

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-301

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-301

SUPPL #

HFD #

Trade Name Apriso

Generic Name Mesalamine

Applicant Name Salix Pharmaceuticals, Inc.

Approval Date, If Known 10/31/08

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)(2)

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# 19-651, 21-830 Asacol, Mesalamine
NDA# 21-252, 20-049 Canasa, Pentasa
NDA# 22-000, 19-618 Lialda, Rowasa/SFRowasa

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:

Two pivotal, Phase 3 studies, MPUC3003 and MPUC3004, to evaluate the clinical efficacy and safety of eMG (encapsulated mesalamine granules) for the maintenance of remission of ulcerative colitis (UC) in patients 18 years and over for consecutive therapy up to six months. In addition, a single open-label long-term extension study, MPUC3005, was submitted.

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 NO

Investigation #2

YES

NO

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 MPUC3003 and Study MPUC3004

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 # 62,113

YES

!

!

! NO

! Explain:

Investigation #2

IND # 62,113

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: Cristi Stark
Title: Regulatory Health Project Manager
Date: 10/30/08

Name of Office/Division Director signing form: Donna Griebel, MD
Title: Director, Division of Gastroenterology Products

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

Appears This Way
On Original

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On Original

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-301 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Gastroenterology Products PDUFA Goal Date: 10/31/08 Stamp Date: 12/31/2007

Proprietary Name: Apriso

Established/Generic Name: Mesalamine

Dosage Form: Extended-release Capsules

Applicant/Sponsor: Salix Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: maintenance of remission of ulcerative colitis in adults

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	5 yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

[#] Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

^{*} Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	5 yr. __ mo.	17 yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): 06/01/13							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

 Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

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 or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-301

NDA ACKNOWLEDGMENT

Salix Pharmaceuticals, Inc.
Attention: Benjamin M. Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

We have received your new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Encapsulated Mesalamine Granules, 0.375 g

Date of Application: December 21, 2007

Date of Receipt: December 31, 2007

Our Reference Number: NDA 22-301

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 29, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited 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:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck
Regulatory Project Manager
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/

Kristen Everett
1/14/2008 03:16:01 PM
signing for Heather Buck, Regulatory Project Manager

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-301	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Apriso Established/Proper Name: Mesalamine Dosage Form: Capsules Strengths: 0.375g		
Applicant: Salix Pharmaceuticals, Inc.		
Date of Receipt: 12/31/07		
PDUFA Goal Date: 10/31/08		Action Goal Date (if different):
Proposed Indication(s): maintenance of remission of ulcerative colitis in adult patients		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "YES," proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 19-651	Pharmacology/Toxicology
NDA 21-252	Pharmacology/Toxicology

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
We do not require a bridge for pharm/tox. Pharm/tox studies only test the drug substance which is the same.

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #6.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #6

If "YES", list the listed drug(s) identified by name and answer question #5(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
- YES NO

If "NO," proceed to question #11.

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Asacol (mesalamine) tablets	NDA 19-651	Yes
Canasa (mesalamine) suppositories	NDA 21-252	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
- YES NO

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: Canasa (NDA 21-252)

- b. Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c. Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d.1.
If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support 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 capsule to solution").
Change in dosage form

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(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))

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(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.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): referenced: Asacol (NDA 19-651), Canasa (NDA 21-252) not referenced: Pentasa (NDA 20-049), Rowasa (NDA 19-618), Lialda (NDA 22-000), Mesalamine (NDA 76-751), Mesalamine (NDA 76-841), Mesalamine (NDA 21-830)

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5541170, 5541171

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

15. 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.)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 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): 5541170, 5541171

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received: 6/23/08

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 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):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 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):

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

/s/

Cristi Stark
10/30/2008 05:40:40 PM
CSO

Cristi Stark, x61007	<input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

8/05



August 1, 2008

Donna Griebel, MD
Division Director
Food and Drug Administration
CDER, Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266
Attention: Cristi Stark, Regulatory Project Manager

**Subject: NDA 22-301
Encapsulated Mesalamine Granules, 0.375 g
Amendment to a Pending Application: Proposed Trade Names and
Labeling Mock-Ups**

Dear Dr. Griebel:

Reference is made to the pending New Drug Application (NDA) for encapsulated mesalamine granules dated December 21, 2007 for the proposed indication of maintenance of remission of ulcerative colitis in patients 18 years of age and older.

Salix Pharmaceuticals, Inc. hereby submits two prospective trade names for evaluation, APRISO™ (primary) and _____ (secondary). Salix requests review of the proposed primary proprietary name APRISO by the Division of Medication Error Prevention and Analysis and Division of Drug Marketing, Advertising, and Communications (DDMAC) member of the Expert Panel Discussion (EPD) for approval. Salix submits the secondary name _____ as a back-up name to be reviewed only in the event significant issues are found with the primary name APRISO.

b(4)

Supporting information for the proposed primary proprietary name APRISO includes two reports (Attachments 1 & 2). The first is a nomenclature research and analysis (Attachment 1) establishing that APRISO is not confusingly similar to existing drug names or names of related products for review by the Division of Medication Error Prevention and Analysis. The second report (Attachment 2) establishes that APRISO is not promotional or misleading and is intended for review by the DDMAC member of the Division of Medication Error Prevention Expert Panel Discussion (EPD). In addition, color mock-ups of APRISO carton and container labels are included in this submission for review.

Salix Pharmaceuticals, Inc. contracted with the [] to conduct a study including the name candidate APRISO. The enclosed reports disclose the conclusions of that study for APRISO in detail, and describe the methodology used to conduct the research. Based on these findings APRISO is regarded as an appropriate proposed proprietary name, and we respectfully request the Division's concurrence.

b(4)



Supporting information for the proposed secondary proprietary name, _____ includes two reports (Attachments 3 & 4). The first is a nomenclature research and analysis (Attachment 3) establishing that _____ is not confusingly similar to existing drug names or names of related products for review by the Division of Medication Error Prevention and Analysis. The second report (Attachment 4) establishes that _____ is not promotional or misleading and is intended for review by the DDMAC member of the Division of Medication Error Prevention Expert Panel Discussion (EPD). Color mock-ups of _____ carton and container labels have not been developed and will be completed and submitted upon request from the agency.

b(4)

The enclosed CD contains the requested color mock-ups in PDF format for the following APRISO carton and container labels:

- Unit carton for the 4 count professional sample bottle
- Container label for the 4 count professional sample bottle
- Container label for the 120 count trade bottle

Salix hereby certifies that the CD included in this submission is virus free. OfficeScan version 7.3 by TrendMicro was used to check the electronic files for viruses.

If there are any questions concerning this submission, please do not hesitate to contact me directly at (919) 447-3404, by fax at (919) 447-3410, or by email at Benjamin.Burgin@Salix.com. In the event of my absence, you may also contact David Dobrowski, Director, Regulatory Affairs at (919) 862-1047.

Sincerely,

Benjamin M. Burgin, RAC
Senior Manager, Regulatory Affairs
Salix Pharmaceuticals, Inc.

Attachments:

Proprietary Name Safety Assessment for APRISO™ to be forwarded to the Division of Medication Error Prevention and Analysis, OSE.

Proprietary Name Promotional Assessment for APRISO™ to be forwarded to the Division of Medication Error Prevention and Analysis for use by the Drug Marketing, Advertising, and Communications (DDMAC), member of the Expert Panel Discussion (EPD).

Proprietary Name Safety Assessment for _____ to be forwarded to the Division of Medication Error Prevention and Analysis, OSE.

b(4)

Proprietary Name Promotional Assessment for _____ to be forwarded to the Division of Medication Error Prevention and Analysis for use by the Drug Marketing, Advertising, and Communications (DDMAC), member of the Expert Panel Discussion (EPD).

b(4)



NDA 22-301

INFORMATION REQUEST LETTER

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

Please refer to your new drug application (NDA) submitted December 21, 2007, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Encapsulated Mesalamine Granules, 0.375 g.

We also refer to your 120-day Safety Update received April 25, 2008.

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

Clinical

1. We received the report of Study SAG-27/UCR for review at the same time that we received the 120-Day Safety Update. This study will primarily be used for the additional information that it may provide regarding safety and tolerability. However, the study's contents were not integrated into the 120-Day Safety Update. Under 21 CFR 314.50(d)(5)(vi)(b), safety update reports are required to include the same kinds of information, and be submitted in the same format, as the integrated summary of safety required under 21 CFR 314.50(d)(5)(vi)(a). Please revise and re-submit the 120-Day Safety Update with the safety data from Study SAG-27/UCR fully integrated into the report.
2. Please provide reconciliation of ISS Table 2.7.4.1, Appendix C and ISS Table 2.7.4.6.1, Appendix C. These tables list differing numbers of subjects who discontinued the study due to treatment-emergent adverse events (TEAEs). Table 2.7.4.1 lists 39 eMG and 30 placebo subjects as having discontinued due to AEs, while Table 2.7.4.6.1 lists 40 eMG and 32 placebo subjects as having discontinued due to TEAEs. Please provide an explanation for these differing values.

Clinical Pharmacology

3. The Clinical Pharmacology section in your annotated labeling refers to summaries, e.g., "Module 2.5, clinical overview, p.11," instead of a specific study as a source of the labeling claim. Please provide study titles as references for labeling.
4. You mentioned that the mean half-lives for 5-ASA and N-Ac-5-ASA were not affected by food. The mean 5-ASA half-lives were 5.79 and 8.42 hours with and without food, respectively; while the mean N-Ac-5-ASA half-lives were 10.05 and 12.56 hours, respectively. Please provide details regarding the half-life estimation, including linear regression plots, for individual subjects. In addition, please provide tabulated PK parameters for individual subjects for studies MPPK 1002 and MPPK 1001. If such information was already submitted, please guide the reviewer to the location (volume # and page).

Chemistry, Manufacturing, and Controls

5. Please clarify the role of [redacted] in the manufacturing process. It appears that they are the manufacturer of secondary packaging. b(4)

6. [redacted]

b(4)

7. Regarding analytical method 030001.02, submit representative chromatograms.
8. System suitability usually specifies a capacity factor, injection repeatability (%RSD), resolution, and tailing factor. Explain why these items are not included in system suitability for the HPLC assay method. Refer to the guidances on validation of analytical methods.
9. The Guidance for Industry Q2B "Validation of Analytical Procedures: Methodology" (November 1996) recommends that the correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares be submitted. A plot of the data should also be included. Submit plots of the data along with slope, y-intercept, and residual sum of squares.
10. The method validation report for method 030001 (VALRPT-01) in module 3.2.P.5.3 Validation of Analytical Procedures states that chromatograms from the specificity study are attached, but they are missing. See paragraph 2.11 of that report. Submit the missing chromatograms.
11. Robustness testing is usually done by making minor changes to the chromatographic conditions in addition to mobile phase pH, such as mobile phase composition, different columns (lots/suppliers), column temperature, flow rate, etc. Explain why pH was the only factor investigated.

12. There is no evidence, e.g., a forced degradation study, to demonstrate that the HPLC method is stability indicating. A forced degradation study should be performed on the pellets, or other evidence should be provided to demonstrate that the assay procedure is stability indicating.
13. With reference to the method validation for residual solvents, the method has not been validated for ~~_____~~ You have proposed a limit of NMT more than [_____]
Validate the method for: ~~_____~~ or provide a reason that it is not necessary.
14. A description of the Identity Test [_____] should be provided. Refer to Table 3.2.P.5.4-2, Bulk Mesalamine Granules Batch number 0304131.
15. There is no photostability data. A photostability study should be performed according to ICH Q1B: Photostability Testing of New Drug Substances and Products.

b(4)

b(4)

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
6/13/2008 04:15:19 PM

b(4)

RECEIVED

JUN 05 2007

CDR / CDER

June 5, 2007

Steven K. Galson, MD, MPH
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
Central Document Room
5901 Ammendale Rd.
Beltsville, MD 20705-1266

RECEIVED

JUN 08 2007

Dear Dr. Galson:

CDER White Oak DR 1

I am writing on behalf of _____ a clinical research organization, and our client companies, to inform you that the Russian Federal Customs Service shut down the export of all clinical samples beginning Monday, May 28, 2007. This includes the export of all clinical samples that are obtained from clinical studies conducted in Russia. The embargo reportedly will last until further notice.

This situation has prompted immediate actions at clinical study sites across Russia. However, these actions could potentially lead to protocol deviations in studies conducted in Russia, including multicenter studies with sites in Russia. Since samples cannot be shipped to any laboratories outside of Russia, samples may have to be stored instead of shipped for testing. The substitution of local laboratories inside Russia for central laboratories outside Russia could also occur to ensure the continued safety of study subjects participating in the clinical studies. Furthermore, there are news reports that government authorities have seized Informed Consent Forms and other study related documents whose absence from clinical study sites might result in deviations from Good Clinical Practice (GCP) requirements. We cannot determine at this time if these records will at any time be returned for inclusion as study documentation.

_____ is currently conducting numerous clinical studies within Russia. We are taking every possible measure to preserve the integrity of these clinical studies and to ensure the safety of study subjects.

Some of these measures are:

- All investigators within Russia are being notified not to attempt to send clinical samples outside Russia.
- All samples intended for testing abroad will be frozen at either -20 C or -70C immediately after collection (for plasma, urine, and any other samples that can tolerate freezing) or as soon as they have been returned to the study site from shipping vendors. The study sites will maintain temperature logs. The frozen samples will then be sent to a central facility in Moscow (run by [redacted] where they will be stored at -70C until they can be exported.
- Essential safety tests (hematology and clinical chemistry tests, and other tests as clinically indicated), which were previously done abroad, will be done at a laboratory within Russia [redacted] Samples will be sent at ambient temperature for this testing. Beginning as soon as possible, duplicate samples will be collected from study subjects for this purpose (one sample for local testing kept at ambient temperature; one sample for possible future testing abroad kept frozen at -70C). [redacted] has not yet been audited by _____ an audit has been scheduled for June 11. However, this laboratory has Russian Federal Laboratory Registration, part of the quality control system within Russia.)

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- When it becomes possible to export samples again, a split sample analysis may be conducted for certain laboratory tests with safety implications, in which both the laboratory within Russia and the central — laboratory outside Russia will perform testing on the same samples to ensure the results are comparable.
- Information will be collected regarding local laboratory testing details, such as range of normal values, CVs of laboratory directors, laboratory certifications, etc.
- Depending on the duration of the embargo, more esoteric testing (efficacy markers, etc.) previously done abroad may be done at local laboratories within Russia, if the same tests are available there. In such an event, steps will be taken to validate new testing procedures at the local laboratories. Notification of these changes of laboratory sites will be submitted to FDA as IND amendments as needed.
- Steps will also be taken to validate the accuracy of test results for samples that have been stored frozen at -70C. The results of such validation will also be submitted to FDA in IND amendments as needed.
- Finally, we would like to work with FDA to develop an approach for handling the missing central laboratory data that may develop as a result of this embargo. Our approach would be to utilize local laboratory data wherever possible and to include replacement data for any missing parameters that cannot be measured locally at the earliest possible time following the lifting of the embargo. Please let us know if this overall approach is acceptable; we would like to obtain your agreement with the overall approach prior to submitting the details in emergency protocol amendments for each study. This entire process will be clearly documented and the documentation will be provided with the final study report in the NDA submission.

b(4)

Please let us know of any additional steps that you recommend.

We will keep you informed of all significant developments as we learn of them, and we ask that FDA keep us apprised of any new information about this situation.

Sincerely yours,

b(4)

b(4)

cc John Jenkins, MD

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/s/

Donna Griebel
4/9/2008 02:52:05 PM

DSI CONSULT: Request for Clinical Inspections

Date: March 27, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer (if known)

Through: Donna Griebel, M.D. Division Director
Division/HFD-180

From: Heather Buck, Regulatory Health Project Manager/Division of
Gastroenterology Products/HFD-180

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA-22-301
Salix Pharmaceuticals
Benjamin Burgin, RAC, Senior Manager, Regulatory Affairs 919-447-3404
Drug: — (mesalamine) Encapsulated Granules
NME: No
Standard or Priority: Standard 10 month
Study Population: > 18 years of age
Pediatric exclusivity: No

b(4)

PDUFA: October 31, 2008
Action Goal Date: October 31, 2008
Inspection Summary Goal Date: August 30, 2008

II. Background Information

Salix has submitted NDA 22-301 for encapsulated mesalamine granules (formally referred to as encapsulated mesalamine pellets). This NDA is for the proposed indication of maintenance of remission of ulcerative colitis in patients 18 years and older. The oral capsule dosage form contains 0.375 g of mesalamine USP (5-aminosalicylic acid, 5-ASA). The clinical and safety data contained in the application consists of results from two identical Phase 3, randomized, double-blind, placebo-controlled, multicenter studies (MPUC3003 and MPUC3004). There was an EOP2 Meeting on October 6, 2004, and a Pre-NDA Meeting on October 29, 2007.

III. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Site # 572 City Polyclinic #38, Centre for Gastroenterology No. 1 26, Kavalergardskaya, 193015, St. Petersburg, Russia	MPUC3003	30	Large number of subjects
Site # 565 and Site #566 Saratov State Medical University, Departmen of Hsopital Therapay Saratov Regional Clinical Hospital 1 Smirnovskoye ravine Saratov, 410053, Russia	MPUC3004	49	Large number of subjects, Russian site with ongoing study after May 28, 2007 (see below)
Site #618 Center for Digestive & Liver Disease, Inc 714 Medical Park Drive Mexico, MO 65265-3726	MPUC3003	12	Largest number of subjects at single US center for protocol MPUC3003
Site #419 Connecticut Gastroenterology Institute Brewster Road Bristol, CT 06010	MPUC 3004	11	Largest number of subjects at single US center for protocol MPUC3004

IV. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- 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:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- 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.

Attached, please find a letter from CRO describing the shut down of all exports of clinical samples from Russia beginning in May 28, 2007. Protocol MPUC 3003 was completed April 26, 2007; however, MPUC3004 was not completed until August 8, 2007. There has been no update on this shut down and the Regulatory Affairs Team Leader has asked that we consult DSI regarding studies involving Russian sites during the period beginning after May 28, 2007. Russian sites 572 (MPUC3003), 573 (MPUC3004), and 566 (MPUC3004) each randomized at least 30 subjects, accounting for nearly one-fifth of all Russian subjects randomized in the respective protocols. The average number of subjects randomized at US sites is 4.1 (MPUC3003) and 3.6 (MPUC3004).

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- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

In protocols MPUC3003 and MPUC3004, the sponsor's pivotal studies, subjects from Russian sites account for a significant number of total-study subjects. For protocol MPUC3003, 47.5 % of subjects are from Russian sites. For protocol MPUC 3004, 59.9% of subjects are from Russian sites.

The average number of subjects randomized at US sites is 4.1 (MPUC3003) and 3.6 (MPUC3004). US site 419 with 11 subjects and site 618 with 12 subjects were well above this average.

V. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Heather Buck at Ph: 301-796-1413 or Dr. John Hyde at Ph: 301-796-0921.

Concurrence: (as needed)

John E Hyde Medical Team Leader John Hyde
Asha Peterson Medical Reviewer Ansha Peterson
John E Hyde for Donna Griebel Director, Division Director (for foreign inspection requests Donna Griebel only)

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
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5/28/05

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January 21, 2008

Daniel Shames, MD
Acting Director
CDER, Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266
Attention: Heather Buck, Regulatory Project Manager

**Subject: NDA 22-301
Encapsulated Mesalamine Granules, 0.375 g
Proposed Trade Name**

Dear Dr. Shames:

Please note the above referenced pending New Drug Application (NDA) for encapsulated mesalamine granules dated December 21, 2007 in accord with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the proposed indication of maintenance of remission of ulcerative colitis in patients 18 years of age and older.

For the Agency's consideration, Salix Pharmaceuticals, Inc. proposes the following trade name for encapsulated mesalamine granules:

Proposed Trade Name: _____

b(4)

If there are any questions concerning this submission, please do not hesitate to contact me at (919) 447-3404, by fax at (919) 447-3410, or by email at Benjamin.Burgin@Salix.com.

Sincerely,

A handwritten signature in black ink, appearing to read "Benjamin M. Burgin". The signature is written in a cursive, flowing style.

Benjamin M. Burgin, RAC
Senior Manager, Regulatory Affairs
Salix Pharmaceuticals, Inc.



NDA 22-301

INFORMATION REQUEST LETTER

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

Please refer to your December 21, 2007 new drug application (NDA) submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act for (mesalamine) Encapsulated Granules. The labeling text for this pending NDA was submitted in Structured Product Labeling (SPL) format, along with the proposed package insert in Physician's Labeling Rule format (PLR) on December 21, 2007.

b(4)

We are reviewing the Physician's Labeling Rule format of the package insert included in your submission and have the following comments and information requests. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

1. Highlights

- a Revise the "Initial U.S. Approval" statement to read "Initial U.S. Approval: 1987"
 - The labeling should reflect..."The verbatim statement "Initial U.S. Approval" followed by the four-year digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients". [Best Practices]. The active ingredient mesalamine was first approved as Rowasa NDA 19-618 on December 24, 1987¹.
- b Change font size from 10 point type to 8 point type, and adjust margins to ½ inch on all sides. Note that these adjustments will likely reduce the section to one-half page as is required.
 - Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11 paper, single spaced, 8 point type with ½ inch margins on all sides, in a two-column format). [Best Practices].
- c Revision Date for a new NDA should be left blank at the time of submission and will be

¹ http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No-019618&TABLE1-OB_Rx

edited to the month/year of the application or supplement approval. Date should read: "Revised: month/year". [Best Practices].

2. Table of Contents

- Change 13.2 subsection title from "Animal Toxicology" to "Animal Toxicology and/or Pharmacology". [Best Practices].
- Create subsection headings that identify the content. Avoid using the word "General". See subsection 5.1 under the Warnings and Precautions. [Best Practices].

3. Full Prescribing Information

- Remove bold from body systems in subsection 6.1. All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly; and use another method for emphasis such as italics or underline. [Best Practices].
- In subsection 6.1 Clinical Studies Experience, include the following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Please address the identified deficiencies/issues and re-submit labeling by August 1, 2008. This updated version of labeling will be used for further labeling discussions.

If you have any questions, call Heather Buck, Regulatory Project Manager, at 301-796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Heather G Buck
3/27/2008 08:26:29 AM

Brian Strongin
3/27/2008 09:58:53 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-301

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

Please refer to your new drug application (NDA) dated December 21, 2007, received December 31, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for ~~_____~~ (mesalamine) Encapsulated Granules.

b(4)

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is October 31, 2008.

During our filing review of your application, we identified the following potential review issues to which you are already aware, that require your response:

1. Insufficient formatting of NDA submission
 - a. Please refer to the email correspondence from Heather Buck to Benjamin Burgin on March 3, 2008 requesting another volume-specific submission to fix formatting issues. You responded on March 7, 2008 with a proposal to do so.
2. Inadequate safety data submitted
 - a. According to 21 CFR 314.50(d)(5)(iv), the clinical data section must contain:
(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

You have already expressed your intention, via phone and email correspondence, of submitting such data.

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.

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 submitted a request for a partial waiver of pediatric studies with this application for pediatric patients ≤ 5 years old, in addition to a request for a deferral of pediatric studies for pediatric patients >5 to < 18 years old. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application. Please submit your pediatric plan for your deferral of pediatric studies by August 28, 2008.

If you have any questions, call Heather Buck, Regulatory Project Manager, at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.,
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
3/14/2008 02:51:35 PM

Volumes to be resubmitted

Biopharm

Module 5 (Volumes 1-38)

Clinical

Module 5 (Volumes 39-189)

Examples to be fixed (based on revised TOC sent 2/29/08)

1. Tab subheadings within each study report and related document by name.
 - a. Example - Module 5, Volume 21 of 189, study MPPK1001 has 1 tab: "Module 5.3.1.2.5". Please add tabs for each document within the Volume and label tab by name. It would also be helpful (not required) to include tabs for tables and figures (e.g. in Module 5, Volume 4, section 14.2 Pharmacokinetic Data summary figures and tables runs from page 60 to 317 without a tab over volumes 4 and 5 and the list of figures is present without page numbers only in page 60 of the Volume 4)
2. List appendices in the Module-specific TOC.
 - a. Appendices are present in the Volume-specific TOC, but not the Module-specific TOCs.
3. Add titles (descriptive, named identifiers) to appendices, tables, and listings in the comprehensive TOC. Currently the "Tab ID" column and the "CTD Module" columns contain the exact same information for most of the TOC items. Please change this so that the information in the "CTD Module" column is descriptive and can be used by the reviewer to locate information.
4. Add the study-specific TOC to the comprehensive and Module-specific TOC for studies MPPK1001, MPPK1002, MPUC3003 and MPUC3004.
 - a. Example - See Volume 85, page 9, and Volume 104, page 9. It would be helpful to list the headings of the study-specific TOCs in the larger TOC e.g., 7. Introduction, 8. Study Objectives, 9. Investigational Plan.
 - b. Please apply this example to all cases where a study exists.
5. Restart page numbering for new Volumes
 - a. See Module 5, Volume 86.
6. In general, make sure that each volume has at least 2 tabs even if all the information in a volume is a single document. Find some logical way to further subdivide the information and include tabs so that reviewers do not have to flip through an entire volume to find particular information.
 - a. Example - Volume 92 has only a single tab. A logical way to further subdivide this information would be to separate line listings of lab results by study sites.

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/s/

Heather G Buck
3/14/2008 12:36:19 PM
CSO

**Screening of New NDA for Statistical Filing
Division of Biometrics 3**

NDA #: 22-301
Drug Name (Trade/generic): Encapsulated Mesalamine (5-aminosalicylic acid or 5-ASA),
Granules (eMG)
Applicant: Salix Pharmaceuticals, Inc.
Indications: Maintenance of Remission of Ulcerative Colitis (UC)
Submission Date: December 21, 2007
Filing Date: February 29, 2008
User Fee Goal Date: October 31, 2008
Medical Officer: Aisha Peterson, M.D.
Statistician: Shahla Farr, M.S.
Project Manager: Heather Buck, M.S., MBA

Summary:

The sponsor has submitted two Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center trial to investigate the efficacy and safety of Encapsulated Mesalamine (5-aminosalicylic acid or 5-ASA), Granules (eMG) for the Maintenance of Remission of Ulcerative Colitis for the duration of 6 months (Study # MPUC3003 and Study # MPUC 3004).

Primary Objective:

To evaluate the efficacy and safety of eMG compared to placebo in men and non-pregnant women for maintenance of remission from UC as measured by rectal bleeding and endoscopic mucosal appearance after 6 months.

Primary Endpoints:

The primary analysis efficacy endpoint is the proportion of subjects who were relapse-free after 6 months of treatment. Relapse or treatment failure was defined as a rectal bleeding score of 1 or more and a mucosal appearance score of 2 or more as described in the revised Sutherland Disease Activity Index. In addition, subjects who experienced a UC flare or initiated medication used previously to treat UC were also considered treatment failure.

Statistical Methods:

Statistical testing was done using 2-sided tests with an alpha level of 0.05. A Cochran-Mantel-Haenszel (CMH) test, controlling for country was performed.

This NDA was submitted in CTD (paper) format. However, the datasets were provided electronically and are located at: \\Cdsub1\nonectd\N22301\N_000\2007-12-21

The following items were checked to determine the fileability of this submission.

Fileability Checklist

Item	Check (NA if not applicable)
Indexes sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	OK
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	OK

Fileability Conclusion:

After the preliminary review of the submission, we have not identified any deficiencies that would be a reason for refuse-to-file. The sponsor provided the required information in this NDA to perform statistical evaluation and therefore, this NDA is fileable.

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/s/

Shahla Farr
2/27/2008 01:30:24 PM
BIOMETRICS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 62,113

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

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

We also refer to the meeting between representatives of your firm and the FDA on October 29, 2007. The purpose of the meeting was to discuss the content and format of your planned NDA submission.

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: October 29, 2007
TIME: 1:00 pm – 2:00 pm
LOCATION: FDA White Oak Campus, Conference Room 1315
APPLICATION: IND 62,113
DRUG NAME: encapsulated mesalamine granules
TYPE OF MEETING: Type B Pre-NDA Meeting

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

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

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
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, Division of Gastroenterology Products
Sue-Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3
Insook Kim, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Mike Welch, Ph.D., Acting Team Leader, Division of Biometrics 2
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, Office of New Drug Quality Assessment
Zei-Pao Huang, M.S., Office of Business Support Staff (OBPS)
Kristen Everett, R.N., Regulatory Project Manager, Division of Gastroenterology Products

SALIX PHARMACEUTICALS, INC. ATTENDEES:

William P. Forbes, PharmD, Vice President R&D and Chief Development Officer
Enoch Bortey, Ph.D., Executive Director – Biostatistics, Data Management, and Programming
Audrey Shaw, Ph.D., Associate Director, Clinical
James Yuan, Ph.D., Senior Biostatistician
Alison Gatherum, Manager, Project Management
Benjamin Burgin, RAC, Senior Manager, Regulatory Affairs
Roland Greinwald, Ph.D., Head of R&D, Dr. Falk Pharma

b(4)

BACKGROUND:

On August 17, 2007, Salix submitted a Type-B Pre-NDA meeting request to discuss the content and format of their planned NDA submission.

On September 27, 2007, Salix submitted the meeting package which contained the background information and questions for the meeting.

On October 25, 2007, the FDA faxed preliminary responses to the questions contained in the September 27, 2007, meeting package.

On October 28, 2007, the FDA received, via email, responses from Salix based on the preliminary responses sent by the Agency.

MEETING OBJECTIVES:

Salix identified the following objectives for this meeting:

- To identify and discuss any major unresolved issues:
- To identify the adequate and well-controlled studies on which Salix is relying to establish the safety and effectiveness of encapsulated mesalamine granules.
- To discuss the proposed statistical analysis plans for the Integrated Summary of Safety and Integrated Summary of Efficacy.
- To obtain agreement on the PREA development plan.
- To acquaint FDA reviewers with the general information to be submitted in the NDA.
- To discuss the data presentation and formatting of the NDA.

DISCUSSION POINTS:

Questions are in plain text, FDA preliminary responses are in **bold** text, responses sent by Salix prior to the meeting are in *italics*, and the meeting discussion is in ***bold italics***.

Clinical

1. Salix is proposing to include in the NDA long-term safety data on approximately 350 and 130 subjects treated with encapsulated mesalamine granules for 6 months and 1 year, respectively. Does the FDA agree that the number of subjects to be included in the safety database is adequate to support submission of the marketing application?

FDA Response (October 25, 2007 fax):

The proposed number of subjects to be included in the safety database appears adequate to support your NDA submission. However, the adequacy of the data is a review issue. Please refer to *Guidance for Industry: Premarketing Risk Assessment*, March, 2005, for further details.

Salix Response of October 28, 2007

Salix does not have any additional comments.

2. Salix plans to use the clinical and pharmacokinetic studies conducted by Dr. Falk Pharma to support the NDA for encapsulated mesalamine granules based on comparable in vitro dissolution profiles between Salix and Dr. Falk Pharma drug product. Does the FDA agree with the approach?

FDA Response (October 25, 2007 fax):

**Since you have modified the composition of the outer coating ——— substituting
you will need to demonstrate
comparability of the dissolution profiles for the two formulations at three different
agitation speeds. The acceptability of Dr. Falk Pharma drug product is a review issue.
For other PK studies, we cannot make any comment without further information (also
see response to Question #4).**

b(4)

Salix Response of October 28, 2007

The excipients that control the delayed and extended release properties are the same for both the Salix and Dr. Falk Pharma formulations. []

b(4)

[] contribute to the delayed and extended release properties of the mesalamine granule. Salix believes the [] whether comprised of [] (Salix to-be-marketed) or [] (Falk) dissolves rapidly during the 2 hour acid phase of the dissolution testing. Based on this information, Salix would like to discuss the need for further dissolution testing to address the comparability of the Salix and Dr. Falk Pharma formulations.

b(4)

Meeting Discussion of October 29, 2007:

If Salix does not do the dissolution testing as recommended above, they should provide data or scientific information in the NDA submission to justify why it is not necessary.

Statistical

3. Does the FDA have any comments on the Statistical Analysis Plans for the Integrated Summary of Safety or Integrated Summary of Efficacy?

FDA Response (October 25, 2007 fax):

The proposed ISE and ISS appear to be acceptable. Please note that efficacy analyses based on the integrated primary studies are generally used to show supportive but exploratory trends in efficacy consistent with that established in the individual studies. The primary efficacy determinations are based on review of the individual studies, each with prespecified analytical plans.

Salix Response of October 28, 2007

Salix does not have any additional comments.

Clinical Pharmacology and Biopharmaceutics

4. Salix believes that all outstanding issues have been addressed concerning the clinical pharmacology and biopharmaceutics programs. Does the FDA agree?

FDA Response (October 25, 2007 fax):

It is not clear if the single-dose PK and multiple-dose PK studies at the proposed dosage regimen was conducted using the to-be-marketed product. If the study SAG-25 BIO is to be used to support single-dose and multiple-dose PK for the to-be-marketed product, it should be clarified if Salofalk[®] granules are the same as the to-be-marketed product.

It is unclear exactly what formulations were used in the various PK studies as various terminology were used in the summary table (e.g. encapsulated loose pellets vs. encapsulated granule). Please clarify.

Salix Response of October 28, 2007

The formulation used in MPPK1001 and MPPK1002 is the same as the to-be-marketed formulation. The dosage form used in the Salix pharmacokinetic studies (MPPK1001 and MPPK1002) was mesalamine granules via sachet. The dosage form used in the Salix Phase 3 studies (MPUC3003, MPUC3004, and MPUC3005) was mesalamine granules via capsule (the to-be-marketed formulation and dosage form). Please note, the terms granules and pellets are used interchangeably, but are being standardized where possible to granules. Please refer to Salix response to Question 2 for comparison of the Dr. Falk Pharma formulation used in SAG25/BIO and the Salix formulation.

Meeting Discussion of October 29, 2007:

Salix clarified that studies MPPK1001/1002 were performed with the granules in the aluminum sachets (the granules have the same components and composition as those in the to-be-marketed capsules) and studies MPUC3003/3004/3005 were performed with the gelatin capsules (the to-be-marketed product). We requested that the information be provided in the NDA submission concerning which formulation was used for each study.

We also request that consistent names be used when it can be applied (e.g. mesalamine, mesalazine, 5-ASA).

Pharmacology

5. Based on the November 9, 2005 meeting with the FDA, Salix has completed a 26-week repeat dose study in dogs and an in vivo mouse micronucleus study using the copolymer coating excipient [redacted]. These studies, in conjunction with the previously conducted toxicology and radiolabeled studies conducted by [redacted] [redacted] which will be incorporated into the subject NDA by reference, support the limited systemic exposure to and overall safety of [redacted]. At this time, Salix considers the toxicology package for the copolymer excipient [redacted] to be complete. Does the FDA agree that the [redacted] toxicology package is adequate to support submission of the marketing application?

b(4)

FDA Response (October 25, 2007 fax):

Your [redacted] toxicology package appears adequate.

b(4)

Salix Response of October 28, 2007

Salix does not have any additional comments.

Chemistry

6. Salix is requesting a Categorical Exclusion for an Environmental Analysis based on 21 CFR 25.31(a). Does the FDA agree with this approach?

FDA Response (October 25, 2007 fax):

If approval of your product will not significantly increase the use of mesalamine, then your request for categorical exclusion will be appropriate.

Salix Response of October 28, 2007

Salix does not have any additional comments.

7. Salix is proposing to submit only one executed drug product batch record that was used for both a primary stability lot and in the Phase 3 clinical program. Does the FDA agree with this approach?

FDA Response (October 25, 2007 fax):

Yes, this is acceptable.

Salix Response of October 28, 2007

Salix does not have any additional comments.

Regulatory

8. Does FDA agree with the proposed plans for the 120-Day Safety Update?

FDA Response (October 25, 2007 fax):

In addition, you need to submit copies of all SAE case report forms with your 120-Day Safety Update.

Salix Response of October 28, 2007

Salix does not have any additional comments.

9. Salix will be submitting a paper submission in the CTD format. Does the FDA have any comments concerning the approach for the NDA format or the proposed Table of Contents?

FDA Response (October 25, 2007 fax):

Your proposed approach appears to be acceptable.

Salix Response of October 28, 2007

Salix does not have any additional comments.

10. Salix is requesting a waiver of the Pediatric Research Equity Act (PREA) requirements. Does the FDA agree that the waiver is appropriate?

FDA Response (October 25, 2007 fax):

No. For your new dosage form, the proposed indication is for the maintenance of remission of UC. Your new dosage form may have potential benefit in pediatric patients with UC. Therefore, the waiver of pediatric studies is not appropriate at this time. You should provide a pediatric study plan or request for deferral of pediatric study along with your justification in your NDA submission.

Salix Response of October 28, 2007

Salix will be including in the NDA a request for deferral of the PREA requirements.

DECISIONS (AGREEMENTS) REACHED:

The FDA agreed that summaries of the findings of the carcinogenicity studies conducted by Dr. Falk Pharma and submitted under a different NDA in lieu of the full data sets for the studies may be submitted in the NDA.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

None

Linked Applications

Sponsor Name

Drug Name

IND 62113

SALIX
PHARMACEUTICALS
INC

MESALAMINE PELLETS

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
11/27/2007

RUYI HE
11/27/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,113

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
Regulatory Affairs, Consultant
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Kashiwase:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b)/505(i) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Pellets.

We also refer to the meeting between representatives of your firm and the FDA on November 9, 2005. The purpose of the meeting was to discuss the new information provided by _____ concerning the polymeric excipient _____

b(4)

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: November 9, 2005
TIME: 11:30 am – 12:30 pm
LOCATION: Conference Room 1313, White Oak Campus, Silver Spring, MD
APPLICATION: IND 62,113
DRUG NAME: Mesalamine Pellets
TYPE OF MEETING: Type C Meeting
MEETING CHAIR: Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist
MEETING RECORDER: Kristen Everett, R.N., Regulatory Project Manager

BETWEEN:

Salix Pharmaceuticals, Inc.

William P. Forbes, Pharm. D., VP R&D and Chief Development Officer
Jody Lockhart, Executive Director Manufacturing and Process Development
Jill Kompa, M.S., Director, Regulatory Affairs

Marty Rose, Research and Development

AND

Division of Gastroenterology Products (DGP)

Brian E. Harvey, M.D., Ph.D., Division Director
Joyce Korvick, M.D., M.P.H., Deputy Division Director
Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist
Sushanta Chakder, Ph.D., Pharmacologist
Ruyi He, M.D., Medical Team Leader
Fathia Gibril, M.D., Medical Officer
Maria E. Ysern, M.S., Review Chemist
Ryan Barraco, Consumer Safety Officer
Kristen Everett, R.N., Regulatory Project Manager

PURPOSE:

To discuss the new information provided by — concerning the polymeric excipient —
— for Mesalamine Pellets.

BACKGROUND:

On August 5, 2005, Salix Pharmaceuticals, Inc. submitted a Type C meeting request. On October 10, 2005, a subsequent background package was submitted.

The Division sent pre-meeting responses to Salix Pharmaceuticals, Inc on November 7, 2005.

DISCUSSION:

Response to question posed by sponsor.

QUESTION FOR THE FDA

1. Based on the information provided by _____ does the Division agree that it would be appropriate to revise the nonclinical studies required to support the use of _____ in Mesalamine Pellets to include the following studies, bacterial reverse mutation test, mouse lymphoma tk assay, and a four (4) week multiple dose mini-pig toxicology study?

b(4)

FDA Response:

No. Your proposed studies are not adequate for chronic use of [_____] . Please conduct the following toxicology studies with [_____] :

b(4)

- i. 6-12 month chronic oral toxicity study in a non-rodent species, preferably dogs,
- ii. Mouse micronucleus assay, and,
- iii. Segment I (Fertility and General Reproductive Performance) and Segment III (Pre- and Post- natal) reproductive toxicity studies in rats.

We are not aware that these studies have been conducted with either [_____] [_____]

b(4)

ATTACHMENTS:

Salix Pharmaceuticals, Inc presentation.

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

Chair Concurrence: _____
Jasti Choudary, B.V.Sc., Ph.D.
Supervisory Pharmacologist

10 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative - 1

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

/s/

Kristen Everett
12/5/2005 12:34:32 PM

Jasti Choudary
12/5/2005 12:40:52 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,113

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
3600 Bayshore Road, Suite 205
Palo Alto, CA 94303

Dear Mr. Kashiwase:

Please refer to the End of Phase 2 meeting between representatives of your firm and FDA on October 6, 2004. The purpose of the meeting was to address questions submitted by your firm contained in your background package submitted to the FDA on September 2, 2004.

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, you may call me at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Consumer Safety Officer
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 6, 2004
Time: 1:00 to 2:30 PM
Location: CDER Parklawn Chesapeake, 3rd Floor Conference Room
Application: IND 62,113 Mesalamine Pellets
Type of Meeting: "B" End of Phase 2 (EOP2) Meeting

Meeting Chair: Dr. Ruyi He, Gastroenterology Team II, Team Leader

Meeting Recorder: Dr. Betsy Scroggs, Pharm.D., Consumer Safety Officer

FDA Attendees, Titles, and Office/Division:

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

Dr. Kathy Robie-Suh, Acting Deputy Director
Dr. Ruyi He, Gastroenterology Team II, Team Leader
Dr. Robert Prizont, Medical Officer
Dr. Jasti Choudary, Supervisory Pharmacologist
Dr. Sushanta Chakder, Pharmacology Reviewer
Dr. Betsy Scroggs, Consumer Safety Officer

Division of Biometrics III (HFD-720)

Dr. Stella Grosser, Team Leader

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. Suliman Al-Fayoumi, Clinical Pharmacology Reviewer

External Constituent Attendees and Titles:

Dr. Lorin Johnson, Chief Scientist
Dr. David Taylor, Chief Medical Officer
Dr. Robert Haake, Executive Director, Biostatistics
Dr. Jody Lockhart, Executive Director, Pharmaceutical Development and Manufacturing
Ms. Janice McKellar, Associate Director, Regulatory Affairs

Dr. James Hinson, Medical Director, Dr. Falk Pharma

b(4)

Background: On July 23, 2004, the firm submitted an End of Phase 2 Meeting Request and on September 3, 2004, a subsequent background package which contained specific questions to be addressed. The purpose of today's meeting is to address the firm's questions contained in the September 3, 2004 background package.

Discussion Points (bullet format): The format of these minutes provide for the firm's questions in regular print, followed by the Agency's responses in **bolded print**.

SPECIFIC QUESTIONS FOR THE AGENCY

Clinical Questions

- 1 Does the Division agree that two identically designed Phase 3 trials of Mesalamine Pellets versus placebo, if successfully completed, will be adequate to support the registration of Mesalamine Pellets for the maintenance of remission of ulcerative colitis?

FDA Response: If successful in demonstrating safety and efficacy of the proposed mesalamine formulation, two adequately placebo-controlled trials should suffice to provide support for the sought indication of maintenance.

Salix Follow-up Comments: No comments.

- 1.1 Are the proposed criteria for verifying diagnosis of ulcerative colitis remission adequate?

FDA Response: The criteria for the definition of remission in adults 18 years and older should include the following: (a) absence of relevant symptoms, i.e., blood in stools, and (b) absence on inflammation on rectosigmoidoscopy (and this includes absence of friability). Traditionally, friability is defined as mucosal bleeding on slight touch. For the sake of clarity, friability should be removed from the endoscopic definition of remission.

Salix Follow-up Comments: Salix acknowledges the Division's request to include (a) the absence of relevant symptoms in the criteria for remission in conjunction with (b) absence of inflammation on rectosigmoidoscopy. In addition Salix agrees to remove friability from the endoscopic definition of remission. The criteria for definition of remission will therefore read as follows:

Remission is defined as (a) absence of rectal bleeding and (b) absence of mucosal inflammation on rectosigmoidoscopy as evidenced by a normal mucosa (score=0) or mucosa with loss of vascular pattern and mild granularity with no mucosal hemorrhage (i.e. no friability) (score=1).

Can the Division confirm that these revised definitions are acceptable?

FDA Meeting Response: These revised definitions are acceptable. Referring to the Sutherland Index, (attachment with noted revision) item # 3, the indices for mucosal appearance scale rating #1 will be revised to read as: "Erythema, decreased vascular pattern, granularity, ~~but~~ no mucosal hemorrhage."

- 1.2 Is the primary endpoint of endoscopic evidence of remission based on the Disease Activity Index (Sutherland Index) acceptable?

FDA Response: Please, refer to answer # 1. Friability should be absent in patients on remission.

Salix Follow-up Comments: Salix acknowledges the Division's request to align the criteria for remission as modified in our response to 1.1 above, with the primary endpoint of relapse of remission. The primary endpoint will therefore be the following:

Relapse, defined as (a) the presence of rectal bleeding and (b) the presence of mucosal inflammation on rectosigmoidoscopy as evidenced by a score greater than 1.

Can the Division confirm that this revised definition is acceptable?

FDA Meeting Response: These are acceptable. It is understood that both must be present for treatment failure.

- 1.3 Is the 6-month study duration adequate?

FDA Response: The proposed duration is adequate.

Salix Follow-up Comments: No comments.

- 1.4 Is the proposed sample size for each study acceptable?

FDA Response: This is acceptable.

Salix Follow-up Comments: No comments.

- 2 Does the Division agree that a combined Salix and Dr. Falk Pharma safety database, 400 patients treated with Mesalamine Pellets for at least 6 months (Salix Studies MPUC3003 and MPUC3004) and available data (up to 450 patients for up to 12 months) from Dr. Falk Pharma Study SAG-27/UCR, in conjunction with the well-characterized safety profile of 5-ASA in ulcerative colitis, will be adequate to support registration for Mesalamine Pellets in the maintenance of remission of the disease? Please note that the Salix Phase 3 studies will use encapsulated Mesalamine Pellets whereas the Dr. Falk Pharma Phase 3 study will use loose Mesalamine Pellets (refer to question 8, below).

FDA Response: This is essentially a review issue. Noteworthy, safety would be largely dependent on data obtained in patients treated by the Salix mesalamine formulation for an extended 1 year period. Safety data from other mesalamine formulations may not be applicable.

Salix Follow-up Comments: Salix acknowledges that safety data is to be derived from patients treated with the Salix Mesalamine Pellets formulation. At this time, the primary safety database is anticipated to include 400 patients treated with Mesalamine Pellets for up to 6 months from the two Salix Phase 3 studies (MPUC3003 and MPUC3004). At the time of submission it is projected that safety data from approximately 100 Mesalamine Pellets patients treated for 12 months, derived from either an open-label follow-on safety study for patients successfully completing Studies MPUC3003 and MPUC3004 or from studies conducted by Dr. Falk Pharma, assuming equivalency to the Salix Mesalamine Pellet formulation can be established (refer to paragraph below). In the event that the projected 100 patients are not available at the time the NDA is ready for submission, can these data be provided during review (e.g., in the 4 month Safety Update)?

FDA Meeting Response: No, you will need about 100 patients at the time of submission from the to be marketed formulation. If the sponsor wishes to use some 1-year data from other than the to-be-marketed product (i.e., the European product manufactured at another site), the use of this data will be discussed at the pre-NDA meeting.

Salix Follow-up Comments: Additionally, with respect to the Division's comment concerning the Salix Mesalamine Pellet formulation versus other Mesalamine Pellet formulations, currently it is anticipated that studies to be conducted by Dr. Falk Pharma will use the equivalent drug substance, polymeric coatings, excipients, and manufacturing process as used by Salix; however, manufacturing may be conducted at a different site. Salix acknowledges the SUPAC-MR guidance and would like to obtain additional general guidance concerning demonstration of equivalence between these two sites. Note that Salix recognizes the comments from the Division concerning the in vitro dissolution methodology (refer to question 8, below).

FDA Meeting Response: Will discuss this further during the pre-NDA meeting. Refer to question 8, below.

- 3 Does the Division have any additional suggestions concerning the proposed Phase 3 clinical program?

FDA Response: Because of the nature of ulcerative colitis (spontaneous recurrences and remissions), the diagnosis of symptomatic and endoscopic remission requires establishing it at study baseline, not on a historical 6 month retrospective evaluation. A history of remission date and medication/s that induced remission is appropriate.

Salix Follow-up Comments: Salix would like to clarify that at the Screen Visit (7

days prior to randomization) each patient will be assessed, per the Sutherland Disease Activity Index, for mucosal appearance by having a baseline sigmoidoscopy and for rectal bleeding (note that patients are also assessed for stool frequency and a Physician's rating of disease activity). Also, a history of remission dates and medication(s) that induced remission will be obtained to verify the baseline data conclusion. Does the Division agree that collection of these data at baseline is sufficient to establish a diagnosis of remission?

FDA Meeting Response: This is acceptable.

- 4 Does the Division agree that a pharmacokinetic study in pediatric patients would fulfill the requirements of the Pediatric Research Equity Act of 2003?

FDA Response: Safety and efficacy in pediatric patients will be needed. A sole pharmacokinetic study will not suffice to fulfill the pediatric requirement.

Salix Follow-up Comments: Salix acknowledges FDA comments concerning the PREA pediatric requirements. Can the Division provide general guidance to assist Salix in the design of these studies? Additionally, based on experience being gained with pediatric studies in the active mild to moderate clinical setting, Salix anticipates patient accrual to be limited. Thus, at the time the NDA is ready to submit, could these studies be deferred?

FDA Meeting Response: At the time of NDA submission, you should include your pediatric study plan and ask for the deferral at the time of submission.

Pharmacology/Toxicology Questions

- 5 Does the Division agree that the nonclinical studies conducted with mesalamine are adequate to support product registration?

FDA Response: Yes. However you need to provide comprehensive summaries of all the studies.

Salix Follow-up Comments: As indicated by the CTD format appropriate summaries of all studies will be provided. With respect to the 2 year mouse carcinogenicity and in vitro mouse lymphoma tk studies that will be incorporated by reference to NDA 19-651 and 21-252, respectively, summaries based on available FOI data in FDA's toxicology review will be provided. Does the Division agree that this approach is acceptable?

FDA Meeting Response: This approach is acceptable.

- 6 As discussed during the August 20, 2003 Pre-IND meeting, _____ contains the identical co-polymer used in _____ (listed on FDA Inactive Ingredient Database), and toxicology data were incorporated by cross-reference to DMF _____. To complement the toxicology studies contained in DMF _____ Salix plans to conduct a 6-month study in a non-rodent species and the standard battery of tests for genotoxicity as described in the ICH guidance (ICH S2A). Does the Division agree that these additional nonclinical studies with the co-polymer in _____ are adequate to support the registration of Mesalamine Pellets for the maintenance of remission of ulcerative colitis? b(4)

FDA Response: In addition to the proposed 6-month oral toxicity study in a non-rodent, and the battery of genotoxicity studies, you need to conduct Segment I (Fertility and General Reproductive Performance) and Segment III (Pre- and Post-natal Toxicity) reproductive toxicity studies in rats (refer to FDA Guidance for Industry, Nonclinical Studies for Development of Pharmaceutical Excipients, Draft Guidance, 2002).

Salix Follow-up Comments: The toxicology studies proposed by Salix and additional toxicology studies recommended by the Division for _____ will be performed under GLP regulations. Certain deviations from GLPs are anticipated regarding test article characterization. The test article mixture (suspension or admixed with diet) used in these studies will not be analyzed for test article stability or homogeneity. Evidence of exposure to the test article or toxicokinetics of test article will not be determined in these studies. Does the Division agree that this approach is acceptable? b(4)

FDA Meeting Response: This approach is acceptable. The sponsor will explore with the supplier methods for determining test article stability and homogeneity.

Clinical Pharmacology and Biopharmaceutics Questions

- 7 Does the Division agree that the studies conducted to support the pharmacology and pharmacokinetics of Mesalamine Pellets are adequate to support product registration?

FDA Response: Yes. The proposed studies appear acceptable in support of application filing.

Salix Follow-up Comments: No comments.

Chemistry Questions

- 8 Does the Division agree that the in vitro comparative dissolution profile between the loose pellets (as used in the Salix Phase 1 studies, MPPK1001 and MPPK1002) and the loose pellets encapsulated in hard gelatin capsules (intended for use in the Salix Phase 3 studies, MPUC3003 and MPUC3004) demonstrates equivalency between the dosage forms?

FDA Response: The results of the comparative dissolution profiles seem to demonstrate similarity between the formulations. This will have to be evaluated in more detail by the Office of Clinical Pharmacology and Biopharmaceutics.

Salix Follow-up Comments: Salix acknowledges the Division's comment relating to the method and will provide this information, when completed, to the IND for review.

Minutes Preparer: Dr. Betsy Scroggs

Chair Concurrence: Dr. Ruyi He

Attachment: *Revised Sutherland Disease Activity Index*

Revised Sutherland Disease Activity Index

#	INDICE	SCALE RATINGS	
1	Stool frequency	0 =	Normal
		1 =	1 to 2 stools/day more than normal
		2 =	3 to 4 stools/day more than normal
		3 =	>4 stools/day more than normal
2	Rectal bleeding	0 =	None
		1 =	Streaks of blood
		2 =	Obvious blood
		3 =	Mostly blood
3	Mucosal appearance	0 =	Intact mucosa with preserved or distorted vessels
		1 =	Erythema, decreased vascular pattern, granularity, no mucosal hemorrhage
		2 =	Mucosal hemorrhage without blood in the lumen or gross ulceration, marked erythema, absent vascular pattern, small ulcers
		3 =	Blood in lumen, gross ulceration, exudates
4	Physician's rating of disease activity	0 =	Normal
		1 =	Mild
		2 =	Moderate
		3 =	Severe
MAXIMUM SCORE		12	

Source: Disease Activity Index found in Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic Acid Enema in the Treatment of Distal Ulcerative Colitis, Proctosigmoiditis, and Proctitis. *Gastroenterology*. 1987;92:1894-1898.

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/s/

Betsy Scroggs
11/4/04 06:13:49 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-301 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Apriso Established/Proper Name: Mesalamine Dosage Form: Extended-Release Capsules 0.375g		Applicant: Salix Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Cristi Stark		Division: Gastroenterology Products
<p>NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) 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) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>NDA 19-651 – Asacol NDA 21-252 – Canasa</p> <p>Provide a brief explanation of how this product is different from the listed drug. Different dosage form and strength</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 10/29/08</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		10/31/08
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Promotional Materials (*accelerated approvals only*)

Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____

Received

Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 6S <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	8/27/08
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then questions should be answered in relation to that supplement; not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? 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. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs 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. 	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)
<ul style="list-style-type: none"> [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). 	<input checked="" 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). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [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.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(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 the rest of the patent questions.

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).

<p>(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?</p> <p>(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 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 OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist³</p>	
<p>Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) 10/31/08</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	<p>10/28/08</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>12/31/07</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>Canasa 6/8/06, Lialda 1/16/07, Pentasa 6/26/07</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	10/15/08
<ul style="list-style-type: none"> ❖ Labeling reviews (indicate dates of reviews and meetings) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 10/8/08 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 10/15/08 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews CSO – 3/27/08
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (indicate date(s)) • Acceptability/non-acceptability letter(s) (indicate date(s)) 	10/8/08
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review) 	505(b)(2) assessment – 10/31/08, stat filing review – 2/27/08, ONDQA filing review – 2/21/08
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (signed by Division Director) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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 (include certification) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (if located elsewhere in package, state where located) 	Located in tcons in Outgoing Communications Tab
<ul style="list-style-type: none"> • Incoming submissions/communications 	
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located) 	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
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<ul style="list-style-type: none"> Incoming submission documenting commitment 	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	10/24/08, 10/15/08, 10/14/08, 10/14/08, 10/10/08, 10/6/08, 10/2/08, 9/26/08, 9/26/08, 9/23/08, 9/11/08, 9/8/08, 8/19/08, 6/13/08, 3/27/08, 3/3/08, 1/14/08
❖ Internal memoranda, telecons, etc.	10/14/08, 8/18/08, 4/9/08, 3/28/08
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date; approvals only</i>) 	<input type="checkbox"/> Not applicable 8/27/08
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg 10/29/07
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg 10/6/04
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	11/9/05
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/31/08
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/29/08
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	10/29/08
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	10/30/08
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	In clinical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	In clinical review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 8/29/08

⁵ Filing reviews should be filed with the discipline reviews.
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Clinical Microbiology <input checked="" type="checkbox"/> None	
Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 9/29/08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 10/7/08
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 9/25/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page25-37
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 10/28/08
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	Included in CMC review

<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	Date completed: 8/4/08 – in CMC review <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An 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 ADRA.