

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : June 5, 2003
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 for Mesalamine Rectal Suspension USP, 4 gram/60 mL to determine if the application is substantially complete for filing.

*Mark H. ... 5 June 2003
Regulatory Support Branch
Chief*

Agis Industries LTD. has submitted ANDA 76-751 for, Mesalamine Rectal Suspension USP, 4 gram/ 60 mL. 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 Agis Industries LTD. on May 30, 2003 for its Mesalamine Rectal Suspension 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".

JUN 13 2003

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 76-751 FIRM NAME Agis Industries (1983) LTD.

DRUG NAME Mesalamine Rectal Suspension USP

DOSAGE FORM Rectal Suspension USP, 4 gram/60 mL

SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence	
<input type="checkbox"/>	Study meets statutory requirements
<input checked="" type="checkbox"/>	Study does NOT meet statutory requirements
	Reason: Lack of in vitro dissolution data
<input type="checkbox"/>	Waiver meets statutory requirements
<input type="checkbox"/>	Waiver does NOT meet statutory requirements
	Reason: N/A

RECOMMENDATION: COMPLETE INCOMPLETE

Reviewed by:

Zakaria Wahba Zakaria Z. Wahba Date: 6/13/03
Reviewer

Gur-Jai Pal Singh Gur-Jai Pal Singh Date: 6-13-03
Team Leader

sa Dale Conner Date: Barbara N. DeWitt
Director, Division of Bioequivalence

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Assay Methodology	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Procedure SOP	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Methods Validation	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Study Results Ln/Lin	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Adverse Events	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
IRB Approval	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Dissolution Data	<input type="checkbox"/>	<input checked="" type="checkbox"/>			required
Pre-screening of Patients	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Chromatograms	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Consent Forms	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Composition	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Summary of Study	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Individual Data & Graphs, Linear & Ln	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
PK/PD Data Disk Submitted)	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Randomization Schedule	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Protocol Deviations	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Clinical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Analytical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Study Investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>			

Medical Records	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Clinical Raw Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Test Article Inventory	<input type="checkbox"/>	<input checked="" type="checkbox"/>			required
BIO Batch Size	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Assay of Active Content Drug	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Content Uniformity	<input type="checkbox"/>	<input checked="" type="checkbox"/>			required
Date of Manufacture	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Exp. Date of RLD	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
BioStudy Lot Numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Statistics	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Summary results provided by the firm indicate studies pass BE criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Waiver requests for other strengths / supporting data	<input type="checkbox"/>	<input checked="" type="checkbox"/>			N/A

Additional Comments regarding the ANDA:

The RLD is Solvay's Rowasa Rectal Enema (NDA #19-618)

The following items are not provided in the submission

- 1. In vitro Dissolution data on the test and RLD product.**
- 2. Test article inventory.**
- 3. Content uniformity**

RECORD OF TELEPHONE CONVERSATION

<p>This call was made to relay the following deficiency:</p> <p>It is required for the drug product stability specifications to meet the USP requirements. The data presented does not provide justification for _____.</p> <p>The firm has agreed to revise and send in new spec sheets.</p>	DATE: 5-4-2004
	ANDA NUMBER: 76-751
	PRODUCT NAME: Mesalamine Rectal Suspension
	Firm Name: <i>Clay Park</i>
	FIRM REPRESENTATIVE: Candice Edwards
	PHONE NUMBER: 718-960-9976
	FDA REPRESENTATIVES: Brenda Arnwine Shahnaz Read Nicole Lee
SIGNATURES:	

CC: ANDA
Telecon Binder

V:firmstz/Watson/telecons/76751.5-4-2004
agis

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-751

CORRESPONDENCE



TEL. EXTENSION
03-5773 -

DIRECT FAX:
03-5773 -

Handwritten notes:
- No dissolution data
- Presentation
- 10/11/03
- July 2003
- Concur.
- 01-JUL-2003
- [Signature]

May 30, 2003

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room # 150
Rockville, MD 20855-2773

Re: ANDA for Mesalamine Rectal Suspension, USP

Dear Mr. Buehler:

Agis Industries (1983) Ltd. hereby submits an original abbreviated new drug application (ANDA) in hard copy format, to seek approval to market Mesalamine Rectal Suspension, USP, that is bioequivalent to the reference listed drug, Rowasa® (Mesalamine) Rectal Suspension Enema, manufactured by Solvay Pharmaceuticals, pursuant to NDA #019618.

This ANDA consists of 9 volumes. Agis Industries (1983) Ltd. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) that contains all the information in archival copy with the exception of the bioequivalence **Section (VI)**. A separate copy of the bioequivalence section is provided in orange folders.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical section of the ANDA (including a copy of the FDA 356h form and a certification that the contents are the true copy of those filed with the Office of Generic Drugs) is being sent to our local district office. This "field copy" is contained in burgundy folders.

For a more detailed information on the organization of this ANDA, please refer to the "Executive Summary" attached after the field copy certification statement.

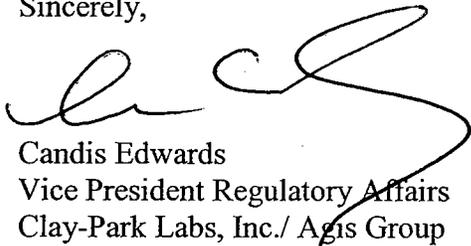
RECEIVED
MAY 30 2003
OGD / CDER

Should you have any comments or require any further clarification on this ANDA, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', with a large, sweeping flourish extending to the right.

Candis Edwards
Vice President Regulatory Affairs
Clay-Park Labs, Inc./ Agis Group
On behalf of Agis Industries (1983) Ltd.

ANDA 76-751

Clay-Park Labs, Inc.
U.S. Agent for: Agis Industries (1983) Ltd.
Attention: Candis Edwards
1701 Bathgate Avenue
Bronx, NY 10457

JUL 1 2004

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated May 30, 2003, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d) (3) for the following reasons:

You have failed to submit complete comparative *in vitro* dissolution profiles comparing your proposed drug product, Lot #ML002, and the reference listed drug. You have also failed to submit content uniformity data for the reference listed drug and your test product. Please provide this data.

You have failed to provide authorization from the holders of the Drug Master Files (DMFs), _____ and _____, for the Agency to access their DMFs in support of your application. Please provide authorization from the holder of the DMFs granting the Agency access to the DMFs.

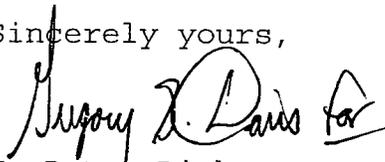
In addition, for any future submissions please provide the U.S. Agent's firm name as well as contact person on the 356h.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Christine Bina
Project Manager
(301) 827-5862

Sincerely yours,

A handwritten signature in black ink, appearing to read "Wm Peter Rickman". The signature is written in a cursive style with a large initial "W" and a stylized "R".

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-751

cc: DUP/Jacket

Division File

HFD-92

Field Copy

HFD-610/R.West

HFD-610/P.Rickman

HFD-615/MBennett

Endorsement: HFD-615/GDavis, Chief, RSB *Davis* 01-JUL-2003 date

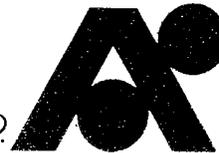
HFD-615/CBina, CSO *CBina* 6-30-03 date

Word File

V:/FIRMSAM\AGIS\LTRS&REV\76751.RTF

F/T File

ANDA Refuse to Receive!



August 5, 2003

TEL. EXTENSION
03-5773 -

DIRECT FAX:
03-5773 -

Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER
Food and Drug Administration
Document Center Room
Metro Park North II
7500 Standish Place - Room 150
Rockville, MD 20855

ORIGINAL AMENDMENT
N/A/C

**Re: Response to Refusal to File Letter
Mesalamine Rectal Suspension, USP, 4 g/60 mL
ANDA # 76-751**

Dear Mr. Rickman:

In response to the Refusal to File Letter dated July, 7 2003 (**See Attachment 1**) for Mesalamine Rectal Suspension, USP ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the requested information in order to render the file sufficiently complete to merit a technical review.

Regarding the comparative *in vitro* dissolution profiles comparing our proposed drug product, Lot # ML002 and the reference listed drug, the following Analytical Documentation is provided:

- **Attachment 2:** R & D Document # 26822-v2: Protocol Comparative In-Vitro Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa® (mesalamine) Rectal Suspension Enema, versus Agis Industries (1983) Ltd.'s Mesalamine Rectal Suspension, USP
- **Attachment 2:** R & D Document # 26863-v1: Report Comparative In-Vitro Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa® (mesalamine) Rectal Suspension Enema, versus Agis Industries (1983) Ltd.'s Mesalamine Rectal Suspension, USP
- **Attachment 3:** R & D Document # 26761-v2 Validation Protocol of HPLC Dissolution Test Method for Mesalamine Rectal Suspension, USP

RECEIVED

AUG 06 2003

OGD/CDER

- **Attachment 3:** R & D Document # 26840-v1
Validation Report of HPLC Dissolution Test Method for Mesalamine Rectal Suspension, USP
- **Attachment 4:** R & D Document # 14913-v2
Dissolution Test Method

On the subject of the content uniformity data for the reference listed drug and Agis Industries (1983) Ltd.'s test product, the average results of the content uniformity test for Agis Industries (1983) Ltd.'s proposed drug product were provided on **pages 3502** (Lot # ML002) and **3612** (Lot # ML003) of the original application. The Certificates of Analysis have been revised to include the individual tests results and are presented in **Attachment 5**. The test results for the reference listed drug, as requested by the Agency are also presented in **Attachment 5**.

*Finished
Dose of CE*

Relating to the Agency's request for authorization from the holder of the Drug Master File (DMF), _____, the letter of authorization was included in the original application on **page 3435**. The Agency acknowledged that they were able to locate the document during a telephone conversation between the US Agent and the FDA Project Manager.

Pertaining to the letter of authorization from _____, Agis Industries (1983) Ltd inadvertently listed _____ as the manufacturer of the _____ in the Table on **page 3440** of the original application. Agis Industries (1983) Ltd. herein uses this correspondence to correct the file and states that _____ is the manufacturer and _____, is the supplier of the _____. Hence, a corrected cGMP certification from _____ is attached herewith (see **Attachment 6**). The Table presented on **page 3440** of the original application, has been revised to incorporate the above-mentioned correction (see **Attachment 7**).

Since _____ does not have a DMF on file with the Agency, Agis Industries (1983) Ltd. submits test results for the USP _____ (see **Attachment 8**). This data supplements the results for USP _____, USP _____ and USP _____ previously submitted on **pages 3419 – 3431** of the original application.

Agis Industries (1983) Ltd. would like to take this opportunity to revise the printer's proof labeling submitted in the original application with regard to the color of the ink. The printer's proof labeling submitted on **page 0073** of the original application is printed using _____ and black ink. Since this labeling will be printed directly onto the bottles and the Stability Study for Lot # ML003 (Printed Bottles) was conducted using black ink only, the labeling has been revised from _____ and black to black only. Twelve (12) copies of the revised draft labeling are presented in **Attachment 9**.

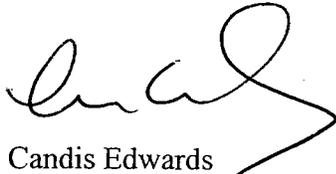
Based on the information provided with this correspondence, we anticipate that sufficient justification has been submitted to warrant a critical technical review for approval.

Should you require any further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', with a long, sweeping tail that extends to the right and then loops back down.

Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

ANDA 76-751

AUG 25 2003

Clay-Park Labs, Inc.
U.S. Agent for: Agis Industries (1983) Ltd.
Attention: Candis Edwards
1701 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made our "Refuse to Receive" letter dated July 1, 2003 and to your amendment dated August 5, 2003.

NAME OF DRUG: Mesalamine Rectal Suspension USP, 4 g/60 mL.

DATE OF APPLICATION: May 30, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 5, 200³7

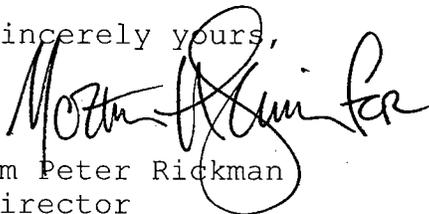
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Nicole Park
Project Manager
(301) 827-5849

Sincerely yours,



Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-751

cc: DUP/Jackets

HFD-600/Division File

Field Copy

HFD-610/G. Davis

HFD-92

Endorsement:

HFD-615/MShimer, Chief, RSB *M. Shimer* date *25 Aug 2003*

HFD-615/CBina, CSO *CMB* date *8-25-03*

Word File V:\Firmsam\Agis\ltrs&rev\76751.ACK

F/T *CMB* 8-25-03

ANDA Acknowledgment Letter!

MODE = MEMORY TRANSMISSION

START=DEC-29 10:23

END=DEC-29 10:24

FILE NO.=757

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	a	917189609907	003/003	00:00:39

-FDA CDER OGD DLPS -

***** - ***** - *****

Fax Cover Sheet

Department of Health and Human Services
 Public Health Service
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Generic Drugs
 Rockville, Maryland 20855

To: Candis Edwards

DATE: December 24, 2003

Phone: 718-960-9976

Fax: 718-960-~~0111~~

9907

SUBJECT: Labeling Comments for ANDA 76-751

From: Koung Lee

Phone: (301) 827-5846

Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments:

*This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.

(3-1)

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

ANDA Number: 76-751

Date of Submission: May 30, 2003

Applicant's Name: Agis Industries (1983) Ltd.

Established Name: Mesalamine Rectal Suspension USP, 4 g/60 mL

Labeling Deficiencies:

1. CONTAINER (60 mL unit-dose)

- a. We encourage you to increase the prominence of "potassium metabisulfite".
- b. Revise the storage temperature statement to "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature)".
- c. Increase the prominence of "For Rectal Use Only".

2. CARTON (7 x 60 mL unit-dose bottles)

See CONTAINER comments

3. INSERT

- a. We encourage you to add the full text of the patient instructions at the end of the labeling.
- b. Although the reference listed drug does not refer to the patient instructions in the PRECAUTIONS section, we encourage you to add a statement to that section that refers to the patient instructions.

b. HOW SUPPLIED

See CONTAINER comment (b).

4. PATIENT INSTRUCTIONS

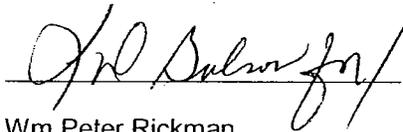
Please explain how the patient instructions will accompany the drug product.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Wm Peter Rickman", written over a horizontal line.

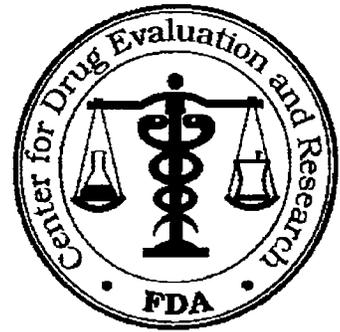
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

MINOR AMENDMENT

ANDA 76-751

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



JAN 22 2004

APPLICANT: Clay-Park Labs, Inc., U.S. Agent for
Agis Industries (1983) Ltd.

TEL: 718-960-9976

FAX: 718-960-0111

ATTN: Candis Edwards

PROJECT MANAGER: (301) 827-5849

FROM: Nicole Lee

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 30, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

Reference is also made to your amendment(s) dated: August 5, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

2. Please acknowledge that Mesalamine Rectal Suspension is an official monograph in the United States Pharmacopeia (USP). The approval to use an analytical procedure that may differ from that in the USP does not release your firm from any obligation to comply with the method and procedure in the USP specified for that product. Therefore, in the event of a dispute, only the results obtained by the official method and procedures in the USP will be considered conclusive.

Sincerely yours,



Florence S. Fang

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research



February 19, 2004

TEL. EXTENSION
03-5773 -DIRECT FAX:
03-5773 -

Nicole Lee
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

RE: ANDA 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Lee,

In reference to the deficiency letter for the Chemistry section dated January 22, 2004 (**Attachment 1**) on our abbreviated new drug application for Mesalamine Rectal Suspension, USP 4 g/60 mL ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response for the Chemistry section designated as a Minor Amendment.

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

RECEIVED

FEB 19 2004

OGD/CDER



February 19, 2004

TEL. EXTENSION
03-5773

DIRECT FAX:
03-5773-

William Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER
Document Control room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF
FPL

LABELING AMENDMENT

RE: ANDA # 76-751 Mesalamine Rectal Suspension USP

Dear Mr. Rickman:

In reference to the deficiency letter of the Labeling Section, dated December 24, 2003 (Attachment A), on our abbreviated new drug application for Mesalamine Rectal Suspension, USP, ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response, designated as a Labeling Amendment.

Should you have any comments or require any further clarification, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

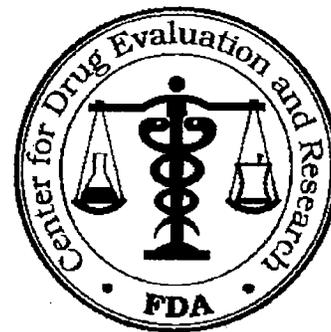
Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

RECEIVED
FEB 19 2004
OGD/CDER

MINOR AMENDMENT

ANDA 76-751

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



MAR 26 2004

APPLICANT: Agis Industries (1983) Ltd. (U.S. Agent
:Clay-Park Labs, Inc.)

TEL: 718-960-9976

FAX: 718-960-0111

ATTN: Candis Edwards

PROJECT MANAGER: (301) 827-5849

FROM: Nicole Lee

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 30, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

Reference is also made to your amendment(s) dated: February 19, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (/ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

h

6

MAR 26 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-751

APPLICANT: Agis Industries (1983) Ltd.

DRUG PRODUCT: Mesalamine Rectal Suspension USP, 4 g/60 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. _____

2. Since Mesalamine Rectal Suspension is a USP product, stability specifications for Impurities should match USP limits for the product.
3. _____

Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



April 6, 2004

TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

Nicole Lee
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/A/M

MINOR AMENDMENT

RE: ANDA 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Lee,

In reference to the deficiency letter for the Chemistry section dated March 26, 2004 (**Attachment 1**) on our abbreviated new drug application for Mesalamine Rectal Suspension, USP 4 g/60 mL ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response for the Chemistry section designated as a Minor Amendment.

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.

On behalf of Agis Industries (1983) Ltd.

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APR 08 2004

OGD / CDER

ORIGINAL



May 5, 2004

TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

Nicole Lee
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A M

**TELEPHONE AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW**

RE: ANDA # 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Lee,

In response to our telephone conversation with the Agency yesterday, May 4, 2004, in reference to ANDA # 76-751 for Mesalamine Rectal Suspension, USP 4 g/ 60 mL, as requested, Agis Industries (1983) Ltd. hereby submits the revised Stability Monograph (see **Attachment 1**) for the drug product. The stability specifications for the impurities have been revised to match the USP limits for the product.

The change in specifications is summarized below:

Stability Evaluation		
Impurities	Old Specifications	New Specifications
Individual Known	NMT —%	NMT 0.2%
Individual Unknown	NMT —%	NMT 0.2%
Total Impurities	NMT —%	NMT 1.0%

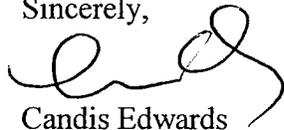
RECEIVED
MAY 06 2004
OGD/CDER

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', with a large, stylized flourish at the end.

Candis Edwards

VP Regulatory Affairs

Clay-Park Labs, Inc.

On behalf of Agis Industries (1983) Ltd.

ORIGINAL



TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

June 17, 2004

Nicole Lee, Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL AMENDMENT
N/A M

**TELEPHONE AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW**

**RE: ANDA # 76-751 Mesalamine Rectal Suspension USP,
4 g/60 mL**

Dear Ms. Lee,

As requested in a telephone conversation with the Agency on June 15, 2004, Agis Industries (1983) Ltd. has revised the finished product and stability test monographs for Mesalamine Rectal Suspension USP, 4 g/60 mL, ANDA # 76-751, to add a dissolution test. The dissolution test method includes the testing parameters and specifications indicated in the OGD correspondence dated June 15, 2004 (see **Attachment A**). The revised finished product and stability test monographs are presented in **Attachment B**.

Also, as requested, dissolution testing was performed on the 18 month Controlled Room Temperature (CRT) stability testing interval for Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # ML002 (bio batch). **Attachment C** presents the updated Stability Summary Report and the Certificate of Analysis for the 18 month CRT testing interval.

We hope that this information satisfies the Agency's requirements for product approval.

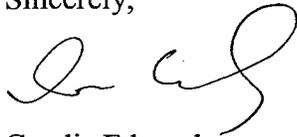
RECEIVED
JUN 18 2004
OGD/CDEH

Should you require any further information please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', written in a cursive style.

Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.



July 23, 2004

TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N / AB

INFORMATIONAL AMENDMENT - BIOEQUIVALENCE

RE: ANDA 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Mr. Buehler:

Agis Industries (1983) Ltd. hereby submits the enclosed document regarding our Abbreviated New Drug Application # 76-751 for Mesalamine Rectal Suspension, USP 4 g/60 mL, designated as an Informational Amendment. The Amendment sets forth our current position regarding the status of the Agency's review and approval of our ANDA.

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

RECEIVED
JUL 26 2004
OGD / CDER

BIOEQUIVALENCY AMENDMENT

ANDA 76-751

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



AUG 27 2004

APPLICANT: Agis Industries (1983) Ltd.
(U.S. Agent :Clay-Park Labs, Inc.)

TEL: 718-960-9976

ATTN: Candis Edwards

FAX: 718-960-0111

FROM: Beth Fabian-Fritsch *BFF*

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 5, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

The Division of Bioequivalence has completed its review of the submission(s) 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and 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 both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

AUG 27 2004

AUG 27 2004

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-751

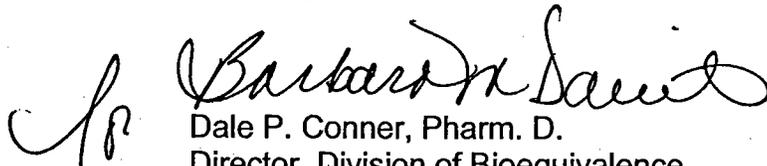
APPLICANT: Agis Industries LTD

DRUG PRODUCT: Mesalamine Rectal Suspension USP, 4 gm/60 mL

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

Please submit comparative dissolution testing in the following media (900 mL): 0.1N HCl, and buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 and 25 rpm. Please ensure that your dissolution method is adequate to distinguish mesalamine dissolved in dissolution media from drug particles. You may modify the filtration method in the dissolution testing, if necessary.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

31

AGIS INDUSTRIES (1983) LTD.



ORIGINAL

September 07, 2004

TEL. EXTENSION
972-3-5773

DIRECT FAX:
972-3-5773

Beth Fabian-Fritsch
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

**BIOEQUIVALENCY AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW**

RE: ANDA #76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Fabian-Fritsch,

In reference to the deficiency letter for the Bioequivalence section dated August 27, 2004 (**Attachment 1**), on our abbreviated new drug application for Mesalamine Rectal Suspension, USP 4 g/60 mL ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response for the Bioequivalence section, designated as a Bioequivalency Amendment.

The Agency has requested the following:

“Please submit comparative dissolution testing in the following media (900 mL): 0.1 N HCl, and buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 and 25 rpm. Please ensure that your dissolution method is adequate to distinguish mesalamine dissolved in dissolution media from drug particles. You may modify the filtration method in the dissolution testing, if necessary.”

As requested by the Agency, Agis Industries (1983) Ltd. has completed the comparative *in vitro* dissolution profile testing on Mesalamine Rectal Suspension USP, 4 g/ 60 mL. The testing was performed using Agis Industries (1983) Ltd.’s validated methodology, Dissolution Test Method # 14913, submitted to the Agency on 08/05/03 in Response to the Refusal to File letter dated 07/01/03, for this ANDA.

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Comparative dissolution testing was performed on Agis Industries (1983) Ltd.'s drug product, Bio batch # ML002, and on the innovator's drug product, Solvay Pharmaceutical Inc.'s Rowasa[®] (Mesalamine) Rectal Suspension Enema, Lot # 92451, and Lot # 92873 using the dissolution conditions specified. The results from the comparative *in vitro* dissolution testing were found to be comparable.

The study protocol and corresponding study report are presented in **Attachment 2** as follows:

Protocol R&D Document #33195-v1: Comparative *In-Vitro* Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa[®] (mesalamine) Rectal Suspension Enema – Versus Agis Industries (1983) Ltd. Mesalamine Rectal Suspension, USP

Report R&D Document #: 33195-v1: Comparative *In-Vitro* Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa[®] (mesalamine) Rectal Suspension Enema – Versus Agis Industries (1983) Ltd. Mesalamine Rectal Suspension, USP

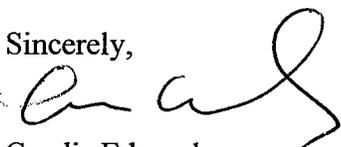
Please note that there are two binders enclosed: one Archival Copy (Blue Folder) and one Bioequivalence Copy (Orange Folder).

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,



Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.