N/A	**No**	
☒	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A)
		Date of Product Quality Review 1/6/2017 IQ - minor Date of Bioequivalence Review 12/11/2015 AQ (see notes) Date of Labeling Review 12/15/2016 IQ If applicable: Date of Last Complete Response 4/29/2016 Date of Microbiology Review N/A Date of Dissolution Review 11/15/2013 AQ Date of Clinical Review N/A Date of REMS Review N/A
☒	☐	Is DMF adequate and/or has the first cycle review been completed (DMF 022999)? AQ per 7/29/2016, annual report only after this.
☒	☐	Are all consults complete?
☒	☐	Are all issues resolved?
☒	☐	Have all Policy issues (e.g., citizen petitions) been resolved? No alerts per 1/30/2017 DLRS PAL *If Policy issue, check with OGDP if necessary (e.g., to see whether CP blocks CR issuance).
☒	☐	Is Overall Manufacturing Inspection Recommendation task acceptable/withhold?
☒	☐	Is OSIS complete (if applicable)? Complete/AQ per 12/11/2015 BE review
		Notes (if applicable): BE guidance revision 6/2016 but per 1/31/2016 email from Eva Chan, bio remains adequate
Draft Complete Response Letter		
☒	☐	Is CR letter drafted and uploaded to "Final Decision" task?
Review Discipline/Division Endorsements		
N/A	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date _____
N/A	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date _____
Project Close-Out		
☒	☐	Is CR checklist uploaded into "Quality Check and Close Project" task?

***Entire Complete Response Checklist to be completed by the RPM*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 08/05/2016 11:44:32 AM
To: gsrinivas@zydususa.com
CC: edward.taylor@fda.hhs.gov
BCC:
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 203286

ANDA 203286

NOTIFICATION --
TARGET ACTION DATE

Zydus Pharmaceuticals (USA), Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: G. Srinivas
Head – Regulatory Affairs

Dear Sir or Madam:

This letter 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), for Mesalamine Delayed-release Tablets USP, 800 mg.

We acknowledge your response to the Complete Response letter dated June 21, 2016.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our new internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated

its comments to the applicant. In that case, the TAD will be met if the last discipline communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target
Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is February 28, 2017.

Please contact your Regulatory Project Manager, Edward Taylor at (240) 402-6094 for an additional status update of your application.

Sincerely,

Edward Taylor
Regulatory Project Manager
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

From:	OPF Facilities Questions
To:	Johnson-Nimo, Maya; OPF Facilities Questions
Cc:	Taylor, Edward
Subject:	RE: ANDA-203286-ORIG-1-AMEND-15
Date:	Friday, January 29, 2016 1:23:29 PM

Good afternoon,
An overall rec: Withhold has been entered for this application. Cadila Healthcare Limited, FEI 3002984011 was issued a Warning Letter in December 2015. If language is needed for a CR Letter, this would be "option B" as it refers to one or more sites that are unacceptable.

Ebern

From: Johnson-Nimo, Maya
Sent: Thursday, January 28, 2016 5:18 PM
To: OPF Facilities Questions
Cc: Taylor, Edward
Subject: ANDA-203286-ORIG-1-AMEND-15

Good Afternoon OPF – I am re-submitting this request as the project TAD (2/22/16) is quickly approaching. Please review and complete the overall mfr inspection recommendation task for this application.

Thank you,
Maya

From: Johnson-Nimo, Maya
Sent: Wednesday, November 18, 2015 11:17 AM
To: OPF Facilities Questions
Cc: Taylor, Edward
Subject: ANDA-203286-ORIG-1-AMEND-15

Good Morning OPF – Please review and complete the overall mfr inspection recommendation task.

Thank you,
Maya

BACKLOG & COHORT YEAR 1-2 COMPLETE RESPONSE CHECKLIST**

RPM: EA Taylor **Action Type: CR**

☒ **RX or** ☐ **OTC** **ANDA #: 203286** **Applicant: Zydus Pharmaceuticals (USA), Inc.** **Cohort Year: Backlog, FY2011**

ANDA Drug Name and Strength: Mesalamine Delayed-release Tablets USP, 800 mg

Basis of Submission (RLD): NDA021830/Asacol HD Delayed-release Tablets **MAPP 5240.3 Priority ANDA:** ☒
(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☐ **Yes** ☒ **No** *(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)*

Regulatory Project Manager Evaluation:		**Date: 4/28/2016**
Yes/N/A	**No**	
☒	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A)
		Date of Product Quality Review 4/28/2016 IQ Date of Bioequivalence Review 12/11/2015 AQ Date of Labeling Review 6/26/2015 AQ If applicable: Date of Last Complete Response 8/13/2015 Date of Microbiology Review N/A Date of Dissolution Review 11/15/2013 AQ Date of Clinical Review N/A Date of REMS Review N/A
☒	☐	Is DMF adequate and/or has the first cycle review been completed (DMF 22999)? AQ w/IR 1/6/2016
☒	☐	Are all consults complete?
☒	☐	Are all issues resolved?
☒	☐	Have all Policy issues (e.g., citizen petitions) been resolved? No Policy Alerts per 4/22/2016 DLRS list *If Policy issue, check with OGDP if necessary (e.g., to see whether CP blocks CR issuance).
☒	☐	Is Overall Manufacturing Inspection Recommendation task acceptable/withhold? OPF WH confirmation date: *1/29/2016* See confirmation email uploaded to quality check . . . task
☒	☐	Is OSIS complete (if applicable)? Complete/AQ per 5/19/2015 BE review
Draft Complete Response Letter		
☒	☐	Is CR letter drafted and uploaded to "Final Decision" task?
Review Discipline/Division Endorsements		
N/A	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date _____
N/A	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date _____
Project Close-Out		
☒	☐	Is CR checklist uploaded into "Quality Check and Close Project" task?

***Entire Complete Response Checklist to be completed by the RPM*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/01/2016 03:01:30 PM
To: gsrinivas@zydususa.com
CC: maya.johnson-nimo@fda.hhs.gov
BCC: Ying.Zhang@fda.hhs.gov, Huiquan.Wu@fda.hhs.gov
Subject: INFORMATION REQUEST for Amendment to Original 203286

Please view the attached document regarding ANDA 203286 and acknowledge receipt of this information request.

Sincerely,
Maya Johnson-Nimo, MHSA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203286
Original ANDA

INFORMATION REQUEST

Zydus Pharmaceuticals (USA) Inc.
Attention: Mr. G. Srinivas, Head Regulatory Affairs
73, Route 31 North
Pennington, NJ 08534

Dear Sir/Madam:

Please refer to your Abbreviated New Drug Application (ANDA) 203286 submitted October 19, 2015 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed Release Tablets, 800mg.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response for the deficiencies indicated below, no later than March 1, 2016 (30 days), in order to continue our evaluation of your ANDA.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

A. Deficiencies

1. (b) (4)

2. (b) (4)

3.

-End of Deficiencies-

If you do not submit a complete response by March 1, 2016 the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Send your submission through the Electronic Submission Gateway:

http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm.

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

INFORMATION REQUEST
Chemistry
Reference #: 216563

If you have any questions, please contact Maya Johnson-Nimo, Regulatory Business Project Manager, at 301-796-5885 or Maya.Johnson-Nimo@fda.hhs.gov.

Sincerely,

Maya J. Johnson-nimo -S

Digitally signed by Maya J Johnson nimo S
DN c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 1300413851 cn Maya J Johnson nimo S
Date: 2016 02 01 14:58:06 05 00

Maya Johnson-Nimo, MHSA
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 10/28/2015 03:04:46 PM
To: gsrinivas@zydususa.com
CC: edward.taylor@fda.hhs.gov
BCC:
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 203286

ANDA 203286

NOTIFICATION --
TARGET ACTION DATE

Zydus Pharmaceuticals (USA), Inc.
73 Route 31 North
Pennington, NJ 08534
Attention: G. Srinivas
Head – Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 12, 2011, received July 13, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed-release Tablets USP, 800 mg.

We acknowledge your response to the Complete Response letter dated October 19, 2015.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug
Administration (FDA), is notifying you of our new internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative

Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated its comments to the applicant. In that case, the TAD will be met if the last discipline communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target
Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target
Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is February 22, 2016.

Please contact your Regulatory Project Manager, Edward Taylor at (240) 402-6094 for an additional status update of your application.

Sincerely,

Edward Taylor
Regulatory Project Manager
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Complete Response Letter Checklists

203286 ANDA

Complete Response Letter (**not cGMP**)

Yes	No	If any statement is checked NO, STOP and DO NOT issue letter
☒	☐	All relevant discipline reviews are complete and finalized in GDRP
☒	☐	DMF first cycle review(s) complete
☒	☐	DMF Deficiency letter(s) issued to DMF holder(s) prior to ANDA CR issuance OR DMF is adequate 5/14/15
☒	☐	Status of the DMF(s) cited in the Product Quality and Microbiology (if applicable) sections is/are current →if needed, update DMF deficiencies to reflect current status per DMF Status and ANDA CR Chart Quality def #1
☒	☐	All amendments have been addressed (reviewed or deferred per IQP 4025.02)
☒	☐	There are no pending consults
☐	☒	Received clearance from REMS Coordinator (if applicable)
☒	☐	ANDA is not on hold for "other" reasons (e.g. safety, tamper resistance, abuse deterrent)
☒	☐	Chemistry (Product Quality) deficiencies have been accurately added to CR letter OR Chemistry is adequate 6/19/15
☒	☐	Bioequivalence deficiencies have been accurately added to the CR letter OR Bioequivalence is adequate 5/19/15
☒	☐	Dissolution deficiencies have been accurately added to the CR letter OR Dissolution is adequate 2/16/12-11/15/13
N/A	☐	Microbiology deficiencies have been accurately added to the CR letter OR Microbiology is adequate (if applicable)
N/A	☐	Clinical deficiencies have been accurately added to the CR letter OR Clinical is adequate (if applicable)
☒	☐	Labeling deficiencies have been accurately added to the CR letter OR Labeling is adequate 6/26/2015
☒	☐	EES is acceptable or withheld (if withheld EES provided approval of selected CR template language) OR RPM followed proper procedure to send with pending inspections Cadila 6/26/15 email
☒	☐	OSI is not pending/is not required OR RPM followed proper procedure followed to send with pending inspections Complete/AQ per 5/19/15 BE review

203286 ANDA MINOR

cGMP Complete Response Letter

Yes	No	If any statement is checked NO, STOP and DO NOT issue letter
☐	☐	All relevant discipline reviews are ADEQUATE and finalized DARRTS (including REMS)
☐	☐	There are no open amendments
☐	☐	There are no pending consults
☐	☐	OSI is adequate/is not pending
☐	☐	Received written confirmation from EES staff authorizing issuance of the cGMP CR letter referencing the withheld facility and approving the selected template language

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 06/15/2015 11:05:03 AM
To: gsrinivas@zydususa.com
CC: carol.yun@fda.hhs.gov
BCC: edward.taylor@fda.hhs.gov; carrie.lemley@fda.hhs.gov
Subject: ANDA 203286 EASILY CORRECTABLE DEFICIENCY

Dear Mr. Srinivas:

Please find attached Easily Correctable Labeling Deficiencies for your pending ANDA 203286.

Provide a complete response to these deficiencies as soon as possible but no later than June 29, 2015. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
Labeling
REFERENCE # 123198

If you do not submit a complete response by June 29, 2015, the review may be closed and the listed deficiencies may be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

Please acknowledge the receipt of this email to Carol Yun at carol.yun@fda.hhs.gov.

If you have any questions, contact Carol Yun, Labeling Project Manager, at carol.yun@fda.hhs.gov.

Sincerely,

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

EASILY CORRECTABLE DEFICIENCY

ANDA 203286

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

APPLICANT: Zydus Pharmaceuticals (USA) Inc. TEL: 609-730-1900

ATTN: G. Srinivas Email: gsrinivas@zydususa.com

FROM: Carol Yun

Dear Mr. Srinivas:

This communication is in reference to your abbreviated new drug application (ANDA), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed-release Tablets USP, 800 mg.

We acknowledge receipt of your amendment dated February 24, 2015.

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

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

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 123198

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

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

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

If you have questions regarding these deficiencies please contact the Labeling Project Manager, Carol Yun, at carol.yun@fda.hhs.gov.

We have completed our review and have the following comments:

LABELING:

1. CONTAINER- 180s (b) (4)
(b) (4)

2. PRESCRIBING INFORMATION
   a. (b) (4) – Revise this section to read as follows:
   HIGHLIGHTS OF PRESCRIBING INFORMATION
   These highlights do not include all the information needed to use MESALAMINE DELAYED-RELEASE TABLETS safely and effectively. See Full Prescribing Information for MESALAMINE DELAYED-RELEASE TABLETS.

   MESALAMINE delayed-release Tablets, (b) (4)

   ii. 11 DESCRIPTION:
   It appears that the imprinting ink is changed from (b) (4) to "Opacode black S-1-17823 in this current submission. Please justify this change with supporting documents, and/or comment.

   iii. 12.3 Pharmacokinetics – (b) (4)
   (b) (4)

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with all differences annotated and explained.

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

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

Sincerely yours,

Carol Yun -S

Digitally signed by Carol Yun -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Carol Yun -S, 0.9.2342.19200300.100.1.1=2001308951
Date: 2015.06.15 11:04:29 -04'00'

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

FDA FAX

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

TO: ZYDUS PHARMACEUTICALS USA INC TEL: 609-730-1900

ATTN: G. Srinivas FAX: 609-730-1999

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 12, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

From: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority Pre-Approval Data Validation Inspection,** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: ANDA 203-286
DRUG: Mesalamine Delayed Release Tablets, USP, 800 mg
SPONSOR: Zydus Pharmaceuticals USA, Inc.

This memo requests an inspection of the analytical portions of the following bioequivalence studies. **The site and sponsor should not be informed in advance of the application, drug name, the study to be inspected, or the focus of the inspection. The information will be provided to the sites at the inspection opening meeting.**

Study Number: MSN-P0-732
Study Title: Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 800 mg Delayed-Release Tablets in Healthy Male and Female Volunteers under Fasting State

Study Number: MSN-P0-733
Study Title: Single Dose, Partial Replicate, Crossover Comparative Bioavailability Study of Mesalamine 800 mg Delayed-Release Tablets in Healthy Male and Female Volunteers under Fed State

Analytical Site: (b) (4)

Contact Person:

Analytical Method:

(b) (4) The inspection should evaluate this possibility. In addition, OSI may identify another study at this facility in order to evaluate overall data integrity.

In addition to the above items, all pertinent items related to the analytical method for the measurement of mesalamine concentrations should be examined and the sponsor's data should be audited. The analytical data provided in the ANDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator, background material will be forwarded directly. **A scientist from DBGC with specialized knowledge may participate in the inspection to provide scientific and technical expertise.** Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspection.

Headquarters Contact Person: Sripal R. Mada, Ph.D.
(301) 796-4112

DFFI Contact Person: Arindam Dasgupta, Ph.D.
(301) 796-3326

cc:
CDER OSI PM TRACK
OSI/DBGC/Haidar/Skelly/Mada/Dejernett/Dasgupta/CF
HFC-130/ORA HQ DFFI IOB BIMO
OGD/DBE2/Davit/Mahadevan
Draft: SRM 03/09/2012
Edit: MFS 03/09/2012; 03/12/2012
DSI: 6322; O:\BE\assigns\bio203286.doc
FACTS: 1391158

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIPAL R MADA
03/12/2012

MICHAEL F SKELLY
03/12/2012
Skelly signing on behalf of Dr. Haidar

BIOEQUIVALENCE AMENDMENT

ANDA 203286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Zydus Pharmaceuticals (USA) Inc. TEL: (609) 730-1900

ATTN: G. Srinivas FAX: (609) 730-1999

FROM: Chitra Mahadevan FDA CONTACT PHONE: (240) 276-8817

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 12, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Delayed Release Tablets USP, 800 mg.

The Division of Bioequivalence II has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached ____ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Long Term Stability

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 203286

APPLICANT: Zydus Pharmaceuticals (USA) Inc.

DRUG PRODUCT: Mesalamine Delayed Release Tablets USP, 800 mg

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

The submitted Long Term Storage Stability (LTSS) data is not sufficient to cover the maximum storage period of the fasting (#MSN-P0-732) and fed (#MSN-P0-733) bioequivalence (BE) studies. Please submit sufficient LTSS to cover at least the maximum storage period (116 days) for the mesalamine fasting and fed BE study samples.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA M DAVIT
03/08/2012

OSI Consult Request for Biopharmaceutical Inspections	
Date	March 6, 2012
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sam H. Haidar, Ph.D., R.Ph. Chief, Bioequivalence Investigations Branch Division of Bioequivalence and GLP Compliance Office of Scientific Investigations
Consulting Office/Division	OGD/DB2
Project Manager	Mahadevan, Chitra
Application Type	PEPFAR? ☐ Yes ☒ No
	☐ NDA ☐ BLA ☒ ANDA
Application Number	203286
Drug Product	Mesalamine Delayed Release Tablets USP, 800 mg
Sponsor Name	Zydus Pharmaceuticals (USA) Inc.
Sponsor Address	73, Route 31 North, Pennington, NJ 08534
US Agent (if applicable)	G. Srinivas
US Agent Address	Zydus Pharmaceuticals USA Inc., 73, Route 31 North, Pennington, NJ 08534
Electronic Submission	☒ Yes ☐ No
PDUFA Due Date Action Goal Date OSI Review Requested By	 June 6, 2012 Barbara M. Davit, Ph.D., J.D.

Inspection Request Detail (All fields should be fill out completely)				
Study #1				
Study Number	MSN-P0-732			
Study Title	Fasting BE Study			
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)

☐ Inspection Request - Clinical Site	☒ Inspection Request - Analytical Site
Facility #1 Name: Address: (Tel) (Fax)	(b) (4)
Clinical Investigator: (email)	Principal Analytical Investigator: (b) (4)
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator: (email)	Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator: (email)
Check one: ☐ Routine inspection ☐ For cause	Check one: ☒ Routine inspection ☐ For cause
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	
☐ Study Report: (location, eg., 5.3.1.2)	☐ Validation Report: (eg., 5.3.1.2) ☐ Bioanalytical Report: (eg., 5.3.1.4)

Study #2				
Study Number	MSN-P0-733			
Study Title	Fed BE Study			
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)

☐ Inspection Request - Clinical Site	☒ Inspection Request - Analytical Site
Facility #1 Name: (or indicate if same as above) Address: (Tel) (Fax)	Facility #1 Name: Same as above Address: (Tel) (Fax)
Clinical Investigator: (email)	Principal Analytical Investigator: (b) (4)
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator: (email)	Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator: (email)
Check one: ☐ Routine inspection ☐ For cause	Check one: ☒ Routine inspection ☐ For cause
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	
☐ Study Report: (location, eg., 5.3.1.2)	☐ Validation Report: (eg., 5.3.1.2) ☐ Bioanalytical Report: (eg., 5.3.1.4)

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection
Please conduct a new routine inspection of the analytical site only. The last inspection request was made in February 2009.

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/s/

CHITRA MAHADEVAN
03/06/2012

BARBARA M DAVIT
03/08/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 203286

Zydus Pharmaceuticals (USA) Inc.
Attention: G. Srinivas
73 Route 31 North
Pennington, NJ 08534

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Mesalamine Delayed-release Tablets USP, 800 mg

DATE OF APPLICATION: July 12, 2011

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 13, 2011

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8675.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Frank J. Nice
Project Manager
240-276-8555

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN H Shimer
09/09/2011
Signing for Wm Peter Rickman

ANDA FILING CHECKLIST

(CTD or eCTD FORMAT)

FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 203286
APPLICANT: ZYDUS PHARMACEUTICALS (USA) INC.
RELATED APPLICATION(S): NA

DRUG NAME: MESALAMINE
DOSAGE FORM: DELAYED-RELEASE TABLETS USP, 800 MG

LETTER DATE: **JULY 12, 2011**
RECEIVED DATE: JULY 13, 2011

☒ P-IV
☒ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST (Approved/Denied)
☐ PEPFAR

Electronic or Paper Submission: Gateway

Type II DMF# MESALAMINE - 22999 (8/3/2009)

BASIS OF SUBMISSION:
NDA/ANDA: 21-830
FIRM: WARNER CHILCOTT
RLD: ASACOL HD

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: **DC2 TM 21** ☒ **Activity**	Bio Team: **DBE 2 TM7: Xiaojian Jiang** ☒ **Activity**
CHEM Team Leader: Radhika Rajagopalan ☒ **No Assignment Needed in DARRTS**	Bio PM: Chitra Mahadevan ☐ **FYI**
CHEM RPM: **Frank J. Nice** ☒ **FYI**	Clinical Endpoint Team: **(No)** ☐ **Activity**
DMF Review Team Leader: **Aloka Srinivasan** ☒ **FYI**	
Labeling Reviewer: **Park, Sarah** ☒ **Activity**	Micro Review: **(No)** ☐ **Activity**

Regulatory Reviewer: **Johnny Young** Date: **September 2, 2011**	Recommendation: ☒ **FILE** ☐ **REFUSE to RECEIVE**

Comments: EC- 1 YES
Therapeutic Code: 8015651 ULCERATIVE COLITIS
On Cards: YES
Archival copy: **ELECTRONIC (GATEWAY)**
Sections: I

- **For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www.fda.gov/cder/regulatory/ersr/ectd.htm**
- **For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
- **For more CTD and eCTD informational links see the final page of the ANDA Checklist**
- **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/**

1. Edit Application Property Type in DARRTS where applicable for

a. First Generic Received
☒ Yes ☐ No
b. Market Availability
☒ Rx ☐ OTC
c. Pepfar
☐ Yes ☒ No
d. Product Type
☒ Small Molecule Drug
e. USP Drug Product (at time of filing review)
☒ Yes ☐ No

2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. EER (in Draft)
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

G. Srinivas 609.730.1900; (f) 609.730.1999

Sent pharm/tox info on consult to DGP on 7/28/2011 for evaluation of proposed Eudragit S (b) (4) level.

Awaiting DBE filing review. Ok to file

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 203286 **FIRM NAME** **Zydus Pharmaceuticals (USA) Inc.**

DRUG NAME Mesalamine Delayed Release Tablets USP

DOSAGE FORM Delayed Release Tablets, 800 mg
SUBJ: Request for examination of: if Zydus Pharmaceuticals (USA) Inc.' s Mesalamine Delayed Release Tablets, 800 mg, satisfies the statutory requirements of "completeness".

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason: Only one strength (800 mg) for this application

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____Ping Ren_____ Date: _____08/09/2011____

Reviewer

_____Xiaojian Jiang_____ Date: _____8/17/2011_____

Team Leader

MODULE 1: ADMINISTRATIVE

		COMMENT (S)
1.1	**Signed and Completed Application Form (356h)** (Rx/OTC Status) Yes (original signature)	
1.1.2	**Establishment Information:** Yes 1. Drug Substance Manufacturer 2. Drug Product Manufacturer 3. Outside Testing Facility(ies)	
1.2	**Cover Letter** Yes	
1.2.1	**Form FDA 3674** (PDF) B	
*	**Table of Contents** (paper submission only) N/A	
1.3.2	**Field Copy Certification** (N/A for E-Submissions) N/A (original signature)	
1.3.3	**Debarment Certification-GDEA** (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes	
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes Disclosure Statement (Form FDA 3455) N/A	
1.3.5	**Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **Patent Certification** 1. Patent number(s) III: '170, '171; IV: '662 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 11/15/2021 a. Pediatric exclusivity submitted? No b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: State marketing intentions? **Patent and Exclusivity Search Results from query on Appl No 021830 Product 001 in the OB_Rx list.**	No unexpired exclusivity

<>

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021830	001	5541170	Jul 30, 2013		Y	U - 141	
N021830	001	5541171	Jul 30, 2013		Y	U - 141	
N021830	001	6893662	Nov 15, 2021		Y	U - 141	

<>

	Appl No **Prod No** **Exclusivity Code** **Exclusivity Expiration** **N021830** **001** **NP** **May 29, 2011**	
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# MESALAMINE - 22999 c. Type III DMF authorization letter(s) for container closure Yes 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	
1.12.4	**Request for Comments and Advice** - Proprietary name requested No If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes N/A 2. No - contact the firm to submit the request as a separate electronic amendment.	
1.12.11	**Basis for Submission** NDA#: 21-830 Ref Listed Drug: ASACOL HD Firm: WARNER CHILCOTT **ANDA suitability petition required?** No If Yes, provide petition number and copy of approved petition **ANDA Citizen's Petition Required?** No If Yes, provide petition number and copy of petition	

MODULE 1: ADMINISTRATIVE (Continued)

		COMMENT (S)
1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use x 2. Active ingredients x 3. Inactive ingredients x 4. Route of administration x 5. Dosage Form x 6. Strength x	
1.12.14	**Environmental Impact Analysis Statement** **(**cite 21CFR 25.31, if applicable) Yes	
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies) N/A	
1.14.1	**Draft Labeling** (Multi Copies N/A for E-Submissions) **1.14.1.1** 4 copies of draft for paper submission only (each strength and container) Yes **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences visually highlighted and annotated Yes **1.14.1.3** 1 package insert (content of labeling) and SPL submitted electronically Yes	(b) (4) 180s, (b) (4) BPs, bulk
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated Yes **1.14.3.3** RLD package insert, 1 RLD label and 1 RLD container label Yes	

MODULE 2: SUMMARIES

		COMMENT (S)
2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** Yes **Word Processed e.g., MS Word** Yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** Yes **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** Yes 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability **2.3.P Drug Product** Yes 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	
2.7	**Clinical Summary (Bioequivalence)**Model BE Data Summary Tables **E-Submission: PDF** Yes **Word Processed: e.g., MS Word** Yes **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Yes Table 4. Bioanalytical Method Validation Yes Table 6. Formulation Data Yes **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution Yes **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Yes Table 3. Statistical Summary of the Comparative BA Data Yes **2.7.1.4 Appendix** N/A **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies Yes	

MODULE 3: 3.2.S DRUG SUBSTANCE

		COMMENT (S)
3.2.S.1	**General Information** (Do not refer to DMF) Yes **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	
3.2.S.2	**Manufacturer** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) x 2. Contact name, phone and fax numbers, email address Yes 3. Specify Function or Responsibility Yes 4. Type II DMF number for API 22999 5. CFN or FEI numbers x	
3.2.S.3	**Characterization** Yes Provide the following in tabular format: 1. Name of Impurity(ies) 2. Structure of Impurity(ies) 3. Origin of Impurity(ies)	
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Yes Testing specifications and data from drug substance manufacturer(s) **3.2.S.4.2 Analytical Procedures** Yes **3.2.S.4.3 Validation of Analytical Procedures** (API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) Yes 1. Spectra and chromatograms for reference standards and test samples Yes 2. Samples-Statement of Availability and Identification of: a. Drug Substance Yes b. API lot number(s) x **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Yes 2. Applicant certificate of analysis Yes **3.2.S.4.5 Justification of Specification** Yes	
3.2.S.5	**Reference Standards or Materials (**Do not refer to DMF) Yes	
3.2.S.6	**Container Closure Systems** Yes	
3.2.S.7	**Stability** 1. Retest date or expiration date of API Yes	

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)
3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition with indication of the function of the inactive ingredient(s) Yes 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) Yes 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) N/A 4. (b) (4) 5. Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration N/A	
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report Yes	
3.2.P.3	**Manufacture** **3.2.P.3.1 Drug Product** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) x 2. Contact name, phone and fax numbers, email address Yes 3. Specify Function or Responsibility Yes 4. CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes 5. CFN or FEI numbers x **3.2.P.3.2 Batch Formula** Yes **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Yes 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified x 3. Master packaging records for intended marketing container(s) Yes 4. If sterile product N/A 5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes **3.2.P.3.4 Controls of Critical Steps and Intermediates** Yes **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A	(b) (4)
3.2.P.4	**Controls of Excipients** (Inactive Ingredients) Source of inactive ingredients identified Yes **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Yes 2. Suppliers' COA (specifications and test results) Yes **3.2.P.4.2 Analytical Procedures** N/A **3.2.P.4.3 Validation of Analytical Procedures** N/A **3.2.P.4.4 Justification of Specifications:** 1. Applicant COA Yes	

MODULE 3: 3.2.P DRUG PRODUCT (Continued)

		COMMENT (S)
3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** Yes **3.2.P.5.2 Analytical Procedures** Yes **3.2.P.5.3 Validation of Analytical Procedures** (if using USP procedure, must provide verification of USP procedure) Yes Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Yes 2. Lot number(s) and strength of Drug Product(s) EMK150 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form Yes **3.2.P.5.5 Characterization of Impurities** Yes **3.2.P.5.6 Justification of Specifications** Yes	
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Yes 2. Components Specification and Test Data Yes 3. Packaging Configuration and Sizes (b) (4) 4. Container/Closure Testing (recommended additional testing for all plastic)Yes a. Solid Orals: water permeation, light transmissionYes b. Liquids: leachables, extractables, light transmissionN/A 5. Source of supply and suppliers address Yes	
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted Yes 2. Expiration Dating Period (b) (4) **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Yes **3.2.P.8.3 Stability Data** 1. Accelerated stability data a. four (4) time points 0,1,2,3 Yes **-OR-** b. three (3) time points 0,3,6 (if 3 time points for accelerated stability data are submitted then provide 3 exhibit batches along with 12 months of room temperature stability data –Refer to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products November 2003, Section B) N/A 2. Batch numbers on stability records the same as the test batch Yes	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	**3.2.R.1.S Executed Batch Records for drug substance (if available)** Select **3.2.R.2.S Comparability Protocols** Select **3.2.R.3.S Methods Validation Package** Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Yes a. Theoretical Yield (b) (4) b. Actual Yield (b) (4) c. Packaged Yield (b) (4) Bulk Package Reconciliation required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: a. Bulk Package Label (1.14.1) Yes b. Bulk Package Stability (accelerated stability data [0,1,2,3] –**OR**- room temperature [0,3,6]) (3.2.P.8) Yes c. Bulk Package Container and Closure information (3.2.P.7) Yes **3.2.R.1.P.2 Information on Components** Yes **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	**Tabular Listing of Clinical Studies** Yes	
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v) N/A **2. Lot Numbers and strength of Products used in BE Study(ies)** EMK150 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. Summary Bioequivalence tables: Table 10. Study Information Yes Table 12. Dropout Information Yes Table 13. Protocol Deviations Yes **5.3.1.3 In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables Yes Table 11. Product Information Yes Table 16. Composition of Meal Used in Fed Bioequivalence Study Yes **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Yes Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Yes Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples Yes **Case Report Forms** should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4	**Literature References**	
	Possible Study Types:	

Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 800 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Yes 3. In-Vitro Dissolution Yes	12 –unit in 3.2.P.2
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80,1.25) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select	
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** **1. Solutions (Q1/Q2 sameness)** Select a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select **2. Suspensions (Q1/Q2 sameness):** a. In-Vivo PK Study Select 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select b. In-Vivo BE Study with Clinical End Points Select 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select	
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) Select 2. Pivotal Study (study meets BE criteria 90%CI of 80-125) Select	
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study Select a. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) Select b. In-Vitro Dissolution Select c. EDR Email: Data Files Submitted Select 2. Adhesion Study Select 3. Skin Irritation/Sensitization Study Select	

Updated 05/16/2011

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021830		Yes	MESALAMINE	TABLET, DELAYED RELEASE; ORAL	800MG	ASACOL HD	WARNER CHILCOTT LLC

Search results from the "OB_Rx" table for query on "021830."

Active Ingredient: MESALAMINE
Dosage Form;Route: TABLET, DELAYED RELEASE; ORAL
Proprietary Name: ASACOL HD
Applicant: WARNER CHILCOTT LLC
Strength: 800MG
Application Number: N021830
Product Number: 001
Approval Date: May 29, 2008
Reference Listed Drug Yes
RX/OTC/DISCN: RX

U - 141 TREATMENT OF ULCERATIVE COLITIS

- Quantitative composition of Mesalamine Delayed Release Tablets USP, 800 mg:

Name of Ingredient	Quantity/ Tablet (mg)	Quantity (% w/w)/Tablet[$]
(b) (4)		
Mesalamine, USP	800.000	(b) (4)
Sodium Starch Glycolate, NF (b) (4)	(b) (4	
Colloidal Silicon Dioxide, NF (b) (4)		
Magnesium Stearate, NF		
(b) (4)		
Microcrystalline Cellulose, NF (b) (4)		
Povidone (b) (4) USP (b) (4)		
(b) (4)		
(b) (4)		
Sodium Starch GlycolateNF, (b) (4)		
Talc, USP (b) (4)		
Colloidal Silicon Dioxide, NF (b) (4)		
Magnesium Stearate, NF		
(b) (4)		
Methacrylic Acid Copolymer, NF - Type B (Eudragit S (b) (4)		
Talc, USP		
Acetyltributyl Citrate, NF		
Titanium Dioxide, USP (b) (4)		
Ferric Oxide Red, NF		
Isopropyl Alcohol, USP*		
(b) (4)		
(b) (4)		
Opacode Black (b) (4)		
Isopropyl Alcohol, USP*		
Total	1102.400	100.000
(b) (4)		

Maximum Daily Dose: 4.8 mg/day
Strength: 800mg

Inactive ingredient(s)	Listing In the Inactive Ingredients Database	Mesalamine Delayed Release Tablets USP, 800 mg	Levels recommended in Inactive Ingredients Database(mg) (Oral route)
Sodium Starch Glycolate, NF	Yes	(b) (4)	
Colloidal Silicon Dioxide, NF	Yes		
Magnesium Stearate, NF	Yes		
Microcrystalline Cellulose, NF	Yes		
Povidone (b) (4) USP	Yes		
Talc, USP	Yes		
Methacrylic Acid Copolymer, NF - Type B (Eudragit S (b) (4)	Yes		
Acetyltributyl Citrate, NF	Yes		
Titanium Dioxide, USP	Yes		
Ferric Oxide Red, NF	Yes		

(b) (4)

INGREDIENT	ROUTE;DOSAGE FORM	UNII	NDA COUNT	LAST NDA	APPROVAL DATE	DIV	MAXIMUM POTENCY/UNIT
(b) (4)							

Mesalamine 800 mg delayed-release tablet 1× 800 mg Scaled Average Bioequivalence		
Fasted Bioequivalence Study (MSN-P0-732)		
Parameter	**Ratio**	**95% Upper bound CI**
AUCt	118.34%	-0.3629
AUCi	116.59%	-0.2075
Cmax	122.94%	-0.4024
Fed Bioequivalence Study (MSN-P0-733)		
Parameter	**Ratio**	**95% Upper bound CI**
AUCt	97.91%	-0.4230
AUCi	95.42%	-0.3489
Cmax	101.05%	-0.8187

Note: The intra-subject CVs (coefficient of variation) for Cmax, AUCt and AUCi exceeded 30% when administered under fasting and fed conditions, hence the scaled bioequivalence approach was used for Cmax, AUCt and AUCi.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHNNY L YOUNG
09/08/2011

MARTIN H Shimer
09/09/2011

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 203286 **FIRM NAME** **Zydus Pharmaceuticals (USA) Inc.**

DRUG NAME Mesalamine Delayed Release Tablets USP

DOSAGE FORM Delayed Release Tablets, 800 mg
SUBJ: Request for examination of: if Zydus Pharmaceuticals (USA) Inc.' s Mesalamine Delayed Release Tablets, 800 mg, satisfies the statutory requirements of "completeness".

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason: Only one strength (800 mg) for this application

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____Ping Ren_____ Date: _____08/09/2011____

Reviewer

_____Xiaojian Jiang_____ Date: _____8/17/2011_____

Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.4 Report of BA and Analytical Methods for Human Studies 5.3.1.4.3: Attachment 5: Fasting study: MSN-P0-732 Bioanalysis of mesalamine in human in support of clinical protocol: Protocol No.SAP1186007. Fed study: MSN-P0-733 Bioanalysis of mesalamine in human in support of clinical protocol: Protocol No.SAP1186008. 5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.4. Protocol or Amendment: Fasting-protocol-and amendment: MSN-P0-732 Fed-protocol-and amendment: MSN-P0-733
Assay Methodology	☒	☐	1	1	5.3.1.4 Report of BA and Analytical Methods for Human Studies
Procedure SOP	☒	☐	3	3	5.3.1.3.3. Study Report Body: disso-test-method: QC/STP/F/2990-03 (Dissolution testing SOP). 5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.4 Report of BA and Analytical Methods for Human Studies 5.3.1.4.3: Attachment 1: (b) (4) Sample Analysis (Chromatographic), (b) (4) (Sample Reanalysis and Reporting Criteria). Attachment 4: (b) (4) (Incurred sample reanalysis)

Methods Validation	☒	☐	1	1	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview: table 4 Bioanalytical Method Validation. 5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies: Appendix 16.6 Analytical method validation report.
Study Results Ln/Lin	☒	☐	2	2	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview: table 6 Summary of Statistical Analysis of Mesalamine Data-Scaled Average BE
Adverse Events	☒	☐	2	2	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview: table 8 Incidence of Adverse Events in Individual Studies (Fasting and Fed studies)
IRB Approval	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.6. IEC IRB Consent Form List
Dissolution Data	☒	☐	1	1	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview: table 5 Summary of In Vitro Dissolution Studies: multiple-media dissolution testing. 5.3.1.3.3. Study Report Body: 5313-in-vit-in-viv-corr-stud-repo-rel-info: raw data of dissolution.
Pre-screening of Patients	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE

					Study Reports 5.3.1.2.3. Study Report Body: 5312-stud-info-formu-data: 9.3. Selection of study populations
Chromatograms	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.4 Report of Bioanalytical and Analytical Methods for Human Studies 5.3.1.4.3: Attachment 3: Chromatograms.
Consent Forms	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.6. IEC IRB Consent Form List
Composition	☒	☐	1	1	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview: table 6 Formulation Data. 3. Quality 3.2.P. Drug Product 3.2.P.1. Description and Composition of the Drug Product: 32p 1-descr-compo-drug-prod
Summary of Study	☒	☐	1	1	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth
Individual Data & Graphs, Linear & Ln	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.3.Study Report Body: fasting-study-rep fed-study-rep
PK/PD Data Disk Submitted)	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.25. Individual Subject Data Listing 5.3.1.2.25.2.1. Data Listing Dataset:

					Mesalamine-Fasting-drug 1 Mesalamine-Fasting-drug 2 Mesalamine-Fed-drug 1 Mesalamine-Fed-drug 2
Randomization Schedule	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.10. Randomization Schedule (fasting and fed BE studies)
Protocol Deviations	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.17 Protocol Deviations: fasting-protocol-deviation fed-protocol-deviation
Clinical Site	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.3. Study Report Body: 5312-summ-bioequi-tables (fasting and fed studies)
Analytical Site	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.3. Study Report Body: 5312-summ-bioequi-tables (fasting and fed studies)
Study Investigators	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.7 List Description Investigator Site: fasting-stud-rep fed-stud-rep
Medical Records	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports

					5.3.1.2.24. Case Report Form
Clinical Raw Data	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.21 Individual Efficacy Response Data: Fasting-ind-eff-response data Fed-ind-eff-response data
Test Article Inventory	☒	☐	1	1	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.3. Study Report Body: Fasting-stud-rep Fed-stud-rep 9.4.8. Treatment Compliance 9.4.8.1. Drug Accountability
BIO Batch Size	☒	☐	1	1	3. Quality 3.2.R. Regional Information 32r-regional-information 3.2.R.1.P.1 Executed Batch Records
Assay of Active Content Drug	☒	☐			5.3.1.3.3. Study Report Body: 5313-summ-bioequi-tables
Content Uniformity	☒	☐			5.3.1.3.3. Study Report Body: 5313-summ-bioequi-tables
Date of Manufacture	☒	☐	1	1	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview. 5.3.1.3.3. Study Report Body: 5313-summ-bioequi-tables
Exp. Date of RLD	☒	☐	1	1	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview. 5.3.1.3.3. Study Report Body: 5313-summ-bioequi-tables

BioStudy Lot Numbers	☒	☐	1	1	5.3.1.3.3. Study Report Body: 5313-summ-bioequi-tables
Statistics	☒	☐	2	2	5.3 CLINICAL STUDY REPORTS 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.2.Comparative BA and BE Study Reports 5.3.1.2.21 Individual Efficacy Response Data: Fasting-ind-eff-response data Fed-ind-eff-response data
Summary results provided by the firm indicate studies pass BE criteria	☒	☐	2	2	2.7.1. Summary of Biopharmaceutic Studies and Associate Analytical Methods: sum-biopharm-studies-asso-anal-meth: 2.7.1.1. Background and Overview: table 3 Statistical Summary of the Comparative BA Data (Reference scaled average BE studies)
Waiver requests for other strengths / supporting data	☐	☒	0	0	N/A, there is only one strength of 800 mg in this application

Additional Comments regarding the ANDA:

1. This Application for Mesalamine Delayed Release Tablets USP, 800 mg, is based on reference listed drug (RLD) Asacol® HD (mesalamine) delayed-release tablet, 800 mg, which was approved in the United States in May 29, 2008 (NDA 021830).

2. Mesalamine Delayed Release Tablets is a locally acting aminosalicylate indicated for the treatment of moderately active ulcerative colitis. In two citizen's petitions[1], the innovators asked the Agency that the applicants for generic formulations of delayed release orally administered mesalamine drug products should show bioequivalence to Asacol and Asacol® HD based on comparative clinical endpoint studies, comparative in vitro dissolution tests, and comparative pharmacokinetic (PK) safety studies under fasting and fed conditions. Yet, in the Agency's responses to the Citizen's Petition, the FDA concluded that in light of new pharmacokinetic data from comparative studies in modified-release mesalamine products, the applications should demonstrate bioequivalence of mesalamine delayed release tablets to reference products (RLD: Asacol and Asacol HD) through a combination of PK bioequivalent (BE) studies and in vitro drug release (dissolution) under multiple conditions representative of the conditions in the GI tract rather than comparative clinical endpoint studies. Also, the Agency suggests using partial AUC (pAUC) or other profile comparison tools to demonstrate

1 Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507

bioequivalence for mesalamine products in addition to standard calculations of AUC and Cmax. The OGD is currently in the process of posting the BE recommendation for this product. In the guidance, the FDA will define the pAUC range and provide the in vitro BE studies (dissolution testing) methods.

3. **The Results of Fasting and Fed BE studies:**

The firm conducted single center, randomized, single dose, 3-period, 3-sequence, partial-reference replicated, crossover study bioequivalence studies in normal healthy male and female subject under Fasting and Fed conditions.

Mesalamine 800 mg delayed-release tablet 1× 800 mg Scaled Average Bioequivalence*		
Fasted Bioequivalence Study (MSN-P0-732), N=88		
Parameter	**Ratio**	**95% Upper bound CI**
AUCt	118.34%	-0.3629
AUCi	116.59%	-0.2075
Cmax	122.94%	-0.4024
Fed Bioequivalence Study (MSN-P0-733), N=83		
Parameter	**Ratio**	**95% Upper bound CI**
AUCt	97.91%	-0.4230
AUCi	95.42%	-0.3489
Cmax	101.05%	-0.8187

*The intra-subject CVs (coefficient of variation) for Cmax, AUCt and AUCi exceeded 30% when administered under fasting and fed conditions; hence the reference-scaled average bioequivalence approach was used for Cmax, AUC0-Tmax, AUCTmax-24hrs, AUCt, and AUCi.

Note: Since the agency is currently in the process of posting the BE guidance and there is no clearly stated pAUC criteria. The pAUC calculation will be a review issue and the study is acceptable for filing at this time.

4. **The results of in vitro comparative BE dissolution study**

Method:

Apparatus: USP Apparatus 2 (paddle)
Pretreatment Stage: 2 hours in 0.1 N HCl at 100 rpm
Evaluation Stage1: Each of pH 6.0-7.5 Phosphate buffer at 50 rpm.
Volume: 900 mL

Results:

Test No.	First Medium	Followed by Media	F2	Comment
1	0.1 N HCl	pH 6.0 Phosphate Buffer	N/A	No individual value exceeds 1% dissolved
2	0.1 N HCl	pH 6.5 Phosphate Buffer	N/A	High %CV and low Concentration
3	0.1 N HCl	pH 6.8 Phosphate Buffer	15.59	High %CV
4	0.1 N HCl	pH 7.2 Phosphate Buffer	62.29	
5	0.1 N HCl	pH 7.5 Phosphate Buffer	51.68	

Note: The firm did not submit the in vitro comparative dissolution study for 2 hours in 0.1 N HCl followed by pH 4.5 Acetate buffer. The firm will be requested to submit the data of in vitro comparative dissolution testing in pH 4.5 Acetate buffer at the time of dissolution review.

5. Quality Control (QC) Dissolution study

USP dissolution method and specifications:
Dissolution Media: (b) (4) 0.1 N hydrochloric acid, 500 mL (Acid stage);
pH 6.0 Phosphate buffer, 900 mL (Buffer stage 1); and
pH 7.2 Phosphate buffer, 900 mL (Buffer stage 2)
Apparatus: USP Apparatus II (Paddle)
Speed: 100 rpm for Acid stage and for Buffer stage 1;
50 rpm for Buffer stage 2.
Times: 2 hours for Acid stage;
1 hour for Buffer stage 1;
90 minutes for Buffer stage 2.
Specifications for acid and buffer stage 1:

Acceptance Table

Level	Number Tested	Criteria
L_1	6	No individual value exceeds 1% dissolved.
L_2	6	Average of the 12 units ($L_1 + L_2$) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved.
L_3	12	Average of the 24 units ($L_1 + L_2 + L_3$) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved.

Specifications for the buffer stage 2:

Not less than 80% *(Q)* of the labeled amount of $C_7H_7NO_3$ is dissolved in 90 min.

Note: There is a USP method for this product. The firm's dissolution testing data with the USP method are acceptable. The firm's proposed specification is the same as the USP specification. The data of QC dissolution testing is acceptable.

6. Formulation

Comparative list of excipients used in the RLD product and the proposed Generic product along with the functions:

Reference Product	Proposed generic drug product	Function
Sodium starch glycolate	Sodium Starch Glycolate, NF (b) (4) (b) (4)	(b) (4)
Colloidal silicon dioxide	Colloidal Silicon Dioxide, NF (b) (4)	
Magnesium stearate	Magnesium Stearate, NF	
Lactose monohydrate	Microcrystalline Cellulose, NF (b) (4)	
Povidone	Povidone (b) (4) USP (b) (4)	
Talc	Talc, USP	
Methacrylic acid copolymer (b) (4) (Eudragit S)	Methacrylic Acid Copolymer, NF (b) (4) (Eudragit S (b) (4)	
Methacrylic acid copolymer (b) (4) (Eudragit L)	----	
Polyethylene glycol	Acetyltributyl Citrate, NF	
Dibutyl (b) (4)	----	
----	Titanium Dioxide, USP (b) (4) (b) (4)	
Ferric oxide red and yellow	Ferric Oxide Red, NF	
Edible black ink	Opacode Black (b) (4)	

Note: Compared to the reference formulation, majority of excipients used in the test product are the same as those presented in the reference product.

7. Overall Comments:

The Division of Bioequivalence II (DB II) acknowledge that the firm has submitted PK data under the fasting and fed conditions, the data of in vitro comparative dissolution study, and QC dissolution testing data to support its bioequivalence of mesalamine delayed release tablets to reference product (RLD: Asacol® HD). The DB II found this application acceptable for filing based on the data of in vitro comparative dissolution testing and standard calculations of AUC and Cmax. Yet, the calculation of pAUC was not used as the standard for filing because it is unclear about correct pAUC criteria at present. Therefore, the DB II recommends that the Office of Generic Drugs receive this application for filing.

Enter Review Productivity and Generate Report

ANDA: 203286

Reviewer: Ren, Ping **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Mesalamine Delayed Release Tablets USP 800 MG

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
14805	7/12/2011	Paragraph 4	Paragraph 4 Checklist	1	1	Edit	Delete
				Bean Total:	1		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Application

First Generic Checklist	1
Total	*1*

Grand Total	**1**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PING REN
08/29/2011

XIAOJIAN JIANG
08/29/2011

BARBARA M DAVIT
08/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0543	
TO *(Division/Office)* DGP - HFD-180 Thru: Richard (Wes) Ishihara, ODEIII HFD-103			FROM: Johnny Young, R. Ph. (OGD)	
DATE: 7/28/2011	IND NO.	ANDA NO. 203286	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 7/12/2011
NAME OF DRUG Mesalamine Delayed-release Tablets USP, 800 mg		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Ulcerative Colitis Product	DESIRED COMPLETION DATE 9/26/2011

NAME OF FIRM Zydus Pharmaceuticals (USA) Inc.

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICIENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

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

IV.DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS:

OGD is requesting this consult in order to determine if the firm's proposed level of Eudragit S (b) (4) used in their product's formulation is acceptable.

Each delayed-release tablet contains (b) (4) of the inactive and is dosed 2 tabs tid. Therefore, the MDD of the inactive is (b) (4)

Please comment whether both the amount per dosage unit and the MDD proposed for this inactive are acceptable. Included with this consult request are pdfs of the pharm/tox report submitted by the applicant in its ANDA and the drug product formulation.

Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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/s/

JOHNNY L YOUNG
07/28/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : July 19, 2011

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 203286 for Mesalamine Delayed release Tablets, 800mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv). **(The new strength and first generic product. is 800 mg.)**

Zydus Pharmaceuticals USA has submitted ANDA 203286 for Mesalamine Delayed release Tablets, 800mg. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Zydus Pharmaceuticals USA on July 13, 2011 for its Mesalamine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

EDA E HOWARD
07/19/2011