

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PATENT CERTIFICATION

In accordance with 21 C.F.R. §§ 314.54 (v) and (vi), Shire Development, Inc. hereby states that U.S. Patent No. 6,773,720 expiring June 8, 2020, is owned by Cosmo S.p.A. and exclusively licensed to applicant Shire Development, Inc. in the United States of America.

**APPEARS THIS WAY
ON ORIGINAL**

PATENT INFORMATION

Patent Number 6,773,720 B1 relates to a controlled release oral formulation of 5-aminosalicylic acid. This formulation provides a delayed release of 5-aminosalicylic acid in the colon. Its proposed indication is the induction of remission in patients with active, mild to moderate ulcerative colitis.

Pursuant to 21 CFR 314.53(d)(1), Shire is submitting the following patent information:

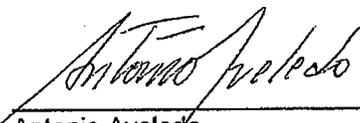
**APPEARS THIS WAY
ON ORIGINAL**

Patent Information

Pursuant to 21 CFR 314.53(d)(1)

- | | |
|------------------------------|----------------|
| 1. Patent number: | 6,773,720 |
| 2. Expiration date: | 06 August 2020 |
| 3. Type of patent: | Formulation |
| 4. Name of the patent owner: | Cosmo S.p.A. |
| 5. Declaration: | |

The undersigned declares that Patent Number 6,773,720 covers the formulation of SPD476, which is the subject of this NDA for which approval is being sought.



Antonio Aveledo
IP Advisor, Legal Department
Shire Pharmaceuticals, Inc.

Aug. 30, 2005
Date

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-000

NAME OF APPLICANT / NDA HOLDER

Shire Development, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Mesavance

ACTIVE INGREDIENT(S)

Mesalamine (5-aminosalicylic acid)

STRENGTH(S)

1.2g

DOSAGE FORM

Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,773,720

b. Issue Date of Patent

8/10/2004

c. Expiration Date of Patent

6/8/2020

d. Name of Patent Owner

Cosmo S.p.A.

Address (of Patent Owner)

Via Colombo, 1

City/State

Lainate-Milan

ZIP Code

Italy

FAX Number (if available)

+39 02 93337663

Telephone Number

+39 02 93337614

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Mr. Philip A. DuBois

Young & Thompson

Address (of agent or representative named in 1.e.)

745 South 23rd Street

City/State

Arlington, Virginia

ZIP Code

22202

FAX Number (if available)

(703) 685-0573 / (703) 979-4709

Telephone Number

(703) 521-2297

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



Aug. 30, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Antonio Aveledo

Address
2250 Alfred Nobel Blvd.

City/State
St. Laurent, Quebec, Canada

ZIP Code
H4S 2C9

Telephone Number
514 787-2319

FAX Number (if available)
514 787-2423

E-Mail Address (if available)
aaveledo@ca.shire.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-000

SUPPL #

HFD # 180

Trade Name Lialda Delayed-Release Tablets, 1.2 g

Generic Name mesalamine

Applicant Name Shire Development, Inc.

Approval Date, If Known January 19, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19651	Asacol (mesalamine) Delayed Release Tablets
NDA# 19618	Rowasa (mesalamine) Rectal Suspension Enema
NDA# 21252	Canasa (mesalamine) Suppository
20-049	Pentasa (mesalamine) Controlled Release Capsules

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study SPD476-301: A Phase III, Randomised, Multi-centre, Double-Blind, Parallel-group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SPD476 (Mesalazine) Given Twice Daily (2.4g/Day) Versus SPD476 Given as a Single Dose (4.8g/Day) in Subjects With Acute Mild to Moderate Ulcerative Colitis.

Study SPD476-302: A Phase III, Randomised, Multi-Centre, Double-Blind, Double-Dummy, Parallel- Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Two Doses of SPD476 (Mesalazine) 2.4g and 4.8g Once Daily, With Reference To ASACOL® 0.8g Three Times Daily, In Subjects With Acute, Mild To Moderate Ulcerative Colitis

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study SPD476-301: A Phase III, Randomised, Multi-centre, Double-Blind, Parallel-group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SPD476 (Mesalazine) Given Twice Daily (2.4g/Day) Versus SPD476 Given as a Single Dose (4.8g/Day) in Subjects With Acute Mild to Moderate Ulcerative Colitis.

Study SPD476-302: A Phase III, Randomised, Multi-Centre, Double-Blind, Double-Dummy, Parallel- Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Two Doses of SPD476 (Mesalazine) 2.4g and 4.8g Once Daily, With Reference To ASACOL® 0.8g Three Times Daily, In Subjects With Acute, Mild To Moderate Ulcerative Colitis

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was

carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 66,193 YES ! NO
! Explain:

Investigation #2
IND # 66,193 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Kristen Everett, R.N.
Title: Regulatory Project Manager
Date: 10 January 2007

Name of Office/Division Director signing form: Brian E. Harvey, M.D., Ph.D.
Title: Director, Division of Gastroenterology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Brian Harvey
1/16/2007 03:30:58 PM

MARKETING EXCLUSIVITY

Shire is claiming a three-year marketing exclusivity under 21 CFR 314.50(j) and 21 CFR 314.108(b)(4)(iv) for SPD476 for the induction of remission in patients with active, mild to moderate ulcerative colitis. This NDA application contains new clinical investigations (other than bioavailability studies) that are essential to the approval of this submission. These new clinical investigations were conducted by Shire, the applicant of this NDA. To the best of Shire's knowledge, these new clinical investigations meet the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).

The submission contains the results of 2 adequate and well controlled clinical studies (SPD476-301 and SPD476-302), and interim results of one long-term, open label, safety and tolerability study (SPD476-303). In addition, this submission contains results from Phase II studies and Phase I pharmacokinetic studies. The submission of this clinical program was discussed with the Agency during a 02 June 2005 Type B meeting with the Division of Gastrointestinal and Coagulation Drug Products.

The following studies contained in this submission that are new clinical investigations as defined by 21 CFR 314.108(a) are:

- SPD476-301 – Phase 3
- SPD476-302 – Phase 3
- SPD476-303 – Phase 3; interim results

These studies were conducted under IND 66,193.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-000 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: December 21, 2005 Action Date: October 21, 2006

HFD 180 Trade and generic names/dosage form: Mesavance (mesalamine) Delayed Release Tablets

Applicant: Shire Development, Inc. Therapeutic Class: 8015651

Indication(s) previously approved:

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: induction of remission in patients with active, mild to moderate ulcerative colitis

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Defer pediatric studies in all age groups until safety and efficacy are established in adults.

Date studies are due (mm/dd/yy): _____ (as per Sponsor)

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 22-000
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 22-000
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

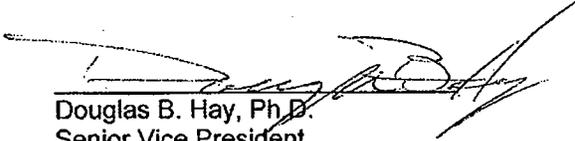
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kristen Everett
8/1/2006 02:29:37 PM

DEBARMENT CERTIFICATION

On behalf of Shire Development, Inc. (Shire), I hereby certify that Shire did not and will not use in any capacity the services of any individual, partnership, corporation, or association debarred under Subsection (a) or (b) of §306 of the Federal Food, Drug, and Cosmetic Act in connection with this New Drug Application for SPD476.


Douglas B. Hay, Ph.D.
Senior Vice President
Global Regulatory Affairs

20 July 2005
Date

ACTION PACKAGE CHECKLIST

Application Information

BLA # NDA # 22-000	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Lialda Established Name: mesalamine Dosage Form: Delayed Release Tablets, 1.2 g		Applicant: Shire Development, Inc.
RPM: Kristen Everett		Division: 180 Phone # 301-796-0453
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected</p> <p>Date:</p>
<p>❖ User Fee Goal Date</p> <p>❖ Action Goal Date (if different)</p>		<p>January 20, 2007</p> <p>January 19, 2007</p>
❖ Actions		
<p>• Proposed action</p>		<p><input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE</p> <p><input type="checkbox"/> NA <input type="checkbox"/> CR</p>
<p>• Previous actions (<i>specify type and date for each action taken</i>)</p>		<input checked="" type="checkbox"/> None
<p>❖ Advertising (<i>approvals only</i>)</p> <p>Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)</p>		<p><input checked="" type="checkbox"/> Requested in AP letter</p> <p><input type="checkbox"/> Received and reviewed</p>

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
Chemical classification (new NDAs only): 5	
NDAs, BLAs and Supplements:	
<input type="checkbox"/> Fast Track	
<input type="checkbox"/> Rolling Review	
<input type="checkbox"/> CMA Pilot 1	
<input type="checkbox"/> CMA Pilot 2	
<input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H	BLAs: Subpart E
<input type="checkbox"/> Accelerated approval (21 CFR 314.510)	<input type="checkbox"/> Accelerated approval (21 CFR 601.41)
<input type="checkbox"/> Restricted distribution (21 CFR 314.520)	<input type="checkbox"/> Restricted distribution (21 CFR 601.42)
Subpart I	Subpart H
<input type="checkbox"/> Approval based on animal studies	<input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements:	
<input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• OC clearance for approval (<i>file communication in Administrative Documents section</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified <input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>)	
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>)	
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	January 10, 2007
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	January 16, 2007
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	December 21, 2005
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) • Most recent applicant-proposed labeling 	December 13, 2006
❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> DMETS 8/25/06, 10/27/06, 12/20/06 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 8/25/06 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents

Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	February 3, 2006
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	1/18/06, 3/2/06, 3/21/06, 6/1/06, 6/26/06, 7/19/06, 8/3/06, 8/7/06, 8/11/06, 8/23/06, 9/7/06, 9/15/06, 11/22/06, 12/4/06, 12/21/06
❖ Internal memoranda, telecons, email, etc.	8/29/06, 10/17/06
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	N/A
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	<input type="checkbox"/> No mtg 6/2/05, 8/18/05, 12/16/05
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	<input checked="" type="checkbox"/> No mtg
❖ Advisory Committee Meeting	4/24/03,
❖ Date of Meeting	<input checked="" type="checkbox"/> No AC meeting
❖ 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	2/13/06, 1/3/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input checked="" type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	1/3/07
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	1/3/07
❖ Facilities Review/Inspection	<input checked="" type="checkbox"/> Not a parenteral product
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 2/8/06 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	8/3/06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	1/8/07, 12/15/06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	12/15/06
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	12/15/06
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	8/14/06
• Bioequivalence Studies	11/8/06
• Clin Pharm Studies	N/A
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/16/07
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/21/06

Appendix A to Action Package Checklist

A NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

12/21/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

DISCIPLINE REVIEW LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed —
— Release Tablets.

We also refer to your submission dated August 30, 2006, which contained the proposed trade name, Lialda, for our review.

We have completed the review of your proposed proprietary name, Lialda, and we find it acceptable.

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Julieann DuBeau
12/21/2006 03:47:55 PM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22; Mail Stop 4447)

DATE RECEIVED: Sept. 08, 2006
DATE OF DOCUMENT: Aug, 30 2006

DESIRED COMPLETION DATE:
October 16, 2006
PDUFA DATE: January 19, 2007

OSE REVIEW #:
2006-180

TO: Brian Harvey, MD
Director, Division of Gastroenterology Drug Products
HFD-180

THROUGH: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Walter Fava, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:
Lialda®
(Mesalamine) — Tablets 1.2 g

SPONSOR: Shire Development, Inc.

NDA #: 22-000

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Lialda. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. Please consult Guiragos Poochikian, the Acting Director of the CDER Labeling and Nomenclature Committee for the proper designation of the established name.
3. DDMAC finds the proprietary name Lialda acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Pre-marketing Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: September 25, 2006
NDA #: 22-000
NAME OF DRUG: Lialda™
(Mesalamine) ————— Tablets
1.2 g
NDA SPONSOR: Shire Development, Inc.

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastroenterology Drug Products (HFD-180), for an assessment of the proprietary name "Lialda" regarding potential name confusion with other proprietary or established drug names. Draft labels and labeling were provided for review and comment. The sponsor also provided an independent name analysis performed by _____ for review and comment.

PRODUCT INFORMATION

Lialda is indicated for the induction of remission _____ in patients with active, mild to moderate ulcerative colitis. Lialda will be available as film coated tablets containing 1.2 grams of mesalamine. The sponsor claims that this product is unique in that it exhibits delayed-release _____ properties. The recommended dose is 2.4 grams to 4.8 grams by mouth once daily. Lialda will be supplied in bottles of \ 120 tablets.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to "Lialda" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database^v and Clinical Pharmacology^{vi} were also conducted. The Saegis^{vii} Pharma-In-

ⁱ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2005, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA)

^v WWW location <http://www.uspto.gov>.

^{vi} Clinical Pharmacology, online version available at <http://cpip.gsm.com>

^{vii} Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (outpatient and inpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Lialda. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed name Lialda.
2. The Expert Panel identified ten (10) proprietary names that were thought to have potential for confusion with Lialda. Of the ten names identified, DMETS found that six names warranted further evaluation based upon look-alike, sound-alike and product characteristics (see Table 1 on page 4). Upon further review of the names gathered from EPD, the names Valstar and Ziana*** were not reviewed further due to lack of convincing look-alike/sound-alike similarities with Lialda, in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation. — was not reviewed due to the fact that the NDA was withdrawn for approval by the sponsor. — was also not reviewed further due to the fact that the sponsor withdrew the name — as a proposed name.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Lialda	Mesalamine tablets: 1.2 g	2.4 g to 4.8 g by mouth once daily	
Haldol	Haloperidol 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, and 20 mg tablets 50 mg/ml and 100 mg/ml decanoate injection, 5 mg/ml injectable	2 mg to 10 mg by mouth twice daily	LA
Cialis	Tadalafil 5 mg, 10 mg, and 20 mg tablets	10 mg by mouth daily	LA
Gliadel	Polifeprosan Carmustine 7.7 mg implantable wafer	7.7 mg to 61.6 mg implanted every 6 weeks	LA/SA
Xeloda	Capecitabine 150 mg and 500 mg	1250 mg/m ²	LA
Aldara	Imiquimod 5% cream	Apply 2 to 5 times a week	LA/SA
Boldo	Peumus boldo 625 mg capsule	625 mg po bid	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Lialda with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Inpatient and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Lialda (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient Lialda 1.2g 4 tabs qd	Lialda 1.2 grams #120 Take 4 tablets daily
Outpatient Lialda 1.2g #120 Take 4 tabs qd	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Lialda, the primary concerns related to the look-alike and/or sound-alike confusion with Lialda are: Haldol, Cialis, Gliadel, Xeloda, Aldara, and Boldo.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Lialda. The names of concern are discussed in detail below:

1. Haldol was identified as a name with similar appearance to Lialda. Haldol is indicated for the treatment of psychotic disorders.

Orthographic similarities include the fact that both names contain similar upstroke letter patterns in the middle of both names ("l" and "d") as illustrated below. Other look-alike similarities include the fact that both names have the letters "A", "L" and "D" together in the same sequence and approximate locations.

L i a l d a
 H a l d o l

Lialda
Lialda

Although the orthographic differences between the two names include the fact that the names contain different letters ("H" and "O" in Haldol vs "L" and "i" in Lialda), these differences may not be as prominent when the two names are scripted. However, Haldol contains an extra upstroke with the last letter ("l") which may help to distinguish the names.

The only overlapping product characteristics shared by Lialda and Haldol are the route of administration (oral) and dosage form (tablet). Differentiating product characteristics include indication for use (ulcerative colitis vs psychotic disorders), frequency of

administration (once a day vs two to three times a day), and units of measure (grams vs milligrams). Another difference between Lialda and Haldol is that Lialda will only be available in a single strength (1.2 gram tablets), whereas Haldol is available as 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg and 20 mg tablets. Thus, a prescriber would have to indicate the specific strength for a Haldol order which may help to minimize confusion.

Despite some look-alike similarities between Lialda and Haldol, the different product characteristics will minimize the potential for confusion.

2. Cialis was identified as a name with similar appearance to Lialda. Cialis is indicated for the treatment of erectile dysfunction.

Orthographic similarities include the fact that both names contain six letters and appear similar in length. Both names contain the letters "i" "a" and "l", in the same sequence as illustrated below. Also, when scripted as in the example below, the beginning letter ("l" vs "c") especially if the letter "c" is not closed in.

<i>Cialis</i>	L i a l d a	Lialda
<i>Lialda</i>	C i a l i s	Cialis

However, the fifth letter ("d") in Lialda could have an upstroke depending on how it is scripted, and thus this may make the name appear different from Cialis.

Although the two names also share some product characteristics such as the route of administration (oral), dosage form (tablet) and frequency of administration (once daily), Cialis is available in several different strengths when compared to Lialda. Thus, the specified strength for a Cialis order may help in proper interpretation of the order.

Although there are some look-alike similarities between Lialda and Cialis, the differentiating strengths minimize the potential for confusion between the two names.

3. Gliadel was identified as a name with both look-alike and sound-alike similarities with Lialda. Gliadel is an oncology drug product indicated for the treatment of head and neck cancers.

Look-alike similarities include the fact that both names have the common letters "i", "a", "l", and "d". Although the sequence of the letters is not identical in both names, their close proximity and similar arrangement in both names could potentially lead to name confusion.

<i>lialda</i>	<i>Lialda</i>
<i>gliadel</i>	<i>Gliadel</i>

Distinguishing orthographic features include the fact that the first letter for both names look different ("G" vs "L"), and depending on how the letter "G" is scripted, it could have a downstroke, which Lialda does not have. Conversely, the different positions of the letter "l" in both names, gives them distinctly different upstroke patterns.

Sound-alike similarities between the two names include the fact that both names are three syllables in length, and the first and second syllables have similar pronunciations (glee - ad vs. lee - ald).

Although look-alike and sound-alike similarities exist between Lialda and Gliadel, there are differentiating product characteristics which minimize the potential for confusion between the two names. These differentiating product characteristics include the fact that Gliadel is available as an implantable 7.7 mg wafer for the treatment of head and neck cancers. Lialda on the other hand is an oral gastrointestinal agent indicated for the induction of remission in active, mild to moderate ulcerative colitis. Lialda will be available as a 1.2 gram film-coated tablet. Gliadel wafers are implanted at six week intervals, whereas Lialda is administered orally at a dose of 2.4 to 4.8 grams once a day. Additionally, Gliadel would be implanted in a surgical setting, whereas Lialda will either be self-administered by patients or administered by nursing (on an inpatient basis).

Despite some look-alike similarities, differentiating product characteristics and different conditions of use, help to minimize the potential for confusion between Lialda and Gliadel.

4. Xeloda was identified as having look-alike similarities with Lialda. Xeloda is indicated for single agent adjuvant treatment of patients with colon cancer and as combination therapy for the treatment of metastatic breast cancer.

Look-alike similarities include the fact that both names contain six letters and appear similar in length. Additionally, both names contain the letters "l", "d", and "a", in a similar sequence (see below). Thus, the latter portion of the names may look similar when scripted.

L i a l d a
X e l o d a

However, the first portion of the names appears to look different when scripted (Lial vs Xelo). Additionally, Lialda has two upstroke letters ("l" and "d") next to each other which Xeloda does not.

Lialda
Xeloda

The dosage form (tablet) and the route of administration (oral), are the only common product characteristics shared between Lialda and Xeloda. The usual dosage of Lialda is 2.4 to 4.8 grams administered once a day, whereas the dosing for Xeloda is based on body surface area (1250 mg/m²) therefore the dose is not standardized and will vary for each patient. Xeloda also has a distinctly different dosing frequency (twice a day for 7 days, followed by a 7 day rest period given as three week cycles). The strengths of the products are also different for Lialda and Xeloda (1.2 gram tablets vs 150 mg and 500 mg tablets).

Although Lialda and Xeloda share some orthographic similarities, the substantially different product characteristics will minimize the potential for confusion between the two drug products.

5. Aldara was identified as having look-alike and sound-alike similarities with Lialda. Aldara is a topical cream indicated for the treatment of Actinic keratosis, superficial basal cell carcinoma, and genital and perianal warts.

Look-alike similarities between Aldara and Lialda are attributed to the fact that both names contain six letters and appear similar in length. Also, they both contain the sequential letter pattern "alda" (see below). However, the beginning letters of each name (Li vs. Al) look different when scripted due to the upstroke of the letter "l" in Aldara.

Lialda
Aldara

lialda
aldara

Phonetically, both names contain three syllables which contributes to the rhyming characteristics between the name pair. However, the pronunciation of the first syllable in Lialda ("LEE"), versus the "AL" sound in Aldara, helps to distinguish the names.

Although both products can be self-administered by patients in an outpatient setting, the two products do not share any overlapping product characteristics. The different product characteristics include dosage form (tablet vs cream), route of administration (oral vs topical), frequency of administration (once daily vs two to five times a week), strength (1.2 gram vs 5%), and usual dose (2.4 grams to 4.8 grams vs one application).

DMETS considers the risk for potential confusion between the two products to be minimized due to orthographic, phonetic and product differences.

6. Boldo was identified as having look-alike similarities to Lialda. Boldo is an over-the-counter herbal product available for purchase through the internet. It is marketed for the treatment of liver, gallbladder, and urinary problems with the disclaimer that "...these statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease".

Look-alike similarities include the fact that a lowercase letters "l" and "i", when scripted together, can look similar to a lowercase letter "b", and the two lowercase letter "o"s in Boldo can look like the two lowercase letter "a"s in Lialda. Boldo also contains the letters "l" and "d" next to each other as does Lialda.

lialda
boldo

lialda

boldo

The only overlapping product characteristics between Lialda and Boldo is the route of administration (oral). Boldo is available as a 625 mg capsule and the usual adult dose is one capsule twice a day by mouth. Lialda, however, will be available in 1.2 gram film coated tablets, and the usual adult dose is 2.4 to 4.8 grams once a day. Lialda is indicated for the treatment of induction of remission of acute, mild to moderate ulcerative colitis, whereas Boldo, is an over the counter herbal supplement which is marketed as a liver, gallbladder, and urinary tract modality.

Despite the look-alike similarities between Lialda and Boldo, the numerous differentiating product characteristics significantly reduce the risk for potential confusion between these two products.

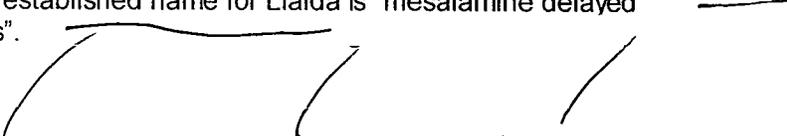
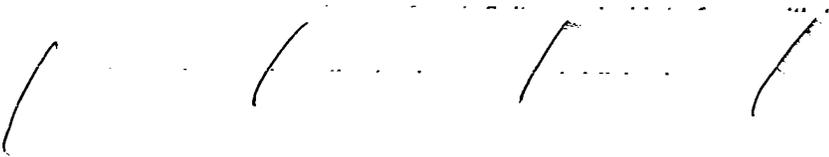
B. INDEPENDENT NAME ANALYSIS

The sponsor submitted an independent name review conducted by _____ concluded that the likelihood of Lialda being confused with other pharmaceuticals or leading to dispensing errors is extremely low. The following names were not identified as potential sound-alike or look-alike products by DMETS, but by _____ Luride, Elidel, Lidex, Levitra, Lioresal, Lidoderm, Librax, Diabeta, Lacri-Lube, Toradol, Lamisil, Avandia, Evista, Dyazide, Esgic, Lunesta, loratidine, and Lozol. Following review of these proprietary names, DMETS concurs that none of the aforementioned names poses a significant safety risk for confusion with Lialda due to lack of substantial look-alike/sound-alike similarities and/or different product characteristics.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Lialda, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENTS

1. The proposed established name for Lialda is "mesalamine delayed release tablets". _____

2. The dosage form currently appears above proprietary name. The dosage form should appear in conjunction with the established name (e.g., mesalamine _____). Relocate the dosage form to appear juxtapose to the established name and ensure that both the established name and dosage form are at least 1/2 the size of the proprietary name per 21 CFR 201.10(g)(2).
3. We recommend relocating and increasing the size and prominence of the 1.2 g that appears above the net quantity to appear directly beneath the established name and away from the net quantity. Additionally, delete the _____ as it is too small and it is redundant as the product strength should only appear once on the container label.
4. The _____ color (described as _____ used for the product strength and the _____ appears too light and is difficult to read. Revise the color in order to increase its readability on the white background of the container label.
5. _____

6. Decrease the size and prominence of the net quantity as it appears more prominent than the product strength.

A

3 Page(s) Withheld

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✓ Draft Labeling

 Deliberative Process

Appendix A:

Prescription Study Results for Lialda

Outpatient Written	Inpatient Written	Verbal
Lialda	Lialda	Vialda
Lialda	Lialda	Vialga
Lialda	Liolda	Lialda
Lialda	Lialda	Vialda
Lialda	Lialda	Vialda
Lialda	Lialda	Vialda
Rialda	Lialda	
Lialda	Lialda	
	Lialda	

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/s/

Walter Fava
12/20/2006 10:35:35 AM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
12/20/2006 10:46:30 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/20/2006 01:48:43 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/20/2006 04:38:17 PM
DRUG SAFETY OFFICE REVIEWER



12/4/06

NDA 22-000

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename (mesalamine) Delayed Release Tablets.

We also refer to your submissions dated October 6, 2006 and October 27, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please confirm that the bottles are not contained in a carton. If this is not the case, please submit a copy of the bottle carton design.

Please change the dosage form to "delayed release" on the bottle labels, _____ and submit copies of these items.

In accord with Section 502(e)(1)(A)(iii) of the Food, Drug, and Cosmetic Act, please add an alphabetical list of the inactive ingredients to the _____ and the bottle cartons (if applicable).

You may wish to check if US Customs regulations require these labels to include the phrase "Made in Italy".

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
12/4/2006 11:15:13 AM

MEMORANDUM

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

DATE: November 3, 2006

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV Nov 7, 06
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-000, Mesavance
(Mesalamine) Delayed — Release Tablets,
Sponsored by Shire Development, Inc.

TO: Brian Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products (DGP)

At the request of DGP, the Division of Scientific Investigations (DSI) conducted a **for cause** audit of the clinical and analytical portions of the following bioequivalence study:

Study SPD476-103: An Open-Label, Randomized, 2-Period, Crossover Study in Healthy Male and Female Volunteers to Evaluate the Effects of Co-administration of SPD476 4.8g with Food on the Bioequivalency of 5-Aminosalicylic Acid (5-ASA)

The for cause audit was to investigate the impact of the reported degradation of 5-amino salicylic acid (5-ASA) at -20°C on the study data and the validity of using a degradation factor to correct for the loss of 5-ASA during storage at -20°C.

The clinical portion of the study was conducted at _____ and the analytical portion at _____ assayed study samples for 5-ASA and N-acetyl-5-ASA (5-NASA).

Following the inspection at — (8/14-17/06), Form 483 was issued (Attachment 1). No Form 483 was issued at — (7/5-7/06). DSI's evaluation of the significant items at the analytical site and the firm's response (Attachment 2) follows:

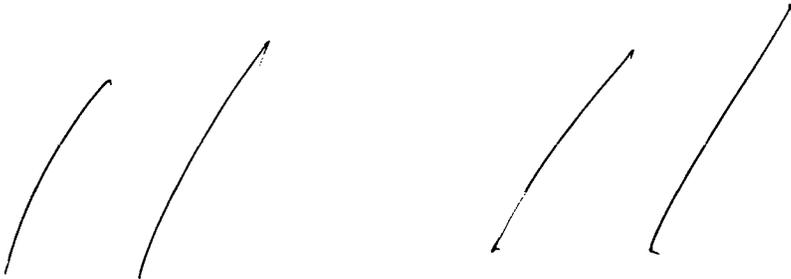
Analytical Site:

— stored the subject plasma samples at -20°C for a total of 48 days between sample receipt and analysis. Since — stability validation showed degradation of 5-ASA at -20°C, — conducted a stability investigation at the sponsor's request. — used stability data from literature and from their stability investigation to mathematically derive a polynomial degradation curve to correct the observed 5-ASA concentrations in Study SPD476-103 for the loss of 5-ASA during storage at -20°C. DSI's investigation of — stability data and Study SPD476-103 revealed the following:

1. The accuracy of 5-amino salicylic acid (5-ASA) concentrations in Study YAH/049 (Protocol SPD 476-103) cannot be assured due to the high inter-matrix set variability in degradation of 5-ASA over time at -20°C in human plasma (48 day data shown in the figures and summary table below for the 800 and 1500 ng/mL stability samples).

Stability Samples Spiked at 800 ng/mL

Stability Samples Spiked at 1500 ng/mL



Sample Set # (prepared in Project)	% Loss of 5-ASA after storage at -20°C				
	17 days	21 days	32 days	41 days	46-48 days
#3 (YAH/049)†	-13%				
#14 — /054)‡	-23%	-26%	-32%	--	--
#11 — /054)‡	--	--	--	-15%	-22%
#10 — /054)*	--	--	--	--	-37%

† Analyzed and reported in Project — /054.

‡ Analyzed and reported in Project YAH/063.

* Data NOT reported. Sample set analyzed in Project — /054

Review of stability data from Projects — /054 and YAH/063 showed a high variability in degradation of 5-ASA over time among stability sample sets prepared in different batches of control plasma (see figures above). As summarized in the table above, at 17 days at -20°C, set# 3 showed a 13% loss of 5-ASA whereas set# 14 showed a 23% loss. Similarly at 46-48 days,

loss of 5-ASA for sets #11 and #10 were 22% and 37%, respectively. Because of this inter plasma batch variability in degradation, the extent of degradation of 5-ASA concentrations in samples from individual subjects cannot be established retrospectively. Furthermore, the polynomial degradation model used for correcting the 5-ASA concentrations fails to account for the inter-batch variability in degradation at -20°C. Also, only selective data was used in establishing the model (data from stability sets #10 and #14 were not used). In summary, because of the high inter-batch variability in degradation of 5-ASA at -20°C, the accuracy of the observed 5-ASA concentrations (corrected and uncorrected) cannot be assured. — concurred with DSI's finding in their written response (Attachment 2).

Also, it has been erroneously stated in the analytical report that this degradation should not affect the comparative assessment in the study as "both sets of samples for each subject were always analyzed within the same run". In fact, for 17 of 32 subjects, some subject plasma samples, often C_{max} samples, were reanalyzed later. Therefore, plasma samples for each subject were not always analyzed in the same run.

For reasons explained above, the accuracy of the 5-ASA concentrations in the Study SPD476-103 cannot be assured.

2. Failure to perform manual integration in a consistent manner for Project YAH/049.

The inspection revealed that — manual integration of QCs biased the acceptance of the runs. For example, although the original integration of the IS peak for one of 5-ASA high QCs in Run 21 was consistent with other IS peaks (Exhibit 1), — manually integrated the peak. The modified integration was not consistent with other integrations. When QC concentrations were estimated using the original integration, both high QCs in Run 21 were inaccurate (— of intended concentration) resulting in the run failing to meet the acceptance criteria (Exhibit 2). Similarly, Runs 11, 13 (5-ASA), and 27 (5-NASA) were also unacceptable. — agreed with DSI's finding.

3. Failure to investigate the discrepancy in freeze-thaw and room temperature stability data (Project — 054) between experiments on March 18 (run 7) and 23 (run 9), 2005 for 5-NASA concentrations at 1500 ng/mL, compared to — reduction in Run 7.

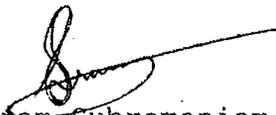
Validation run 9 evaluated conversion of 5-NASA to 5-ASA following 3 freeze-thaw (F-T) cycles and 24 hours at room temperature (RT) using samples spiked with only 5-NASA. Although no conversion to 5-ASA was observed, it was observed that the 5-NASA concentrations for the 1500 ng/mL F-T and R-T samples in Run 9 were significantly different from F-T and R-T stability data reported in Run 7 for 5-NASA at 1500 ng/mL. did not investigate the reason for this discrepancy.

Conclusions:

Due to the high variability in the degradation of 5-ASA in different plasma batches at -20°C (Item 1), DSI finds that the accuracy of 5-ASA concentration in subject samples cannot be assured in Study SPD476-103.

Also, the 5-ASA concentration data from Subjects 9, 11 and 20 are not valid as the analytical runs 11, 13 and 21 were inaccurate (Item 2).

After you have reviewed this memo, please append it to the original NDA submission.


Sriram Subramaniam, Ph.D.

Final Classifications:

NAI: (((

VAI:

cc:

HFD-45/RF

HFD-48/Himaya/Subramaniam(2)/CF

OND/ODEIII/DGP/Everett/NDA 22-000

HFD-880/Bashaw

HFR-NE250/Murphy

Draft: SS 10/2, 30/06

Edit: MKY 10/4/06, JAO 11/3/06

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FACTS ID 727339

9 Page(s) Withheld

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/s/

Sriram Subramaniam
11/8/2006 02:58:09 PM
PHARMACOLOGIST
Hardcopies available upon request.

MEMORANDUM OF TELECON

DATE: October 17, 2006

APPLICATION NUMBER: NDA 22-000

BETWEEN:

Name: Patrick Martin, Vice President, Clinical Pharmacology
Tracy Rockney, Senior Director, Regulatory Affairs
Nurit Rojstaczer, Manager, Regulatory Affairs
Rick Couch, Senior Vice President, Pharmaceutical Technology
Jason Burdett, Director, New Product Supply
Jo Ferdinando, Senior Vice President, Global Pharmaceutical Sciences
Srini Tenjarla, Director, Pharmaceutical Sciences
Vallente Romasanta, Manager, Pharmaceutical Sciences
David Pierce, Senior Director, Clinical Pharmacology & Pharmacokinetics

Phone: 484-595-8308

Representing: Shire Development, Inc.

AND

Name: Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead, Office of
New Drug Quality Assessment
George Lunn, Ph.D., Chemistry Reviewer, Office of New Drug Quality
Assessment
Dennis Bashaw, Pharm.D., Director, Office of Clinical Pharmacology 3
Kristen Everett, R.N., Regulatory Project Manager, Division of
Gastroenterology Products

Division of Gastroenterology, HFD-180

SUBJECT: Discussion of Storage Options for SPD-476

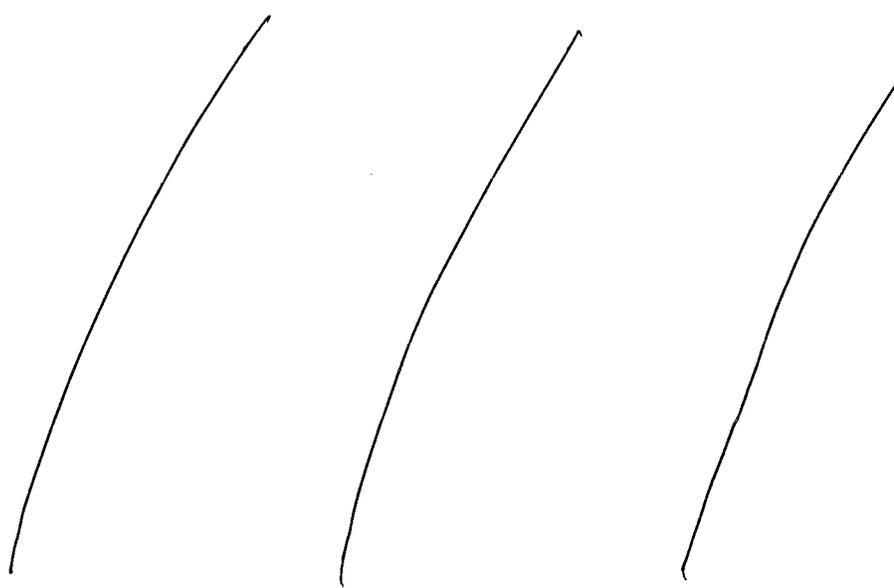
Following the teleconference on August 29, 2006, Shire submitted the information requested during that teleconference. The purpose of the teleconference today was to discuss the storage options the FDA feels are appropriate, given the data Shire has provided.

Today, we presented two options to Shire:

1.



2. The name of the product, SPD-476, would be Delayed Release, and the drug could be stored at room temperature, and they may use drug substance from either drug supplier.



Shire stated that they had no further questions and that they would need to discuss the options presented today and will provide a written response with their decision to the Agency. We advised that they should submit their decision regarding the two options in the form of an amendment to the NDA.

The phone call ended.

Kristen Everett
Regulatory Project Manager

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/s/

Kristen Everett
10/26/2006 03:34:45 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

9/7/06
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed Release Tablets.

On August 30, 2006, we received your August 29, 2006 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 21, 2007.

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Brian Harvey
9/7/2006 04:52:21 PM

MEMORANDUM OF TELECON

DATE: August 29, 2006

APPLICATION NUMBER: NDA 22-000

BETWEEN:

Name: Tracy Rockney, Senior Director, Regulatory Affairs
Nurit Rojstaczer, Manager, Regulatory Affairs
Roger Adsett, Product General Manager
Rick Couch, Senior Vice President, Global Pharmaceutical Technology
Jason Burdett, Director, New Product Supply
Srini Tenjarla, Senior Director, Pharmaceutical Sciences
Jo Ferdinando, Senior Vice President, Global Pharmaceutical Sciences
Vallente Romasanta, Pharmaceutical Sciences Manager

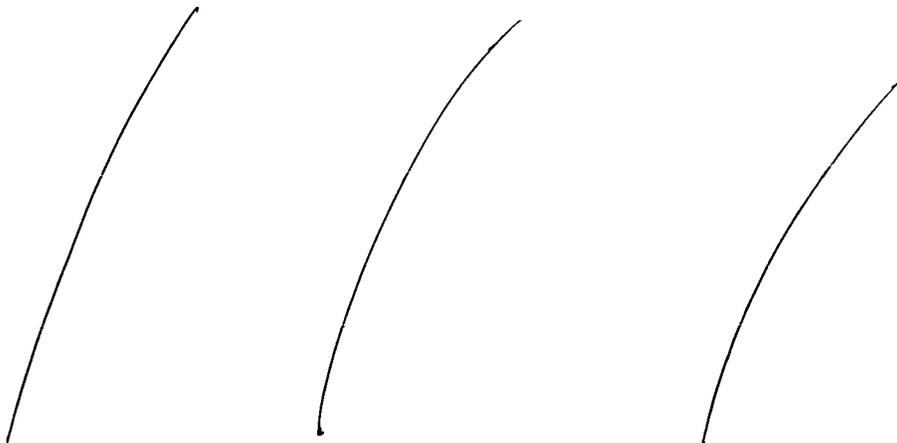
Phone: 484-595-8308

Representing: Shire Development, Inc.

AND

Name: Brian E. Harvey, M.D., Ph.D., Director, Division of Gastroenterology Products
Kristen Everett, R.N., Regulatory Project Manager, Division of
Gastroenterology Products
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, Office of
New Drug Quality Assessment
George Lunn, Ph.D., Chemistry Reviewer, Office of New Drug Quality
Assessment

SUBJECT: Discussion of unresolved chemistry issues with Shire's pending NDA.



C

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/s/

Kristen Everett
9/5/2006 02:43:10 PM
CSO

8/23/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

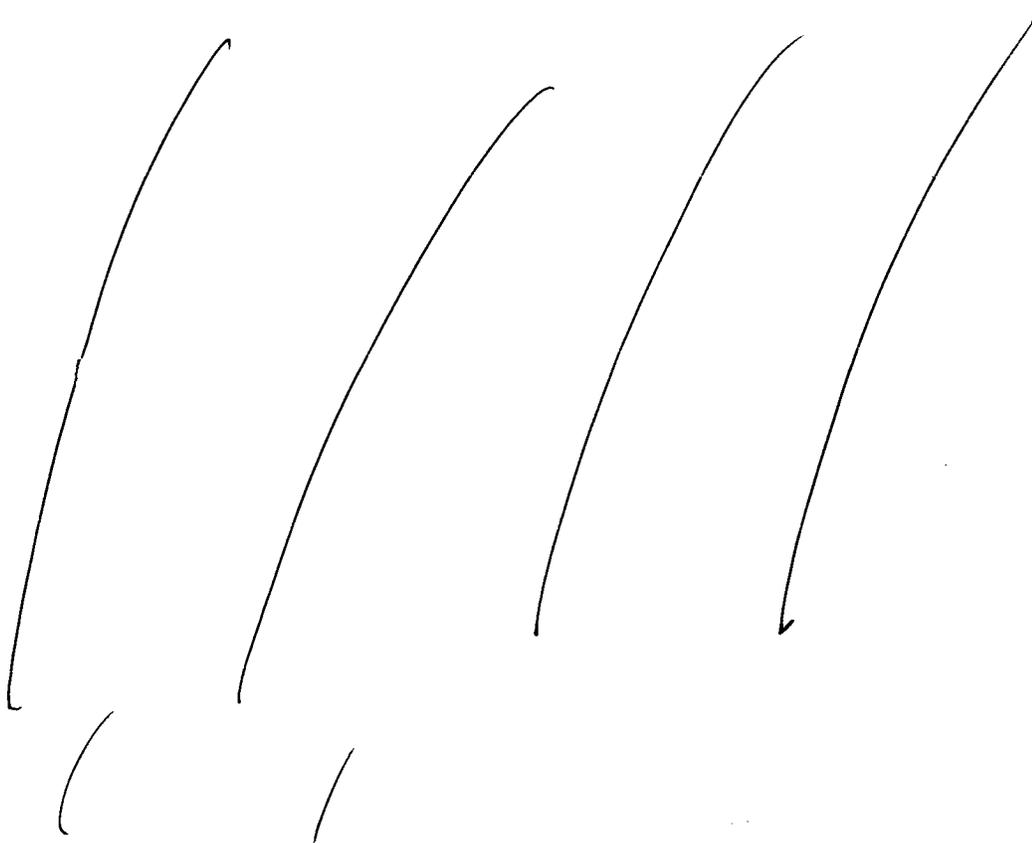
Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed and Extended release tablets.

We also refer to your submission dated August 11, 2006, which contained your response to our August 7, 2006, Chemistry, Manufacturing, and Controls Information Request letter.

Based on the response in your August 11, 2006, submission, we have the following comments.



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/s/

Moo-Jhong Rhee
8/23/2006 02:40:26 PM
Chief, Branch III

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 2, 2006

TO: Kristen Everett, Regulatory Project Manager
Fathia Gibril, M.D., Clinical Reviewer
Division of Gastroenterology Products, HFD-180

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-000

APPLICANT: Shire Development, Inc.

DRUG: Mesavance (mesalamine) Delayed → Release Tablets

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment — ulcerative colitis

CONSULTATION REQUEST DATE: February 28, 2006

DIVISION ACTION GOAL DATE: June 21, 2006

PDUFA DATE: 10/21/06

I. BACKGROUND:

Ulcerative colitis (UC) is a serious chronic inflammatory disease of the colon and rectum. The main clinical feature is diarrhea. The characteristic course for most individuals is one of remissions and exacerbations over the course of years. Morbidity can be long lasting and can be associated with various extra intestinal and late complications.

Ulcerative colitis can occur in people of any age, but it usually starts between the ages of 15 and 30, and less frequently between 50 and 70 years of age. It affects men and women equally and appears to run in families, with reports of up to 20 percent of people with ulcerative colitis having a family member or relative with ulcerative colitis or Crohn's disease.

The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Patients also may experience anemia, fatigue, weight loss, loss of appetite, rectal bleeding, dehydration, malabsorption, skin lesions, and joint pain. About half of the people diagnosed with ulcerative colitis have mild symptoms. Others suffer frequent fevers, bloody diarrhea, nausea, and severe abdominal cramps. The goal of drug therapy is to induce and maintain remission, and to improve the quality of life. Several types of drugs are available, including aminosalicylates, drugs that contain 5-aminosalicylic acid (5-ASA), help control inflammation. Sulfasalazine is a combination of sulfapyridine and 5-ASA. 5-ASAs are given orally, through an enema, or in a suppository, depending on the location of the inflammation in the colon. Most people with mild or moderate ulcerative colitis are treated with this group of drugs first. The sulfapyridine component carries the anti-inflammatory 5-ASA to the intestine. It has been prescribed for this disease for over 50 years. However, sulfapyridine may lead to side effects such as nausea, vomiting, heartburn, diarrhea, and headache. Other 5-ASA agents, such as olsalazine, mesalamine, and balsalazide, have a different carrier, fewer side effects, and may be used by people who cannot take sulfasalazine.

The test article, SPD476, differs from all other available oral forms of 5-ASA because it possesses a _____
 _____ The tablet core consists of 5-ASA in _____
 _____ which is then coated with a gastro-resistant polymer film. The
 active ingredient, 5-ASA, is released _____

For this study, the primary efficacy endpoint was remission after eight weeks of treatment. Remission is defined as an Ulcerative Colitis Disease Activity Index (UC-DAI) score of ≤ 1 , with scores of zero for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

Dr. Salcedo is _____ He has no prior inspections by CDER. Dr. Goff is _____ He has no prior inspections by CDER. Both clinical investigators (CIs) were chosen because they're high enrollers. Dr. Jackowski _____ and no prior inspections. His site was chosen because of high enrollment and unusual results on the primary efficacy variable. Subjects at his site had a high response rate for all treatment groups, including placebo.

NDA 22-000 Product Name: mesalamine
 Summary Report of U.S. and Foreign) Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
Dr. John Goff site 111	Lakewood, CO	476-301	4/17-4/20/2006	5/8/2006	VAI
Dr. Julio Salcedo site 122	Washington, D.C.	476-301	4/25-4/26/2006	6/13/06	NAI
Dr. Lechoslaw Jackowski site 633	Grudziadz, Poland	476-302	5/29-6/2/06	7/18/06	NAI

*If international site, please insert column for country.

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # 476-301

1. John Goff, Lakewood, CO; site 111: The data were acceptable.
 - a. The inspection took place 4/17-4/20/2006. Eight subjects were enrolled, and all records were reviewed for the inspection.
 - b. There were no limitations to the inspection.
 - c. There were two observations on the Form FDA 483. One concerned inadequate record keeping related to observations made during a sigmoidoscopy. The results of the sigmoidoscopy were incorrectly reported which resulted in an inaccurate UCDAI score. The other deficiency concerned failure to follow the protocol in that adverse events were not always reported to the sponsor within protocol specified guidelines. Also, one subject had an incomplete listing of concomitant meds.
 - d. There was one protocol violation that might have affected data integrity. However, the sigmoidoscopy score is only one component of the UCDAI score, and this occurred in a single subject so it is unlikely to have had an effect on overall data reliability.
2. Julio Salcedo, M.D., Washington, D.C.: site 122
 - a. The inspection took place 4/25-4/26/2006. Seven subjects were enrolled, and all records were reviewed for the inspection.
 - b. There were no limitations to the inspection.
 - c. There were minor record keeping discrepancies. There was a single incidence of a subject being enrolled who was not eligible. The subject's UCDAI score was rounded up to the next whole number. The error was caught by the study monitor. Since the subject had nearly completed the study by the time the error was discovered, the medical monitor granted a waiver to allow the subject to complete the study.
 - d. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

B. Protocol # 476-302

1. Lechoslaw Jackowski, M.D., Grudziadz, Poland; site 633
 - a. The inspection took place May 29 to June 2, 2006. Twenty four subjects were enrolled, and all records were reviewed for the inspection.
 - b. There were no limitations to the inspection.
 - c. There were no discrepancies between the source documents, case report forms (CRFs), and data listings supplied by the sponsor. No 483 was issued.
 - d. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The studies appear to have been well conducted at all the sites. One Form FDA 483 was issued at Dr. Goff's site. No follow up other than routine surveillance is recommended

Dianne Tesch, Consumer Safety Officer
GCPB Reviewer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dianne Tesch
8/8/2006 10:59:50 AM
CSO

Leslie Ball
8/14/2006 03:34:50 PM
MEDICAL OFFICER

8/11/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed Release Tablets.

We also refer to your submission dated May 31, 2006.

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In Study 105, subjects received the study drug after a standard breakfast. Please indicate what the meal was composed of, its carbohydrate/protein/fat content, and the corresponding calories.

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
8/11/2006 04:07:43 PM

8/7/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed Release Tablets.

We also refer to your submission dated July 18, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

[Redacted content]

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/s/

Moo-Jhong Rhee
8/7/2006 11:28:02 AM
Chief, Branch III

8/3/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PREA WAIVER DENIED

NDA 22-000

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your submission dated December 21, 2005, requesting a waiver under 505B(a)(4) of the Federal Food, Drug, and Cosmetic Act for pediatric studies for SPD476.

We have reviewed your submission and do not agree that a waiver of pediatric studies in patients < 6 years of age is justified for SPD476 for the induction of remission in patients with active, mild to moderate ulcerative colitis.

We are denying this waiver for the following reasons:

The rationale you provide, "the size of the SPD476 tablet is most likely too large for a child < 6 years old to ingest," is not an adequate justification. Therefore, you will need to develop an appropriate pediatric formulation for children < 6 years of age, or provide a rationale for why this is not possible.

We have determined that a deferral of all pediatric studies for patients is justified for the induction of remission in patients with active, mild to moderate ulcerative colitis. The reason for granting the deferral is your desire to defer commencement of pediatric studies until the efficacy and safety are established in adults. The requirements for your deferred pediatric studies will be fully addressed upon approval of this product. Deferred studies are considered required postmarketing study commitments.

If you have questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
8/3/2006 04:23:48 PM

7/19/66



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) 1.2 g Delayed Release Tablets.

We also refer to your submission dated March 22, 2006.

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The following information requests all pertain to the **hpbio** folder contained in the March 22, 2006, submission.

- 1. Study Report YAH/049: Determination of 5-Aminosalicylic Acid (5-ASA) and N-Acetyl-5-Aminosalicylic Acid in Plasma Samples from a Study to Assess the Effects of Co-administration of SPD476 with Food on the Bioavailability of 5-ASA (Shire Protocol: SPD476-103)**
 - Indicate how many samples were used at each time point in Table 1: Summary of Stability Data (page 98).
 - Show the individual data points and average value for Figure 1: Degradation of 5-ASA at -20°C (page 99). Use different symbols to differentiate individual data points from the mean values.
 - Please clarify if the polynomial equation was used to correct data in the YAH/049 final report.
- 2. Study Report YAH/063: Investigation into the Stability of 5-Aminosalicylic Acid in Human Plasma Stored at Nominal -20°C**
 - It is critical to demonstrate that samples from Study 103 behave the same way as the spiked samples described in Study Reports YAH/063 and YAH/049. The simple linear regression formula used in the analysis does not adequately describe the data

and almost all data points representing samples stored at -20°C for more than 40 days were above the regression line (Figure 2, page 25). Because the first order kinetics appears to adequately describe the data with the spiked samples, this approach should also be explored with the samples from Study 103. Furthermore, different symbols should be used in the plots to differentiate the QC (or spiked) samples from the samples obtained in Study 103.

3. Study Report YBS/054: Validation of an Analytical Method for the Determination of 5-Aminosalicylic Acid (5-ASA) and N-Acetyl-5-Aminosalicylic Acid (5-NASA) in Human Plasma Using Protein Precipitation for Sample Preparation and Liquid Chromatography with Tandem Mass Spectrometric Detection

- Several sample handling/storage conditions (temperature and duration) were validated. Please clarify whether these conditions cover all the actual sample storage/handling conditions for all studies submitted to the NDA.

4. Study 106

- Clarify whether this study has been initiated or completed.

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Susan Daugherty, R.N.
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
7/19/2006 10:19:59 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

6/26/06

NDA 22-000

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed Release Tablets.

We also refer to your submission dated April 27, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- The name that you propose for this product is Mesavance (mesalamine) Delayed Release Tablets. We recommend that you change the name to Mesavance (mesalamine) Tablets.
- In the Amendment dated April 27, 2006, you state that the
- In the Amendment dated April 27, 2006, you supply a comparison of the equipment used to manufacture the process validation batches described in the original submission and the commercial product manufactured in the new building. Please also list the class and sub-class (as described in SUPAC-IR) for each piece of equipment and also discuss if the equipment used to manufacture the commercial batches is of the same design and operating principle as that used for the validation batches. We look forward to receiving in-process control and batch release data from the three validation batches in due course.
- In the Amendment dated April 27, 2006, you supply a Certificate of Analysis to show that the talc conforms to the appropriate USP specification. However, this Certificate of

Analysis for talc, although it conforms to the latest USP 29 specifications, does not state that _____

- We note that the package insert does not mention _____ Do you intend to market tablets packaged in _____

- _____

- Please provide data to show that the characteristics of the bottles used for the stability samples and the proposed commercial bottles are similar.

- _____

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6/1/2006



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed Release Tablets.

We are reviewing the Statistical section of your submission and have the following information requests.

- Please specify the variables and data sets used to create Table 4 (Summary of Efficacy Results - ITT Population Study, SPD476-301) and Table 5 (Summary of Efficacy Results - ITT Population Study, SPD476-302) in the Summary of Clinical Efficacy--SPD476, along with any instructions needed to reproduce the results presented in these tables.
- Please provide CRF's for site SPD302-633.

We request a prompt written response to this information request in order to continue our evaluation of your NDA.

If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Melissa Furness
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Melissa Furness
6/1/2006 03:57:47 PM

725 Chesterbrook Blvd.
Wayne PA 19087-5637 USA
866 744-7362
Fax 484 595-8653



20 April 2006

Brian E. Harvey, M.D.
Director
Division of Gastroenterology Products (HFD-180)
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Product Name: SPD476 (mesalamine) Delayed — Release Tablets, 1.2g
Submission Type: Four-Month Safety Update Report
NDA: 22-000

Dear Dr. Harvey,

In accordance with 21 CFR 314.50(d)(5)(vi)(b), Shire is submitting a Four-Month Safety Update Report containing a summary of safety information for the referenced New Drug Application (NDA) 22-000 for SPD476 Delayed — Release Tablets for the induction of remission in patients with ulcerative colitis.

The original NDA for SPD476 was submitted to the Division on 21 December 2005.

Please note that the information for this submission is provided on one CD-ROM and the total file size is 220 MB. The media has been scanned with Symantec™ AntiVirus Version 8.00.9374, scan engine 4.1.0.15 (corporate edition) and with a virus definition file version 4/12/2006 revision 5. No viruses were detected and we certify that the CD-ROM is virus-free.

Please do not hesitate to contact me at (484) 595-8308 or Tracy Rockney at (484) 595-8825 if you have any questions regarding this submission or if you require additional information.

Sincerely,

A handwritten signature in black ink that reads "Nurit Rojstaczer". The signature is written in a cursive, flowing style.

Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs

Enclosures

3/21/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-000

INFORMATION REQUEST LETTER

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph. D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) Delayed Release Tablets 1.2 g.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please confirm that, except as indicated for batches 5302 and 5303 in Table 1 of 3.2.P.2.2, all the batches of tablets described in Tables 2 and 3 of 3.2.P.2.2 use the same amounts of excipients.
2. In the section 3.2.P.3.4, please describe how many tablets are used for each in-process control. Please also describe how _____ is determined.
3. In section 3.2.P.3.5, you state that process validation was undertaken with _____ drug substance and that "It shall be noted that, prior to commercialization, manufacture of the product will move to a new building, which will contain larger processing equipment. Three validation batches will be manufactured in this new building to release to the market, and the data submitted for regulatory review on request." Please supply the details of these commercial batches, both in-process control and release data and please also supply a comparison of the equipment used to manufacture the process validation batches described above and the commercial product manufactured in the new building. Additionally, please provide release data for the process evaluation batches made from _____ drug substance and a comparison of the equipment used for these batches and the commercial product manufactured in the new building.
4. Please supply Certificates of Analysis to show that carnauba wax; magnesium stearate, _____, silica colloidal hydrated, sodium carboxymethylcellulose, stearic acid, and talc conform to the appropriate USP/NF specification. In addition, please show that silica colloidal hydrated corresponds to a USP/NF grade material.

5. Please provide certification that the stearic acid is not of animal origin.

6.

7.

8. Please supply the packaging site for the batches shown in Tables 1-68 and the bottle sizes for the batches shown in Tables 3-37 of the drug product stability section. In section 3.2.P.5.6, you state that "It is important to note that the stability and the clinical samples were packaged separately at different locations." Please clarify this statement.

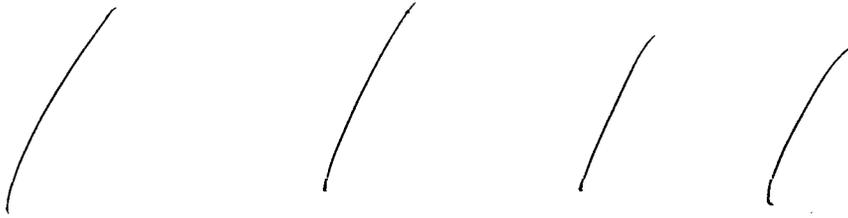
9.

10.

11.

12. Methval.pdf is a series of methods validation original reports, but it is not a Methods Validation Package. Please provide a complete Methods Validation Package as described in the draft Analytical Procedures and Methods Validation Guidance, available at: <http://www.fda.gov/cder/guidance/2396dft.htm>. This should include a tabular list of all samples to be submitted, detailed descriptions of the analytical procedures, etc.

13.



If you have any questions, call Kristen Everett, Regulatory Project Manager, at 301-796-0453.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
3/21/2006 11:34:47 AM
Chief, Branch III

3/2/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-000

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mesavance (mesalamine) 1.2 g Delayed Release Tablets.

We also refer to your submission dated January 23, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 19, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

- Our preliminary review of your safety data indicates that the total number of ulcerative colitis subjects exposed for 6 months or 12 months to SPD476 at a dose level intended for clinical use does not appear adequate (refer to ICH E1A Guidance).
- It is unclear how many studies were affected by the stability problems. Document how you determined which samples in what studies were affected by this issue. Submit data that were used to generate the correction curve and describe how these data were obtained. Provide the correction formula and goodness-of-fit indicators/plots. List the individual corrected and uncorrected data side-by-side along with study number, subject number, period number, fed/fasted condition and sampling time for easy comparison.
- Since some samples from the food effect Study 103, titled "A Phase 1, Randomized, Open-Label, Single-Dose, Two-Period, Cross-Over Study in Healthy Male and Female Volunteers to Assess the Effects of Co-Administration of SPD476 4.8 g With Food On the Bioavailability of 5-Aminosalicylic Acid (5-ASA)" had stability issues, the results of this study may not be reliable and the study may need to be repeated. Any correction of the data should be justified and provided for our review.
- In addition to stability problems observed at -20°C, it is unclear whether the stability of

5-ASA in plasma samples at room temperature has been determined. The assay method, including sample handling and analysis elapse time, should be validated. This should be done before samples from your future Study 105 are assayed.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Kristen Everett, R.N., Regulatory Project Manager, at (301) 796-0453.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
3/2/2006 01:00:05 PM

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: February 28, 2006

TO: Dr. Viswanathan, Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Kristen Everett, Regulatory Project Manager, Division of Gastroenterology Products,
HFD-180

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-000
Shire Development, Inc.
Mesavance (mesalamine) Delayed — Release Tablets 1.2 g

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
SPD476-103		

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **August 7, 2006**. We intend to issue an action letter on this application by **October 21, 2006**.

Should you require any additional information, please contact Kristen Everett, R.N., 301-796-0453.

This foreign analytical site inspection is requested because of the following reason:

- **Stability Issues:** in the pre-NDA meeting, the sponsor reported degradation of 5-ASA occurring after plasma samples were stored at -20de C. The sponsor modeled degradation using a polynomial curve and data were adjusted prior to pharmacokinetic analysis. In addition, because degradation of 5-ASA can occur at -20 deg C, we are uncertain if stability at room temperature is sufficient to allow for sample handling and processing during assay.

Please also refer to the NDA submission, if needed: \\CDSESUB1\N22000\N_000\2005-12-21

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/s/

Kristen Everett
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Dennis Bashaw
3/2/2006 09:58:10 AM

DSI CONSULT: Request for Clinical Inspections

Date: February 28, 2006

To: Constance Lewin, M.D., Acting Branch Chief, GCP1
Leslie Ball, M.D., Branch Chief, GCP2

cc: Joseph Salewski, Acting Director, DSI
Brian E. Harvey, M.D., Ph.D., Director, Division of Gastroenterology
Products

From: Kristen Everett, R.N., Regulatory Project Manager
Division of Gastroenterology Products

Subject: **Request for Clinical Site Inspections**
NDA 22-000
Shire Development, Inc.
Mesavance (mesalamine) Delayed — Release Tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site 633 Dr. Lechoslaw Jackowski NZOZ GCP Dobra Praktyka Lokarska Ul. Chelminska 74 86-300 Lublin Poland	SPD476-302	24	Induction of remission (clinical and endoscopic) in patients with active, mild to moderate ulcerative colitis

Request for Clinical Inspections

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site 111 Dr. John Goff Rocky Mountain Gastroenterology Associates 7000 W. Colfax Ave. Lakewood, CO 80215 USA	SPD476-301	8	Induction of remission (clinical and endoscopic) in patients with active, mild to moderate ulcerative colitis
Site 122 Dr. Julio Salcedo Morowitz, Marion, Lessig, Shocket, Bashir, Steinberg, and Salcedo 106 Irving St., NW, Suite 205 Washington, DC 20010 USA	SPD476-301	7	Induction of remission (clinical and endoscopic) in patients with active, mild to moderate ulcerative colitis

Domestic Inspections:

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects in the USA
- High treatment responders (specify:)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: SPECIFY

International Inspections:

We have requested inspections because (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted from this study

Request for Clinical Inspections

- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: Site 633 had unusual results on the primary efficacy variable - high response rate for all treatment groups including placebo. This is also the largest site, with 24 patients. This study had no sites in the USA.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) August 7, 2006. We intend to issue an action letter on this application by (division action goal date) October 21, 2006. The PDUFA due date for this application is October 21, 2006.

Should you require any additional information, please contact Kristen Everett, at 301-796-0453.

Concurrence: (if necessary)

Ruyi He, M.D., Medical Team Leader
Fathia Gibril, M.D., Medical Reviewer
Brian Harvey, M.D., Ph.D., Division Director (for foreign inspection requests only)
Stella Grosser, Ph.D., Biometrics Team Leader

Please also refer to the NDA submission, if needed: \\CDSESUB1\N22000\N_000\2005-12-21

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/s/

Ruyi He

3/3/2006 04:06:35 PM

Dr. Brian Harvey, the Division Director. concurred with this
DSI consult.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-000 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Mesavance
Established Name: mesalamine
Strengths: 1.2 g Delayed — Release Tablets

Applicant: Shire Development, Inc.
Agent for Applicant:

Date of Application: December 21, 2005
Date of Receipt: December 21, 2005
Date clock started after UN:
Date of Filing Meeting: January 30, 2006
Filing Date: February 19, 2006
Action Goal Date (optional): User Fee Goal Date: October 21, 2006

Indication(s) requested: Induction of remission in patients with active, mild to moderate ulcerative colitis

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: NDA 21-252 Canasa (mesalamine) rectal suppository – Axcan Scandipharm;
Exclusivity expires November 5, 2007

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? N/A YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO

If an electronic NDA, all forms and certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format? All parts of the application were submitted electronically, except for the below.

Additional comments: the original, signed FDA forms were not included in this submission, with the exception of the Form 356h. The original forms will be submitted by the sponsor as an amendment to the NDA.

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO

If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 3 Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 66,193

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) June 2, 2005, August 18, 2005; December 16, 2005 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Risk Management Plan consulted to ODS/IO? N/A YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to

ODS/DSRCS?

N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A YES NO

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 30, 2006

BACKGROUND: Shire Development, Inc., submitted a New Drug Application (NDA), Mesavance (mesalamine) Delayed Release 1.2g Tablets, on December 21, 2005. This NDA is for a new formulation of mesalamine since it is an delayed release tablet and a new dosage of 1.2 g. Other approved mesalamine products on the market include Pentasa Extended Release 250 mg Capsule, Canasa 1 gm Rectal Suppository, Asacol Delayed Release 400 mg tablet, and Rowasa 4 g Rectal Enema and 500 mg Rectal Suppository.

ATTENDEES: Dr. Jasti Choudary, Dr. David Joseph, Kristen Everett, Dr. Sue Chih Lee, Dr. Fathia Gibril, Dr. Ruyi He, Dr. Marie Kowblansky, Dr. George Lunn, Ryan Barraco, Dr. Brian E. Harvey, Dr. Joyce Korvick

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Fathia Gibril, M.D.
Secondary Medical:	
Statistical:	Stella Grosser, Ph.D.
Pharmacology:	David Joseph, Ph.D.
Statistical Pharmacology:	
Chemistry:	George Lunn, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Sue Chih Lee, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
Regulatory Project Management:	Kristen Everett, R.N.
Other Consults:	DDMAC, DMETS, DSI

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE
STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
• Biopharm. inspection needed?			YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
PHARMACOLOGY	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
• GLP inspection needed?			YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
CHEMISTRY	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
• Establishment(s) ready for inspection?			YES	<input type="checkbox"/>	NO	<input type="checkbox"/>
• Microbiology			YES	<input type="checkbox"/>	NO	<input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Kristen Everett, R.N.
Regulatory Project Manager, HFD-180
Division of Gastroenterology Products

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/s/

Kristen Everett
2/3/2006 03:48:17 PM
CSO

1/18/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-000

NDA ACKNOWLEDGMENT

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Dr. Rojstaczer

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Mesavance (mesalamine) 1.2 g Delayed Release Tablets
Review Priority Classification:	Standard (S)
Date of Application:	December 21, 2005
Date of Receipt:	December 21, 2005
Our Reference Number:	NDA 22-000

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 19, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 21, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 22-000

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-0453.

Sincerely,

{See appended electronic signature page}

Kristen Everett, R.N.

Regulatory Project Manager

Division of Gastroenterology Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Kristen Everett
1/18/2006 04:04:24 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,193

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPD476 (mesalamine) 1.2g Tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2005. The purpose of the meeting was to discuss additional finding related to the pharmacokinetics of SPD476 Tablets that were not available at the June 2, 2005 Pre-NDA meeting.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0453.

Sincerely,

{See appended electronic signature page}

Kristen Everett, R.N.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 16, 2005
TIME: 2:00 pm – 3:00 pm
LOCATION: FDA, White Oak Campus, Conference Room 1415
APPLICATION: IND 66,193
DRUG NAME: SPD476 (mesalamine) 1.2 g Tablets
TYPE OF MEETING: Type C

MEETING CHAIR: Ruyi He, M.D., Medical Team Leader

MEETING RECORDER: Kristen Everett, R.N., Regulatory Project Manager

BETWEEN:

FDA ATTENDEES:

Joyce Korvick, M.D., M.P.H., Deputy Director, Division of Gastroenterology Products
Ruyi He, M.D., Medical Team Leader, Division of Gastroenterology Products
Fathia Gibril, M.D., Medical Reviewer, Division of Gastroenterology Products,
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, Division of Clinical Pharmacology and
Biopharmaceutics (DCPB2)
Sue Chih Lee, Ph.D., Biopharmaceutics Reviewer, Division of Clinical Pharmacology and
Biopharmaceutics (DCPB2)
Ryan Barraco, Regulatory Project Manager, Division of Gastroenterology Products
Kristen Everett, R.N., Regulatory Project Manager, Division of Gastroenterology Products

AND

EXTERNAL CONSTITUENT ATTENDEES:

Douglas Hay, Ph.D., Senior Vice President, Global Regulatory Affairs, Shire Development, Inc.
Raymond Joseph, M.D., Senior Director, Clinical Research and Development, Shire Development, Inc.
Patrick Martin, M.D., Vice President, Clinical Pharmacology, Shire Development, Inc.
Eliseo Salinas, M.D., Executive Vice President, Global Research and Development, Shire
Development, Inc.
Richard Franklin, B.Sc., M.Sc., Ph.D. Senior Director, Biosciences,
Tracy Rockney, J.D., Senior Director, Regulatory Affairs Shire Development, Inc.
Nurit Rojstaczer, Ph.D., Manager, Regulatory Affairs, Shire Development, Inc.
Srini Tenjarla, Ph.D., Director, Pharmaceutical Sciences, Shire Development, Inc.

PURPOSE:

To discuss additional finding related to the pharmacokinetics of SPD476 Tablets that were not available at the June 2, 2005 Pre-NDA meeting.

BACKGROUND:

On October 5, 2005, Shire Development, Inc. submitted a meeting request to discuss additional findings related to the pharmacokinetics of SPD476 Tablets that were not available at the June 2, 2005 Pre-NDA meeting.

On November 16, 2005, Shire Development, Inc. submitted a background meeting package to the Agency.

On December 14, 2005, responses to the questions contained in the meeting package were faxed to Shire Development, Inc.

DISCUSSION:

Response to sponsor's questions:

Questions and Responses:

1. Shire is submitting the SPD476 NDA on 23 December 2005. Study SPD476-105 is targeted to begin in January 2006, and results are expected to be reported towards the end of the review cycle. Would the Division want to see the results of this study during the review period?

FDA Response:

- **PK information is included in the overall assessment of safety and efficacy and dosing recommendation of a drug product. Currently available data suggest unusual gender-specific food effect (Study 103) and supra-proportionality with dose (Study 102). We recommend that Study 105 be submitted prior to the submission of the NDA. Since the stability issue is associated with some of the existing data, the NDA should not be submitted prior to receiving feedback from us on Study 105.**
 - **In addition to stability problems observed at -20 degrees C, it is unclear whether the stability of 5-ASA in plasma samples at room temperature has been determined. The assay method, including sample handling and analysis elapse time, should be validated. This should be done before samples from Study 105 are assayed.**
 - **The proposed design for Study 105 has 2 dose levels (2.4g and 4.8 g). In view of the supra-proportionality suggested by the current data, it is recommended that an additional dose level of 1.2 g (at least as a single dose) be included in the study.**
2. If so, Shire proposes to provide the data from this study as a Minor Amendment with no impact on the PDUFA review timeline. If the Division concurs, what is the latest date during the review period we can submit the data from this study?

FDA Response:

We recommend that Study 105 be submitted prior to the submission of the NDA.

Additional Comments:

1. Document how you determined which samples in the studies (e.g., Study 102, Study 103) were affected by stability problems. Please submit this information for our review prior to NDA submission.
2. Since some samples from the food effect Study (103) had stability issues, the results of this study may not be reliable and the study may need to be repeated. Any correction of the data should be justified and provided for our review.
3. If you plan to submit this NDA under 505 (b) (2), you will need to provide results from a relative bioavailability study comparing your drug to an approved product.

Meeting Discussion: Handouts (attached) provided by Sponsor and discussed during the meeting.

Shire intends to submit Study 105 as soon as possible after the submission of their NDA.

The Agency is interested in the sponsor's proposed 3 way cross-over dose proportionality study that will be conducted in parallel with Study 105. The study reports will be submitted when they are available.

ATTACHMENTS:

Shire Development, Inc. Power Point presentation.

Minutes Preparer: _____
Kristen Everett, R.N.
Regulatory Project Manager

Chair Concurrence: _____
Ruyi He, M.D.
Medical Team Leader

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/s/

Kristen Everett
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Ruyi He
1/11/2006 01:33:19 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,193

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rojstaczer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPD476 — tablets.

We also refer to the meeting between representatives of your firm and the FDA on August 18, 2005. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Control (CMC) issues prior to submission of the SPD476 New Drug Application (NDA).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8347.

Sincerely,

{See appended electronic signature page}

Kristen Everett, RN
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 18, 2005
TIME: 1:00 pm – 2:00 pm
LOCATION: Potomac Conference Room, Parklawn Building, Rockville, MD
APPLICATION: IND 66,193
DRUG NAME: SPD476
TYPE OF MEETING: Type B Meeting: CMC Pre-NDA
MEETING CHAIR: Liang Zhou, Ph.D. Chemistry Team Leader
MEETING RECORDER: Kristen Everett, R.N., Regulatory Project Manager

BETWEEN:

Shire Development, Inc.

Richard Franklin, B.Sc., M.Sc., Ph.D. Senior Director, Biosciences
Tracy Rockney, J.D., Senior Director, Regulatory Affairs
Nurit Rojstaczer, Ph.D., Manager, Regulatory Affairs
Srini Tenjarla, Ph.D., Director, Pharmaceutical Sciences

AND

Division of Gastroenterology Products (DGP), HFD-180

Joyce Korvick, M.D., M.P.H., Deputy Director
Liang Zhou, Ph.D., Chemistry Team Leader
Maria E. Ysern, Ph.D., Review Chemist
Ruyi He, M.D., Medical Team Leader
Lolita A. Lopez, M.D., Medical Officer
Kristen Everett, R.N., Regulatory Project Manager
Monika Houstoun, Pharm. D., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Sue-Chih Lee, Ph.D., Clinical Pharmacology Reviewer

PURPOSE:

The purpose of the meeting was to discuss Chemistry, Manufacturing, and Control (CMC) issues prior to submission of the SPD476 New Drug Application (NDA) and the requirements for qualifying an additional manufacturing site.

BACKGROUND:

On June 2, 2005, Shire Development, Inc. had a Pre-NDA meeting to discuss their planned November NDA submission to SPD476.

On June 14, 2005, Shire Development, Inc. submitted a Type B Meeting Request for a Pre-NDA CMC meeting. On July 19, 2005, a subsequent background package was submitted.

The Division sent pre-meeting responses to Shire Development, Inc. on August 11, 2005. The Division sent revised responses to address an error in the response for Question #2 on August 12, 2005.

In response to the Agency responses, Shire Development, Inc. submitted additional information on August 16, 2005.

DISCUSSION POINTS:

Question 1

The proposed dissolution specification for SPD476 is as follows:

pH 1 after 2h	NMT	→
pH 6.4 after 1h	NMT	—
pH 7.2 after 1h	NMT	—
pH 7.2 at 2h		— 0
pH 7.2 at 6h	NLT	—

Does the Agency agree with these proposed dissolution specifications? (Please see Shire's justification in Section 8 of this Information Package)

FDA Response:

The following information should be provided to determine the acceptability of the dissolution method and specification:

- a. Dissolution methods explored
- b. Conditions (apparatus, stirring speed and media) employed in the proposed dissolution method and the rationale for the selection of the proposed conditions
- c. Individual dissolution data for bio batches and stability batches at various sampling time points
- d. Plasma concentration-time profiles

Pending this data, the acceptability of the proposed dissolution specification cannot be determined at this time.

/ / / /

Question 2

Shire plans to qualify an additional manufacturing site for SPD476. _____
_____, is the primary manufacturing site that will be submitted in the
NDA.

Shire is seeking the Agency's guidance on how to qualify an alternate

manufacturing site
of this Information Package).

(Please see Shire's proposal in Section 8

FDA Response:

a bioequivalence study is necessary.

You should also provide:

- a. One batch with three months of accelerated data and one batch of long term stability data reported in annual report if significant body of data is available.
- b. Up to three batches with three months accelerated stability data and up to three batches of long term stability data reported in the annual report.
- c. A multipoint dissolution profile.
- d. Compare and contrast manufacturing and controls between the 2 sites.

A satisfactory cGMP inspection would also be required.

Question 3

Shire proposes to file with — stability data for the three registration batches manufactured with — drug substance and — stability data for the three registration batches manufactured with — drug substance. Is this acceptable to the Agency?

FDA Response:

Yes, it is acceptable.

Question 4

For clinical supplies, Shire sourced the — bottles from a vendor — There is extensive stability data with this packaging configuration. For commercial supplies, Shire plans to source the — bottles' — from a vendor — At the time of submission, Shire plans to provide — stability data with the — bottles from the new vendor. Is this acceptable to the Agency?

FDA Response:

Yes, it is acceptable. However, please provide data to support the equivalence of these two container closure systems.

ATTACHMENTS:

Shire Development, Inc. power point presentation.

Minutes Preparer: _____
Kristen Everett, R.N.
Regulatory Project Manager

Chair Concurrence: _____
Liang Zhou, Ph.D.
Chemistry Team Leader

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/s/

Kristen Everett
9/8/2005 04:50:55 PM

Liang Zhou
9/8/2005 04:52:29 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,193

Shire Development, Inc.
Attention: Nurit Rojstaczer, Ph.D.
Manager, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, Pennsylvania 19087

Dear Dr. Rojstaczer:

Please refer to your Investigational New Drug Application (IND) file for SPD476 1.2 gm
— Tablets.

We also refer to the meeting between representatives of your firm and the FDA on
June 2, 2005. The purpose of the meeting was to your planned November 2005 NDA
submission for SPD476 (mesalamine delayed — release tablet, 1.2 gm).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any
significant differences in understanding regarding the meeting outcomes.

If you have any questions please call me at (301) 827-9333.

Sincerely,

{See appended electronic signature page}

Monika Houstoun, Pharm.D.
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

Memorandum of Meeting Minutes

Meeting Date: June 2, 2005
Meeting Time: 11:00-12:30 p.m.
Meeting Location: 13B-45 Conference Room, Parklawn Building

Application Number: IND 66,193
Drug Name: SPD476
Type of Meeting: Type B
Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Monika Houstoun, Pharm.D.

BETWEEN:

Shire Development, Inc. Attendees:

Todd Butler, Director, Clinical Programs
Richard Franklin, Director, Biosciences
Douglas Hay, Senior Vice President, Global Regulatory Affairs
Raymond Joseph, Senior Director, Global Clinical Medicine
Liz King, Director, Program Management
Michelle Palmer, Associate Director, Biostatistics
Tracy Rockney, Senior Director, Regulatory Affairs
Nurit Rojstaczer, Manager, Regulatory Affairs
Michael Swalina, Manager, Regulatory Operations
Timothy Whittaker, Vice President, Global Clinical Medicine

AND

Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180

Brian E. Harvey, M.D., Ph.D., Director
Ruyi He, M.D., Medical Team Leader
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader
Fathia Gibril M.D., Medical Reviewer
Sushanta Chakder, Ph.D., Pharmacologist
Maria Ysern, Ph.D., Chemistry Reviewer
Zei Pao Huang, Information Technology Specialist
Monika Houstoun, Pharm.D., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer

Division of Biometrics II (HFD-715)

Stella Grosser, Ph.D., Statistical Team Leader

PURPOSE:

To discuss the planned November 2005 NDA submission for SPD476 (mesalamine delayed —
— release tablet, 1.2 gm).

BACKGROUND:

On November 15, 2002, Shire Development, Inc. submitted an Investigational New Drug Application (IND) file for SPD476 1.2 g ————— Tablets.

On March 2, 2005, received March 3, 2005, Shire Development Inc. submitted a request for a preNDA meeting to discuss their planned November 2005 NDA submission for SPD476 (mesalamine delayed — . release tablet, 1.2 gm).

On April 28, 2005, the sponsor submitted a background package containing regulatory, preclinical, and clinical questions.

Responses to the questions posed by the sponsor were faxed to the sponsor on June 1, 2005.

DISCUSSION:

Response to questions from the firm.

List of questions

Application Format

1. Shire proposes that the NDA will be fully electronic and will be a hybrid of an eNDA and the Common Technical Document (CTD) format as described in FDA's Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999. All data and analysis of CMC, nonclinical, clinical pharmacology, and clinical efficacy and safety, as described in FDA's guidance for format and content of an NDA, will be presented within the structure of a CTD. The hybrid CTD submission will consist of CTD Documents and a Table of Contents specific to each module, in an eNDA defined folder structure. Does the Division concur with this proposal?

FDA Response:

Yes. You may send your electronic NDA in either CTD or eCTD format.

Nonclinical Pharmacology and Toxicology Information

2. As identified in the original IND (submitted November 15, 2002; Serial No. 000), SPD476 has not been studied in animals. The drug substance, mesalamine, has been in clinical use for more than 20 years, and the drug-release mechanism is specifically designed for the human gastrointestinal system. Additionally, the prodrug sulfasalazine has been used for more than 50 years. Therefore, new studies in animals were not deemed

necessary. Shire intends to present only published and publicly available data on mesalamine as the non-clinical data for Module 4 of this application. A Non-clinical Overview of these data will be provided in Module 2. Tabular summaries will not be provided due to the limited amount of detailed information publicly available. Does the Division concur with this approach?

FDA Response:

Yes.

Clinical Information

This NDA is supported by 2 adequate and well-controlled studies, Study SPD476-301 and SPD476-302. Study SPD476-301 was conducted under the IND; Study SPD476-302 was conducted entirely outside the US. Both studies were placebo-controlled. In addition to placebo, Study SPD476-302 included a mesalamine comparator solely as a reference arm. These studies evaluated the efficacy and safety of 2 doses of SPD476 in patients with acute, mild to moderate UC. Supportive data from phase II studies are also provided.

3. Does the Division agree that the following studies constitute "covered clinical studies" requiring compliance with financial disclosure requirements: SPD476-102, SPD476-201, SPD476-202, SPD476-301, SPD476-302, and SPD476-303?

FDA Response:

Your proposal appears acceptable. However, you should attempt to provide all available information on all studies.

4. In accordance with 21 CFR 314.50(f)(2), Shire intends to submit copies of case report forms (CRFs) for each patient who died during a clinical trial or who discontinued the trial due to an adverse event, whether believed to be drug-related or not, and for each patient who had a serious adverse event. Narratives will also be included. Does the Division concur with this plan?

FDA Response:

We request that you also include CRFs for all patients who discontinued the trial for any reason, in addition to those CRFs.

We agree with the sponsor that the utility of providing CRFs on placebo patients does not appear to be useful at this time, however, should there be a signal in the treated group, this information may be requested.

5. Shire will provide case report tabulations (CRTs) in SAS transport format by domain in the CRF. Each dataset will consist of a single file and will include both raw data collected

directly from the CRF and derived data. Each dataset refers to one CRF domain and each makes reference to the CRF pages from which the data are collected and derived. In addition, other datasets intended for exploratory efficacy analyses will also be present. Data definition files will accompany these CRTs. Navigational links to both the CRTs and definition files will be provided in the define.pdf file, per Guidance for Industry- Providing Regulatory Submissions in Electronic Format – NDAs (January 1999). Also, an annotated CRF will be provided for ease of review.

- Does the Division concur that providing the datasets by CRF domain profiles will allow for an adequate review of the NDA?

FDA Response:

The label for each variable in the file should fully interpret the meaning of the variable in accordance with the Guidance. Please provide an example of your data definition file prior to the Pre-NDA meeting.

- Does the Division require the raw datasets in addition to the derived datasets?

FDA Response:

Please include both the raw and derived datasets.

- Will the Division accept the SAS Transport files in version 8?

FDA Response:

According to the Guidance for Industry, the SAS transport files should be in version 5.

- Will the Division accept electronic datasets in files larger than 50MB in size?

FDA Response:

We accept datasets larger than 50MB and less than 100MB. However, for analysis datasets, the size should be no larger than 25MB.

Pediatric Use Information

6. Shire's development plan has been to demonstrate that SPD476 is safe and effective in adults before evaluating its effect in the pediatric population. Therefore, Shire is requesting a deferred submission of pediatric studies at this time. Does the Division concur with a deferred submission?

FDA Response:

You should submit your pediatric study plan and formal request for deferral in your NDA as per the Pediatric Research Equity Act (PREA).

Labeling

- 7 Shire plans to submit the proposed product labeling in PDF and Word format. The recently issued Guidance for Industry entitled, "Providing Regulatory Submissions in Electronic Format - Content of Labeling" (April 2005), states that during the "transition to the automated system, the Agency is able to accept the content of labeling in either PDF or SPL file format.

Shire plans to submit this NDA in November 2005. Based on the recently issued Guidance for Industry, does FDA concur with Shire's plan to submit PDF and Word formats?

FDA Response:

Your plan to submit the proposed product labeling in PDF and word formats is acceptable.

- 8 Based on the primary end-points of the 2 adequate and well-controlled trials (Studies SPD476-301 and -302), Shire proposes the following indication for SPD476:

"Induction of remission in patients with —, mild to moderate ulcerative colitis."

Does the Division concur with this proposed indication?

FDA Response:

It is premature to address this issue at this time. The proposed indication should be data driven.

The sponsor clarified that — ulcerative colitis is the same as active ulcerative colitis.

Integrated Efficacy Summary

9. Shire proposes to group the primary and secondary efficacy data from Studies SPD476-301 and SPD476-302 because they are the only placebo-controlled studies. Study SPD476-303 is a long-term extension study for subjects from Studies SPD476-301 and SPD476-302, Study SPD476-201 is an active control study, and Study SPD476-202 is a dose ranging study.

Shire will perform pooled exploratory subgroup analyses across the studies for common treatment arms. Data from efficacy studies, SPD476-201, -202, and -303 will not be pooled, nor pooled with data from Studies SPD476-301 and -302 for the following reasons:

- Studies SPD476-202 and SPD476-303 Acute Phase did not include a placebo or active comparator arm
- Study SPD476-201 uses different efficacy measures
- Study SPD476-201 had a different study population
- Study SPD476-303 Acute Phase was an open-label study and
- Study SPD476-303 investigates maintenance of remission.

Does the Division concur with this proposal?

FDA Response:

Your proposal for presenting IES appears acceptable.

Integrated Safety Summary

10. Shire proposes to pool the double-blind, placebo controlled phase III studies SPD476-301 and SPD476-302. The integrated safety summary will focus on the results of this pooled analysis. Adverse events, laboratory, outliers, vital signs and treatment exposure will be analyzed for this pool, which will involve presenting the results by total daily dosing, thereby not differentiating in frequency of dosing.

A second pool includes all double-blind, 8-week acute treatment data in subjects with UC (studies SPD476-201, -202, -301, and -302).

A third pool includes all subjects with UC (studies SPD476-201, -202, -301, -302, -303), despite the longer treatment exposure for patients in study SPD476-303. Study -303 consists of an Acute phase and a Maintenance phase. Patients not in remission at the end of Studies -301 or -302 or at early withdrawal visit from these studies were given the opportunity to enter the acute phase of Study SPD476-303 for 8 weeks. The analyses of both these pools would consider adverse events and laboratory outliers and will present the results of an all active treatment group.

A fourth pool that includes the phase I studies conducted by Shire SPD476-101, SPD476-102, and SPD476-103 is also proposed. Adverse events only will be presented for this pool. This pool excludes phase I studies conducted by Giuliani SpA due to the differences in design, data collection and data capture.

- Does the Division agree with these four pools of data presented above?
- Does the Division agree that the safety analysis of the pooled phase III, placebo controlled data can present results by total daily dosing and not split by frequency of dosing?

FDA Response:

For ISS, safety data analysis should include both by total dose as well as by frequency of dosing for all patients who have taken at least one dose of study drug.

11. Does the Division have any additional guidance that Shire should be aware of prior to submission of this NDA?

FDA Response:

We will provide additional comments during the meeting as necessary.

ATTACHMENTS

- Shire Development, Inc. power point presentation

Minutes Preparer: _____
Monika Houstoun, Pharm.D.
Regulatory Project Manager

Chair Concurrence: _____
Ruyi He, M.D.
Medical Team Leader

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/s/

Monika Houstoun
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Ruyi He
6/29/05 06:20:28 PM



IND 66,193

Shire Pharmaceutical Development Inc.
Attention: Amy Butscher, MS
Manager, Regulatory Affairs
1801 Research Blvd., Suite 600
Rockville, MD 20850

Dear Ms. Butscher:

Please refer to your Investigational New Drug Application (IND) submitted November 15, 2002 under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPD476 —
1.2 gram Tablets.

We also refer to the following:

1. Your amendment (serial number 001) dated December 20, 2002 containing a meeting request.
2. The Division's meeting denial letter dated January 6, 2003 containing the assurance that we would address your clinical questions in writing.
3. The January 13, 2003 telephone call between yourself and Dr. Betsy Scroggs in which you thanked us for agreeing to respond to the clinical questions contained in your meeting request, however, in which you expressed concern that your current drug development program progress also hinged on receiving responses to your Chemistry, Manufacturing and Controls questions contained in your meeting request. At that time, you were directed to submit a letter to the Division stating your concerns.
4. We also refer to your subsequent January 30, 2003 submission containing a request for the Division to address your Chemistry, Manufacturing and Controls questions.

We have completed review of your submissions and in order to assist you in your drug development, we have provided the following comments and recommendations.

- I. Regarding the November 15, 2002 submission
 - A. Clinical
 1. **You define remission as an ulcerative colitis-disease activity index (US-DAI) score of less than 1, with rectal bleeding and stool frequency scores of 0, and a sigmoidoscopy score reduction of 1 point or more from baseline.**

To demonstrate clinical significance and remission, the patient should have a minimum rectal bleeding score of 2 at baseline that improves to 0 after treatment.

- 2. An additional secondary objective should be to compare treatment failures among the treatment arms. Treatment failures should be defined as the proportion of patients who develop severe or fulminant ulcerative colitis (UC) requiring steroid therapy or hospitalization during the course of the study.**
- 3. A human immunodeficiency virus (HIV) blood test may be useful at screening, since patients who are HIV positive may be more susceptible to infectious etiologies for colitis. Thus, they may need further work up to rule out enteric pathogens other than a single stool culture.**
- 4. Consider patients who discontinue the study prior to 8 weeks as treatment failures in the primary analysis. You may perform a supplementary analysis using a last observation carried forward, however, the primary analysis should consider premature terminations as treatment failures.**

B. Chemistry, Manufacturing and Controls Comments and Advice

- 1. As research progresses towards an NDA please provide additional information as appropriate:**
 - a. Provide the _____ during the manufacturing process.**
 - b. Include Certificates of Analysis for the raw materials.**
 - c. Include storage temperature statement on the label.**
 - d. Provide an additional identification test in drug product specifications.**
 - e. Characterize and qualify any unknown impurities found at more than - percent.**

Responses to the questions in your December 20, 2002 Meeting Request

- 1. Shire believes that the proposed confirmatory phase 3 study designs for SPD476-301 and SPD476-302 will provide evidence of efficacy and safety in UC patients in support of an NDA submission. Does the Agency agree with the overall designs of clinical studies SPD476-301 and SPD476-302 to support the proposed label claim of "induction of remission in patients with mild to moderate — ulcerative colitis"?**

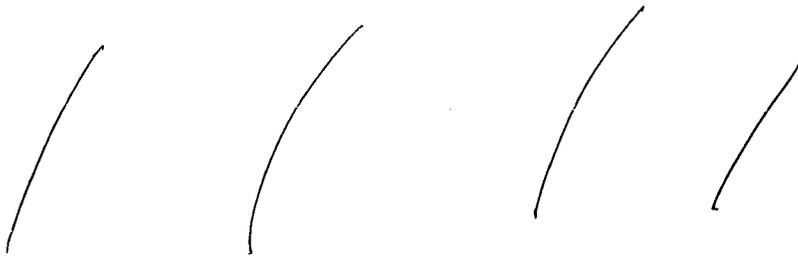
Response: In general, these appear adequate (see protocol recommendations above) however, the Agency cannot comment on whether these protocols will support labeling claims until the complete protocol for study SPD476-302 has been submitted and reviewed.

- 2. The primary objective of the phase 3 clinical study SPD476-301 is to compare the percentage of subjects in remission after 8 weeks of treatment for the 3 treatment groups: SPD476 1.2 g BID (2.4g/day), 4.8 g QD (4.8g/day), and placebo. The phase 3 clinical study SPD476-302 will compare the percentage of subjects in remission after 8 weeks of treatment for the 4 treatment groups: SPD476 1.2 g BID (2.4g/day), 4.8 QD (4.8g/day), Asacol 800mg TID**

(2.4 g/day), and placebo. The primary objective of the study is the comparison of SPD476 doses against placebo with Asacol as a reference. In both studies, remission is defined as UC-DAI score of less than 1, with rectal bleeding and stool frequency scores of 0, and a sigmoidoscopy score reduction of 1 point or more from baseline. Does the agency find the proposed definition of remission sufficient to support the proposed label claim of induction of remission?

Response: This definition of remission is satisfactory. However to demonstrate clinical significance, the patient should have a minimum rectal bleeding score of 2 at baseline that improves to 0 after treatment.

3.



Chemistry, Manufacturing and Controls Questions

1. Shire proposes that following submission of the NDA for SPD476, continued testing of each batch of drug substance to be used in the production of SPD476 commercial batches to USP will not be required, provided that the mesalazine manufactured by — has been shown throughout the SPD476 development to be compliant with the USP monograph and that all drug substance batches continue to be tested according to the current drug substance manufacturer's — in-house specification. Does the Agency agree with this proposal?

Response: In addition to abiding by the USP monograph, updating the specifications for the active pharmaceutical ingredient (API) is recommended since it is used for a modified release form. It is your responsibility to assure that the drug substance is in accordance with the USP monograph and acceptance specifications need to be provided (e.g. Identity and Assay).

If you have any questions, call Dr. Betsy Scroggs, Consumer Safety Officer,
at 301-827-1250.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
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for Dr. Robert Justice