

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202292Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202292

SUPPL #

HFD # 180

Trade Name Fulyzaq

Generic Name crofelemer

Applicant Name Salix Pharmaceuticals, Inc

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒

NO ☐

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

505(b)(1)

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

YES ☒

NO ☐

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

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Five

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?

N/A

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#

NDA#

NDA#

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:

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"):

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 #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	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: Kevin Bugin

Title: Regulatory Health Project Manager

Date: 11/14/2012

Name of Office/Division Director signing form:

Title:

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

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

/s/

JULIE G BEITZ
12/18/2012

1.3.3 Debarment Certification

Salix Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act in connection with this application to NDA 202292.



William P. Forbes, PharmD
Executive Vice President, Medical, Research & Development
and Chief Development Officer
Salix Pharmaceuticals, Inc.

Dec 06, 2011

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202292 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Fulyzaq Established/Proper Name: crofelemer Dosage Form: 125 mg, tablet		Applicant: Salix Pharmaceuticals Agent for Applicant (if applicable):
RPM: Kevin Bugin		Division: DGIEP
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: 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.		
❖ Actions		
- Proposed action - User Fee Goal Date is <u>09/05/2012</u>		☒ AP 12/31/2012 ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☐ None

¹ 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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics ³	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): 1 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☒ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the 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	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[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).	☐ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☐ 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).

(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? (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). <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> <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>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist⁴	0103/2013
Officer/Employee List	
❖ 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>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 12/31/2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	12/19/2012
Original applicant-proposed labeling	12/05/2011
Example of class labeling, if applicable	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
Original applicant-proposed labeling	
Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	12/19/2012
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>) - Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	Prop Name Review (11/05/2012)
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM 02/16/2012 ☒ DMEPA 11/02/2012; 09/12/2012; 09/05/2012; 08/24/2012; 07/26/2012; 06/29/2012; 03/02/2012; ☒ ODPD (DDMAC) 08/15/2012 ☒ SEALD 12/10/2012 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	02/17/2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC <u>07/25/2012</u> If PeRC review not necessary, explain: _____ - Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	☒ Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	12/10/2012; 12/12/2012; 12/20/2012; 12/20/2012; 12/03/2012; 11/28/2012; 11/27/2012; 11/16/2012; 11/15/2012; 10/23/2012; 09/04/2012; 08/24/2012; 08/23/2012; 08/21/2012; 08/17/2012; 08/17/2012; 08/03/2012; 08/03/2012; 08/02/2012; 07/31/2012; 07/25/12; 07/20/2012; 07/18/2012; 07/09/2012; 07/03/2012; 06/27/2012; 06/26/2012; 06/12/2012; 06/08/12; 06/07/12; 06/05/2012; 05/23/12; 05/18/2012; 05/14/12; 04/26/2012; 04/20/12; 03/27/12; 03/20/2012; 03/20/2012; 03/12/12; 02/29/12; 02/28/12; 02/17/12; 02/07/12; 02/03/12; 01/31/12; 12/23/12; 12/16/11
❖ Internal memoranda, telecons, etc.	08/24/2012 TC; 08/08/2012 TC; 08/06/12 TC; 07/26/12 TC; 06/14/12 TC; 04/06/12 TC;
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	☐ No mtg Center Director Briefing: 08/06/12
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg 01/19/11
• EOP2 meeting <i>(indicate date of mtg)</i>	☐ No mtg 05/24/04
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	CMC: 05/24/11
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☐ None 12/31/2012
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None 12/14/2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None 12/28/2012
PMR/PMC Development Templates <i>(indicate total number)</i>	☐ None 10
Clinical Information⁶	
❖ Clinical Reviews	

⁶ Filing reviews should be filed with the discipline reviews.

• Clinical Team Leader Review(s) (indicate date for each review)	See CDTL Review
• Clinical review(s) (indicate date for each review)	10/03/2012
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	See Clinical Review (section 3.3)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☐ None 08/31/2012
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	☐ None requested 08/09/2012 Sum; 08/03/12 VAI; 08/03/12 VAI; 07/31/12 VAI; 07/09/2012;
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ None
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☐ None 12/18/2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 08/23/2012
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☐ None 08/30/2012
• Supervisory Review(s) (indicate date for each review)	☒ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 08/02/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☐ None 12/31/2012
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None 12/31/2012 CMC 2 nd Review; 12/21/2012 OBP; 08/01/2012 Biopharm; 07/13/2012 CMC;
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☐ None 08/10/2012 Secondary BRT; 08/08/2012 BRT;
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	
☒ Review & FONSI (indicate date of review)	08/17/2012; 08/17/2012
☐ Review & Environmental Impact Statement (indicate date of each review)	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: See CMC Review ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix 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.

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/s/

KEVIN B BUGIN
01/03/2013

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Post marketing Commitment Comments - December 20, 2012
Date: Thursday, December 20, 2012 2:37:30 PM
Importance: High

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

We further refer to your submission dated December 19, 2012, where you submitted your commitment to the CMC PMCs and provided revised text in module 1 for these PMCs. We have the following requests for revisions to PMC 7 and 8 as written in that submission. No change to PMC 6 as stated in your submission.

- 7 (b) (4) Characterize the (b) (4) crofelemer (b) (4)
[Redacted]
[Redacted]
- 8 Revise (b) (4) the **current** HPLC methods for assay and related substances for the drug substance and drug product **or develop new methods. The revised or new methods must be stability-indicating and appropriately validated.**

Please let me know if you have any questions.

Regards,

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
12/20/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 - Fulyzaq (crofelemer) - Post marketing commitment comments - December 20, 2012
Date: Thursday, December 20, 2012 8:39:54 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Below please find the two post marketing commitments from the Office of Biotechnology Products that you will be responsible for.

PMC – 9 To revise the specification for the crofelemer cell-based assay after XX lots of crofelemer have been manufactured.

Final report provided by:

PMC – 10 To validate and implement a cell-based potency assay that uses (b) (4)

Final report provided by:

Please propose number of lots for PMC 9 and goals for completion of PMC 9 and 10, above. If you have any questions, let me know.

Regards,

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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KEVIN B BUGIN
12/20/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Labeling and Post-Marketing Comments - December 12, 2012
Date: Wednesday, December 12, 2012 5:05:49 PM
Attachments: [Redlined_NDA_202292_Fulyzaq_\(crofelemer\) - FDA Labeling Revisions - 12Dec2012.doc](#)
[Clean_NDA_202292_Fulyzaq_\(crofelemer\) - FDA Labeling Revisions - 12Dec2012.doc](#)

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Please find attached two WORD documents containing FDA's revisions to the proposed labeling for crofelemer. The recent Salix version submitted December 07, 2012, with Salix revisions "accepted" was used as the base for this version. One version is clean and one contains revisions tracked for ease of review.

Also, below please find the three post marketing commitments from the Office of New Drug Quality Assessment that you will be responsible for.

PMC – 6

(b) (4)

Final Report Submission: 12/2013

PMC – 7

(b) (4)

Final Report Submission: 12/2013

PMC – 8

(b) (4)

Final Report Submission: 12/2013

As with the other PMR/PMCs, we will need an official correspondence submitted to the NDA with your acknowledgement and commitment to the above. If you have any questions, or need discussion of the above, please let me know as soon as possible.

Regards,

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
12/12/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com> \(Jennifer.Richards@salix.com\)](#)
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Office of Biotechnology Products Information Request - December 10, 2012
Date: Monday, December 10, 2012 1:41:06 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Please propose appropriate drug substance (API) and drug product (125 mg tablets) release and stability acceptance criteria for the Crofelemer potency bioassay.

If you have any questions, please let me know.

Regards,

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
12/10/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Labeling Comments - December 3, 2012
Date: Monday, December 03, 2012 2:10:18 PM
Attachments: [NDA 202292 Fulyzaq \(crofelemer\) - FDA Revisions to Section 11 - December 3, 2012.doc](#)

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Attached please find a MS Word document with revisions to the Aug 23, 2012, version of Section 11 from the proposed labeling. Other sections of the labeling have been omitted to allow ease of review.

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

KEVIN B BUGIN
12/03/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Post marketing requirements comments - November 28, 2012
Date: Wednesday, November 28, 2012 11:02:18 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Below please find revisions to the nonclinical PMR text and milestones.

PMR – 2 A 6-month rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

Proposed timelines:

SPA Submission:	<u>10/2013</u>
Final Protocol Submission:	<u>01/2014</u>
Study Completion:	<u>12/2014</u>
Final Report Submission:	<u>06/2015</u>

PMR – 3 A 2-year rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

Proposed timelines:

SPA Submission:	<u>12/2013</u>
Final Protocol Submission:	<u>04/2014</u>
Study Completion:	<u>10/2016</u>
Final Report Submission:	<u>06/2017</u>

Review and resubmit your acknowledgement/commitment to conduct the above. If you require discussion on this topic, we can add this to the agenda for the forthcoming teleconference to discuss labeling.

For your reference, please see the following guidance:

Guidance for Industry Carcinogenicity Study Protocol Submissions

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078924.pdf>

Guidance for Industry Special Protocol Assessment

<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm080571.pdf>

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

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/s/

KEVIN B BUGIN
11/28/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Labeling and Post-marketing Comments - November 16, 2012
Date: Friday, November 16, 2012 6:27:35 PM
Attachments: [Redlined NDA 202292 - Labeling - FDA Revisions_16Nov2012.doc](#)
[CLEAN NDA 202292 - Labeling - FDA Revisions_16Nov2012.doc](#)

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Please find attached two WORD documents containing FDA's revisions to the proposed labeling for crofelemer. The August 23, 2012, version of labeling with Salix revisions "accepted" was used as the base for this version. One version is clean and one contains revisions tracked for ease of review.

Also, below please find list of post marketing requirements and commitments that you will be responsible for. Note, that we anticipate additional Chemistry, Manufacturing, and Controls commitments, and those will be conveyed at a later time.

PMR -1 Deferred pediatric study to evaluate pharmacokinetics (PK), efficacy and safety with different doses over a four week period in pediatric patients ages 1 month to 17 years of age.

Final Protocol Submission:	<u>06/05/2013</u>
Study/Trial Completion:	<u>06/05/2017</u>
Final Report Submission:	<u>12/05/2017</u>

PMR -2 Carcinogenicity studies with orally administered crofelemer in mice and rats.

Final Protocol Submission:	<u>12/01/2013</u>
Study/Trial Completion:	<u>06/30/2016</u>
Final Report Submission:	<u>12/30/2016</u>

PMC -3 An in vitro study to determine whether (b) (4) crofelemer is an inhibitor of the transporters, P-glycoprotein and BCRP.

Final Protocol Submission:	<u>03/05/2013</u>
Study/Trial Completion:	<u>09/05/2013</u>
Final Report Submission:	<u>03/05/2014</u>

PMC -4 An in vivo study in human subjects to evaluate the effects of crofelemer on CYP 3A4 using a probe that is a pure substrate of CYP 3A4.

Final Protocol Submission:	<u>03/05/2013</u>
Study/Trial Completion:	<u>09/05/2013</u>
Final Report Submission:	<u>03/05/2014</u>

We will need an official correspondence submitted to the NDA with your acknowledgement and commitment to the above.

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

"Not everything that counts can be counted, and not everything that can be counted counts."
— Alfred Einstein

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/s/

KEVIN B BUGIN
11/16/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Bioassay Protocols Advice - November 15, 2012
Date: Thursday, November 15, 2012 2:43:28 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Also, refer to the amendment submitted on November 13, 2012.

In general, your validation protocols are acceptable. However, we have the following comments, *which you should address in your validation report submission.*

1.

2.

3.

4.

5.

6.

(b) (4)

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

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301-796-2302

"Not everything that counts can be counted, and not everything that can be counted counts."

— Alfred Einstein

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KEVIN B BUGIN
11/15/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - DMEPA Container Labeling Comments - October 23, 2012
Date: Tuesday, October 23, 2012 9:24:19 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

We have the following request for information and comment regarding your container label.

1. Although the active ingredient ('crofelemer') is at least half the size of the proprietary name, it lacks prominence relative to the proprietary name. Increase the prominence of the active ingredient taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with CFR 201.10(g)(2).

2. Increase the prominence of the dosage form (delayed release tablets) such that it has the same prominence as the active ingredient.

3. Relocate the strength so that it appears directly below the established name (active ingredient and dosage form) and increase its size to ensure its prominence is greater than that of the net quantity statement.

4. Remove the (b) (4) which contains the net quantity ('60 tablets') and the 'Rx only' statements. As currently presented, the (b) (4) affords the net quantity and the 'Rx only' statements more prominence than the product name and strength. Once you remove the (b) (4) change the (b) (4) to improve readability. Additionally, decrease the font size of these statements to allow room to address comments A2 above and A5 below.

5. Add the statement 'Tablets should be swallowed whole. Do not crush or chew' and locate this statement below the dosage strength on the principal display panel.

6. Revise the net quantity statement from '60 tablets' to '60 enteric coated tablets'.

If you have any questions, please let me know.

Kind regards,

Kevin Bugin, MS, RAC

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

FDA\CDER

301-796-2302

"The sufficiency of my merit is to know that my merit is not sufficient."
— St. Augustine

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/s/

KEVIN B BUGIN
10/23/2012



NDA 202292

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Salix Pharmaceuticals, Inc.
8510 Colonnade Center Drive
Raleigh, NC 27615

ATTENTION: Jennifer Richards
Associate Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated and received December 5, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Crofelemer Tablets, 125 mg.

We also refer to your correspondence dated and received August 27, 2012, requesting review of your proposed proprietary name, Fulyzaq.

We have completed our review of the proposed proprietary name, Fulyzaq and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your August 27, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Kevin Bugin at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/12/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Labeling Request
Date: Tuesday, September 04, 2012 11:24:29 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

- We noted that a label for the carton was not included with this NDA. Please submit the carton label for review.
- Regarding the immediate container (bottle) label, please revise the dosage form to delayed-release tablets.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302
"Opportunities are seldom labeled."
- John A. Shedd

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/s/

KEVIN B BUGIN
09/04/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Request for Information - August 24, 2012
Date: Friday, August 24, 2012 3:18:13 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

We have the following request for information and comment.

What additional work/steps are being planned between now and (b) (4) which is the time you indicated you will be prepared for a cGMP inspection? The Agency stresses that an inspection of the (b) (4) facility is necessary to make the final determination regarding the acceptability of the bioassay.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

+++++

If you are not the intended recipient you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2302 or by return e-mail.

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

 Please consider the environment before you print.

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/s/

KEVIN B BUGIN
08/24/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Fulyzaq (crofelemer) - Clinical and Statistics Request for Information - August 23, 2012
Date: Thursday, August 23, 2012 8:00:15 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fulyzaq (crofelemer).

In reviewing the clinical and statistics information in your NDA, we have the following question. We need this information to continue labeling review and negotiations. Please respond by Tuesday, August 28, 2012.

Please explain the apparent lack of a treatment effect among Blacks/African-Americans. Our analysis of clinical response by race shows:

		Crofelemer 125 mg*	Placebo
Black/African American:	N	51	53
	Clinical Response Rate (%)	7.8	9.4
	Treatment Effect	-1.6	-
	95% confidence interval	[-13, 10]	
White/Caucasian:	N	53	58
	Clinical Response Rate	24.5	8.6
	Treatment Effect	15.9	-
	95% confidence interval	[2.2, 30]	
Hispanic	N	32	25
	Clinical Response Rate	18.8	4.0
	Treatment Effect	14.8	-
	95% confidence interval	[-3.3, 32.3]	

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

F-301-796-9904

+++++

If you are not the intended recipient you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2302 or by return e-mail.

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

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/s/

KEVIN B BUGIN
08/23/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 (b) (4) (crofelemer) - Urgent Request for Information - August 21, 2012
Date: Tuesday, August 21, 2012 6:26:17 PM
Importance: High

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer).

The Office of Drug Evaluation III, the Office of New Drug Quality Assessment and the Office of Biotechnology Products have the following requests for information and comments.

1. Bioassays:

- (b) (4)

2. To-Be-Marketed Lots:

- Provide details of any available to-be-marketed drug substance lots, their quantity, and release testing results.
- Provide details of any available to-be-marketed drug product lots, number of doses, and release testing results.
- Provide the correlation between the drug product and drug substance lot numbers.

3. (b) (4) Facility:

- Provide information regarding when this facility would be able to perform (b) (4) assays in conformity with CGMPs.

We request that you respond to these requests by no later than August 23, 2012, COB.

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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/s/

KEVIN B BUGIN
08/21/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Labeling Comments - August 17, 2012
Date: Friday, August 17, 2012 2:13:38 PM
Attachments: [NDA 202292 - Labeling - FDA Proposed Revisions - Version 1 - 17Aug2012.doc](#)

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Please find attached an annotated WORD document containing FDA's revisions to the proposed labeling for crofelemer. Please note that there may be additional revisions upon further review from our consultants in DDMAC, DMEPA, and upon further review from our senior leadership.

Please also refer to a clinical information request sent earlier today, as it relates to one of the comments in the Clinical section of the labeling.

We are continuing to work on post marketing commitments and requirements. These will be sent under a separate communication.

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
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17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KEVIN B BUGIN
08/22/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Clinical Request for Information - August 17, 2012
Date: Friday, August 17, 2012 12:50:53 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

Furthermore, please refer to 'IR8 Figure 1' in your July 12, 2012 Response to Clinical and Statistics Information Requests (Sequence 0018).

1. Please redo the figure by limiting the crofelemer 125 mg subjects to only those subjects who continued into the PF phase. Thus, the final figure will include: (a) crofelemer 125 mg subjects who continued into the PF phase and (2) placebo subjects who crossed over to crofelemer 125 mg. The figure should be generated for Stage I, Stage II and for both stages combined.
2. In addition, provide a graph for the crofelemer 125 mg subjects only, starting with the PF phase. Parallel to the x axis, display the number of subjects who were in the study (i.e., did not drop out) at each of the following timepoints: 0 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, and 20 weeks of the PF phase.

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
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/s/

KEVIN B BUGIN
08/22/2012

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 08, 2012
Meeting Time: 3:30 to 4:00 pm EST
Meeting Type: Teleconference
Applications: NDA 202292 Crofelemer tablets, 125 mg
Sponsor/Applicant: Salix Pharmaceuticals, Inc.
Meeting Chair: Julie Beitz, Ph.D.
Meeting Recorder: Kevin Bugin, M.S., R.A.C.

FDA ATTENDEES:

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODEIII)
Anil Rajpal, MD, MPH, Medical Team Leader, DGIEP
Kevin Bugin, MS, RAC, Regulatory Health Project Manager, DGIEP

EXTERNAL CONSTITUENT ATTENDEES:

Salix Pharmaceuticals, Inc

Linda Young, Vice President, Regulatory
Pam Golden, PhD, Executive Director, Nonclinical and Clinical Pharmacology
Jennifer Richards, Associate Director, Regulatory

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TELECONFERENCE DISCUSSION:

The Agency requested this teleconference to stress the importance of the need for the bioassay to ensure batch-to-batch consistency. The Agency noted that not only would a timeline for implementation be needed, but the Applicant would also need to commit to putting these additional measures in place. These steps would be needed before additional review work and labeling negotiations could continue.

The Applicant agreed and would supply a timeline, commitment, lab info for the (b) (4) assay, and in time the data generated on the proposed marketing batches. This preliminary information would be supplied by the end of week (Aug 17).

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/s/

KEVIN B BUGIN
08/21/2012

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 06, 2012
Meeting Time: 4:00 to 4:30 pm EST
Meeting Type: Teleconference
Applications: NDA 202292 Crofelemer tablets, 125 mg
Sponsor/Applicant: Salix Pharmaceuticals, Inc.
Meeting Chair: Julie Beitz, Ph.D.
Meeting Recorder: Kevin Bugin, M.S., R.A.C.

FDA ATTENDEES:

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODEIII)
Andrew Mulberg, MD, FAAP, CPI, Deputy, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Anil Rajpal, MD, MPH, Medical Team Leader, DGIEP
Sushanta Chakder, PhD, Nonclinical Team Leader, DGIEP
Kevin Bugin, MS, RAC, Regulatory Health Project Manager, DGIEP
Marie Kowblansky, PhD, Quality Assessment Team Leader, Office of New Drug Quality Assessment (ONDQA)
Mark Seggel, PhD, Biopharmaceutics Reviewer, ONDQA
Nina Ni, PhD, Quality Reviewer, ONDQA
Shaw T Chen, MD, PhD, Deputy Director, Office of Drug Evaluation IV, Botanical Review Team Leader
Jinhui Dou, PhD, Pharmacognosy Reviewer, Botanical Review Team

EXTERNAL CONSTITUENT ATTENDEES:

Salix Pharmaceuticals, Inc
William Forbes, PharmD, Executive Vice President Research and Development and Chief Development Officer
Craig Paterson, MD, Vice President, Medical and Clinical Development
Linda Young, Vice President, Regulatory
Jody Lockhart, Associate Vice President, Pharmaceutical Development and Manufacturing
Pam Golden, PhD, Executive Director, Nonclinical and Clinical Pharmacology
Jennifer Richards, Associate Director, Regulatory

CONFIDENTIAL

TELECONFERENCE DISCUSSION:

[Discussion topics are listed in plain font below. Discussion from the meeting is captured in **bold** font.]

1. Per the outcomes of the recent Center Director Briefing held to discuss this application, there is a need for Potency Bioassay for release and stability control of future batches. Specifically (b) (4) Assay, which is clinically relevant.

Discussion:

The Applicant believes the (b) (4) Bioassay approach is feasible. The Applicant inquired to the whether all batches would undergo this testing and the Agency confirmed it would. The Agency confirmed that this is something needed for approval.

The Applicant will discuss further internally and provide the Agency with a response.

Discussion:

The Agency noted that other release assays could be considered, (b) (4)
The Applicant will consider also these other options for a release assay. The Applicant also noted that there was preliminary research on an (b) (4) The Applicant would decide on one approach, (b) (4) and get back to the Agency by the end of the week (August 10).

The Agency clarified that it would need to see information regarding the level of validation work required, how it would be utilized to ensure batch-to-batch consistency and what timeframe would be needed to implement. This information would be needed as soon as possible to make a determination of approvability and begin labeling.

2. The Agency will need to see data from the new (b) (4) assays for more batches.

Discussion:

The Applicant understands the request.

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/s/

KEVIN B BUGIN
08/21/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202292

**PROPRIETARY NAME
REQUEST WITHDRAWN**

Salix Pharmaceuticals, Inc.
8510 Colonnade Center Drive
Raleigh, NC 27615

Attention: Jennifer Richards
Associate Director, Regulatory Affairs

Dear Ms Richards:

Please refer to your New Drug Application (NDA) dated December 5, 2011, received December 5, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Crofelemer Tablets, 125 mg.

We acknowledge receipt of your correspondence, dated and received July 27, 2012, notifying us that you are withdrawing your June 27, 2012 request for a review of the primary proposed proprietary name (b) (4) and alternate name (b) (4). This proposed proprietary name request is considered withdrawn as of July 27, 2012.

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Kevin Bugin at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
08/02/2012

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 26, 2012
Meeting Time: 2:00 to 3:00 pm EST
Meeting Type: Teleconference
Applications: NDA 202292 Crofelemer tablets, 125 mg
Sponsor/Applicant: Salix Pharmaceuticals, Inc.
Meeting Chair: Julie Beitz, Ph.D.
Meeting Recorder: Kevin Bugin, M.S., R.A.C.

FDA ATTENDEES:

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODEIII)
Giuseppe Randazzo, MS, Regulatory Affairs, ODEIII
Maria Walsh, RN, Regulatory Affairs, ODEIII
Andrew Mulberg, MD, FAAP, CPI, Deputy, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Anil Rajpal, MD, MPH, Medical Team Leader, DGIEP
Wen-Yi Gao, MD, PhD, Medical Reviewer, DGIEP
Sushanta Chakder, PhD, Nonclinical Team Leader, DGIEP
Sruthi King, PhD, Nonclinical Reviewer, DGIEP
Kevin Bugin, MS, RAC, Regulatory Health Project Manager, DGIEP
Marie Kowblansky, PhD, Quality Assessment Team Leader, Office of New Drug Quality Assessment (ONDQA)
Mark Seggel, PhD, Biopharmaceutics Reviewer, ONDQA
Catherine Tran-Zwanetz, Regulatory Project Manager, ONDQA
Shaw T Chen, MD, PhD, Deputy Director, Office of Drug Evaluation IV, Botanical Review Team Leader
Jinhui Dou, PhD, Pharmacognosy Reviewer, Botanical Review Team
Lisa Kammerman, PhD, Biostatistics Reviewer, Office of Biostatistics III
Mahesh Ramanadham, Office of Compliance, Division of Manufacturing and Product Quality

EXTERNAL CONSTITUENT ATTENDEES:

Salix Pharmaceuticals, Inc
William Forbes, PharmD, Executive Vice President Research and Development and Chief Development Officer
Craig Paterson, MD, Vice President, Medical and Clinical Development
Linda Young, Vice President, Regulatory
Enoch Bortey, Vice President Clinical Operations
Jody Lockhart, Associate Vice President, Pharmaceutical Development and Manufacturing
Holly Owens, Manager QC Analytical Science
Pam Golden, PhD, Executive Director, Nonclinical and Clinical Pharmacology
Chris Martin, Associate Director, Technical Operations
Jennifer Richards, Associate Director, Regulatory
Lueann Duke, Manager, R&D Operations

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TELECONFERENCE DISCUSSION:

[The Sponsor's initial questions/comments are in plain font below. The Agency response is in **bold** font. Discussion from the meeting is captured in ***bold italics*** font.]

1. Salix would like to confirm that initiation of a treatment protocol is contingent upon the NDA not being approved by the September 5, 2012 PDUFA date.

FDA Response:

Yes.

Discussion:

N/A

2. Salix would like to confirm that a treatment protocol can be filed under the current IND (IND 51,818) (as opposed to a separate Treatment IND).

FDA Response:

Yes.

Discussion:

N/A

3. If the treatment protocol is initiated, Salix intends to enroll patients with the currently sought indication (i.e., HIV+ patients with diarrhea currently on anti-retroviral therapy [ART]). Please confirm that this is acceptable.

FDA Response:

Yes.

Discussion:

N/A

4.

(b) (4)

Discussion:

(b) (4)

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The Agency noted that different lots and different facilities should be considered for the treatment protocol.

The Applicant inquired to the length of the treatment protocol. The Agency did not have any specific timeframe in mind and that it would depend on the status of the review of the NDA. It was clarified that the Applicant could request to charge, but this would need to be renewed annually. The treatment protocol itself, once reviewed, could stay open indefinitely until the NDA was approved.

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/s/

KEVIN B BUGIN
08/21/2012



NDA 202292

INFORMATION REQUEST

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Associate Director, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crofelemer 125 mg Tablets.

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

1. We have evaluated your revised dissolution test that is based on USP <711> Dissolution, Delayed-Release Dosage Forms, Method A, and employs USP Apparatus II (Paddle) at 75 rpm. While we acknowledge that there are currently limited data, the following acceptance criteria are supported and should be incorporated into the regulatory specification for crofelemer delayed-release tablets.

- Acid Stage: no individual unit exceeds (b) (4) dissolved at 2 hours, rather than (b) (4) hour as proposed.
- Buffer Stage: $Q =$ (b) (4) at 45 minutes, rather than $Q =$ (b) (4) minutes.

It should be noted that Level A2 and A3 testing (acid stage) are allowed per USP<711>, Acceptance Table 3.

Accordingly, please submit a revised Section 3.2.P.5.1, Drug Product Specification.

2. We also request that you continue to obtain dissolution profiles (15, 20, 30, 40, 45, and 60 minutes) using the revised methodology (and 2-hour acid stage) on at least three batches at release and on stability.

We note that you previously agreed to continue to obtain dissolution profiles using the original dissolution test methodology on release and stability until a final regulatory specification has been established. Please continue to obtain these profiles on at least three batches for which you are also obtaining profiles using the USP<711> methodology. This

will provide further linkage of the *in vitro* performance of clinical trial batches and the commercial product, and of the test methodologies.

3. As previously requested, please provide dissolution profiles of uncoated tablets from three validation or commercial batches of drug product along with the profiles of the corresponding coated tablets.

The dissolution profiles obtained as requested under #2 and #3 should be submitted in a Prior Approval Supplement (PAS) providing for deletion of the (b) (4)

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE
07/20/2012
Chief, Branch IV

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - DMEPA Comments - July 25, 2012
Date: Wednesday, July 25, 2012 8:06:56 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

The Division of Medication Error Prevention and Analysis has the following comments on your prescribing information and container labeling. Please submit revised labeling to address these comments.

A. Prescribing Information

1. The dangerous symbols '<', '>', '≤', and '≥' which appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations² and may be mistaken and used as opposite of intended, the abbreviations 'BID' and 'ART' as well as the symbol '+' following the word HIV (i.e. HIV +).

As part of a national campaign to decrease the use of dangerous symbols, the FDA agreed not to use such error-prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, we recommend replacing all instances of the symbol '<' with phrase "less than", the symbol '>' with phrase "greater than", the symbol '≤' with phrase "less than or equal to", and the symbol '≥' with phrase "greater than or equal to". Replace the abbreviation 'BID' with "twice daily", 'ART' with "anti retroviral therapy", and 'HIV +' with "HIV positive".

2. Revise Section 3 *Dosage Forms and Strengths* to include the product strength (i.e. 125 mg).

3. Revise Section 16 *How Supplied/Storage and Handling* to include the storage information (i.e. 'Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) per USP 10.30.60 Controlled Room Temperature.

B. Container Label

1. Increase the prominence of the dosage form to have the same prominence (i.e. font size and type) as the established name to ensure that it is in accordance with CFR 201.10(g)(2).
2. Relocate the strength so that it appears directly below the established name, and increase its size to ensure its prominence is greater than that of the quantity statement. Additionally, delete the hyphen that appears between '125' and 'mg' to avoid crowding and confusion. There should be a space between the numerical value and the unit of measure.

The revised strength statement should appear as follows: '125 mg'. For consistency, use the same format on the container label and the Prescribing Information, where the product strength appears.

3. Remove the (b) (4) containing the net quantity and the 'Rx only' statements. As currently presented, the (b) (4) affords the net quantity and the 'Rx only' statements more prominence than the product name and strength. Once you remove the (b) (4), change the white text to black to improve readability. Additionally, decrease the font size of the net quantity and 'Rx only' statements to allow room to address comment B.2 above.

4. Decrease the prominence of the company logo (i.e. Salix). As currently presented, the large size of the logo can distract from other information such as the dosage statement, on the side panel.

5. Revise the storage information statement (b) (4) to be in accordance with the USP definition of controlled room temperature (i.e. 20°C to 25°C (68°F to 77°F) per USP 10.30.60 *Controlled Room Temperature*), and consistent with the presentation of the storage information in the Prescribing Information after addressing comment A.3 above. Additionally, avoid the use of hyphen, to reduce potential confusion when reading the numbers denoting the storage temperature range (the hyphen may be misinterpreted as 'negative').

If you have any questions, please do not hesitate to ask.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
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/s/

KEVIN B BUGIN
07/25/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202292

**PROPRIETARY NAME
REQUEST WITHDRAWN**

Salix Pharmaceuticals, Inc.
8510 Colonnade Center Drive
Raleigh, NC 27615

Attention: Jennifer Richards
Associate Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated December 5, 2011, received December 5, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crofelemer Tablets, 125 mg.

We acknowledge receipt of your correspondence, dated and received June 27, 2012, notifying us that you are withdrawing your May 1, 2012 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of June 27, 2012.

We also acknowledge your correspondence dated June 27, 2012, requests review of your proposed name, (b) (4).

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Kevin Bugin at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/18/2012



NDA 202-292

INFORMATION REQUEST

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Associate Director, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer 125 mg Tablets.

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

An information request letter has been sent to the holder of DMF (b) (4) referenced for (b) (4).
Contact the DMF holder to resolve any pending issues.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE
07/03/2012
Chief, Branch IV

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

DATE: May 31, 2012

TO: Administrative File, NDA 202292

FROM: Nitin M. Patel.
Project Manager
Office of Surveillance and Epidemiology

APPLICATION: NDA 202292: (b) (4) (crofelemer)

APPLICANT: Salix Pharmaceuticals, Inc.

SUBJECT: DMEPA requested this teleconference to inform the Applicant of our concerns with the proposed proprietary name (b) (4) and in particular the fact that the proprietary name is (b) (4), which is problematic from a medication error perspective.

Participants:

FDA: Lubna Merchant, PharmD, M.S. Team Leader, DMEPA
Anne Tobenkin, PharmD, Safety Evaluator, DMEPA
Nitin M. Patel, Project Manager, OSE
Anil Rajpal MD, TL DGIEP, OND
Kevin Bugin Project Manager, DGIEP, OND

Salix: Jennifer Richards, Sr. Manager, Regulatory Affairs
Bill Forbes, Executive Vice President, Medical, R&D
Linda Young, Vice President, Regulatory
Enoch Bortey, Vice President, Clinical Operations
Craig Paterson, Vice President, Medical and Clinical Development
Pam Golden, Executive Director, Nonclinical and Clinical Pharmacology
Matt Mitcho, Associate Brand Director
Jennifer Richards, Associate Director, Regulatory Affairs
Lueann Duke, Manager, R&D Operation

Issues:

Teleconference with Salix Pharmaceuticals
May 31, 2012

Although DMEPA is still in the preliminary stage of the review of the proposed name (b) (4) DMEPA wanted to notify the Sponsor about the safety concerns with their proposed name, (b) (4) as follows:



Salix was informed they can either choose to withdraw the current name and submit a new name or DMEPA can complete a full assessment of their name and issue a formal letter informing them of their decision. Salix agreed to consider DMEPA's concerns and will inform DMEPA in the following week of their decision.

The teleconference ended cordially.

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/s/

NITIN M PATEL
06/29/2012



NDA 202-292

**METHODS VALIDATION
MATERIALS RECEIVED**

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Jennifer Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Crofelemer, 125 mg tablets and to our June 5, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on June 27, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/27/2012



NDA 202-292

INFORMATION REQUEST

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Associate Director, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer 125 mg Tablets.

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

- Provide all available IR spectra generated from all clinical and stability batches of crofelemer drug substance.
- Elaborate how the IR spectra obtained from testing samples are considered concordant with the IR spectrum obtained from crofelemer reference standard as per the proposed specification.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE

06/26/2012

Chief, Branch IV

MEMORANDUM OF MEETING MINUTES

Meeting Date: June 14, 2012
Meeting Time: 9:00 to 10:00 am EST
Meeting Type: Teleconference
Applications: NDA 202292 Crofelemer tablets, 125 mg
Sponsor/Applicant: Salix Pharmaceuticals, Inc.
Meeting Chair: Marie Kowblansky, Ph.D.
Meeting Recorder: Kevin Bugin, M.S., R.A.C.

FDA ATTENDEES:

Office of Drug Evaluation III (ODE III)

Julie Beitz, M.D. Director

ODE III/Division of Gastroenterology and Inborn Errors Products

Andrew Mulberg, M.D. Deputy
Anil Rajpal, M.D. Medical Team Leader
Wen-Yi Gao, M.D. Medical Reviewer
Sushanta Chakder, Ph.D. Pharmacology Team Leader
Sruthi King, Ph.D. Pharmacology Reviewer
Kevin Bugin, M.S., R.A.C. Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Kristina Estes, Pharm.D. Reviewer

Office of New Drug Quality Assessment

Marie Kowblansky, Ph.D. Chemistry Lead
Nina Ni, Ph.D. Chemistry Reviewer
Catherine Tran-Zwanetz, Regulatory Project Manager, ONDQA

Office of Drug Evaluation IV/Botanical Review Team

Shaw T. Chen, M.D., Ph.D. Deputy Director
Jinhui Dou, Ph.D., Pharmacognosy Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Salix Pharmaceuticals, Inc

William Forbes, PharmD, Executive Vice President Research and Development and Chief Development Officer
Craig Paterson, MD, Vice President, Medical and Clinical Development
Linda Young, Vice President, Regulatory
Enoch Bortey, Vice President Clinical Operations
Jody Lockhart, Associate Vice President, Pharmaceutical Development and Manufacturing
Holly Owens, Manager QC Analytical Science
Pam Golden, PhD, Executive Director, Nonclinical and Clinical Pharmacology

CONFIDENTIAL

Chris Martin, Associate Director, Technical Operations
Jennifer Richards, Associate Director, Regulatory
Lueann Duke, Manager, R&D Operations

(b) (4) Consultant
(b) (4), Consultant

TELECONFERENCE DISCUSSION:

[The Agency's CMC requests for information are in **bold font** with the Sponsor's response in normal typeface. Discussion from the meeting is captured in ***bold italic*** font.]

As a natural botanical substance, crofelemer is comprised of units that occur both in random order and with random bonding. These linear chains occur in lengths of anywhere from 3 to 30 units. The natural variation in monomer unit sequences, unit bonding, and chain lengths gives rise to a wide variety of polymeric proanthocyanidins and a large number of possible isomers, creating a highly complex product.

Based on the discussion in our conference call with FDA on April 6, 2012, it was agreed that Salix would provide additional information on the oligomeric contribution to crofelemer. Upon researching options for providing this additional characterization information, we elected to use

(b) (4)

We submitted the results from this method in our submission on June 1, 2012. Herein, we acknowledge FDA's comments, received on June 12, 2012, and provide additional clarification regarding this method and its limitations.

* * *

The method for oligomer composition, as submitted in the June 1st amendment, is not acceptable.

Salix believes we have provided a level of compositional analysis for crofelemer that 1) confirms identification, 2) is stability indicating, 3) reflects the most advanced analytical methodology, and 4) is in accordance with the *FDA CDER Guidance for Industry for Botanical Drug Development (Chemistry - June 2004)*. It is our opinion that no further analyses can be conducted at this time that would provide better information than our current methods (QCTP-244 and QCTP-245).

- The method (b) (4) is unusual, making the accuracy/validity of the resulting data questionable

4 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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/s/

KEVIN B BUGIN
07/23/2012



NDA 202292

INFORMATION REQUEST

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Senior Manager, Regulatory Affairs
8510 Colonnad Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer tablets, 125 mg.

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

The submitted Environmental Assessment (EA) has the following deficiencies. Please address these issues in a revised EA or in an amendment to the EA:

1. According to CDER EA Guidance, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>, the applicant should provide:
 - A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. (For species covered under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), CDER could request copies of relevant permits).
 - A brief description of the applicant's oversight of the harvesting.

If governmental oversight or permits are not required, the applicant should state this.

2. In addition, the applicant is required to submit the certification statement, below. Provide the certification in an amendment to the EA or as item 9 in a revised EA.

Certification

{Applicant Name} confirms that it and the other parties with which it contracts for this harvesting (e.g., any and all buyers and collectors) have complied with all requirements under *{Country/State where harvested}* law to date relating to the harvesting of *{plant species}* for *{Applicant Name}*. *{Applicant Name}* commits that it will continue to comply with all requirements under *{Country/State where harvested}* law relating to such harvesting, including any additional requirements that may be imposed in the future, and will take appropriate measures to ensure that all such other parties continue to comply as well.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE
06/12/2012
Chief, Branch IV

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Botanicals Information Request - June 08, 2012
Date: Friday, June 08, 2012 7:36:59 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

We are reviewing Botanical Raw Materials sections of your submission and have the following comments and requests for information.

Control of Contaminants in Botanical Raw Material Crude Plant Latex / Crofelemer Botanical Drug Substance

1. Add control of aflatoxins using USP methods [(**<561>** Articles of Botanical Origin, Test for Aflatoxins)] to Crude Plant Latex (CPL) and Crofelemer botanical drug substance (BDS) specifications.
 - Provide data on levels of aflatoxins in representative batches of CPL and Crofelemer BDS to justify if testing only BDS or CPL (but not both) is acceptable.
2. Provide full reports on testing methods for pesticide residues (**(b) (4)**)
Test the Crofelemer BDS for the pesticide residues with standard methods and establish appropriate specifications.
 - If your methods are not validated or are outdated, CPL and Crofelemer BDS should be tested according to the standards of the USP [(**<561>**) Articles of Botanical Origin, General Method for Pesticide Residues Analysis] or relevant compendial methods/standards [e.g., US EPA, European Pharmacopoeia, “WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues (2007)”].
 - Test each of the **(b) (4)** pesticides **(b) (4)**
(b) (4)
(b) (4) and any other pesticides that have been used in the Eco-Geographic Regions (EGRs). Test additional pesticides as these start being used in the EGRs.
 - Provide data on pesticide residue levels in representative batches of CPL and Crofelemer BDS to justify if testing of certain pesticide residues in either BDS or CPL (but not both) is acceptable.

CPL Specifications

3. Establish a total phenolic specification with both low and high limits.
4. Establish a specification for Taspine, a characteristic chemical marker compound in CPL, with

both low and high limits.

-

If you have any questions, please do not hesitate to contact me.

Kind regards,

Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
06/08/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Statistics Information Request - June 07, 2012
Date: Thursday, June 07, 2012 1:47:42 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

We are reviewing Statistics sections of your submission and have the following comments and requests for information.

Background:

Based on our statistical review of ADVENT, we believe a one-sided p-value of 0.023, instead of the one-sided p-value of 0.0096 reported in the clinical study report, more accurately represents the level of significance for the test of the hypothesis of no difference in clinical response between the crofelemer 125 mg and placebo treatment groups. Our analysis uses exact methods for the calculation of the level of significance, in contrast to the asymptotic methods used in the NDA.

Our review shows that Pearson chi-square test statistics were calculated for the comparisons required by the Posch and Bauer methods. The one-sided p-value of 0.0096 was obtained based on the assumption that the Pearson chi-square test statistics are distributed approximately as chi-square. However, because of the relatively small clinical response rates that were observed for the treatment groups, exact methods are preferred. The p-value of 0.023 arises from the use of an exact distribution for the Pearson chi-square test statistics. We used StatXact for this analysis.

Requests:

1. The observed clinical response rates (ranging from 2% to 20%) are much smaller than the presumed rates of 35% (placebo) and 55% (crofelemer) that were used in the sample size calculations and in the simulations for showing control of the Type I error rate.
 - We request that you repeat the simulations in order to describe the level of the Type I error rate that is being controlled when the response rates and sample sizes are consistent with what were observed in ADVENT.
 - Include a copy of the simulation code. The code should include internal comments and annotation in sufficient detail to allow us to easily review and understand the program.
2. Our review shows that the p-values and confidence intervals reported for the tests of hypotheses within Stage I are not adjusted for multiplicity.
 - Calculate multiplicity-adjusted p-values for the tests of hypotheses within Stage I. For the reasons described above, the p-values need to be derived through the use of exact methods.
3. Our review of the SAS macro that was used to implement the Posch and Bauer methods indicates that Yule confidence intervals, rather than Wald confidence intervals, were calculated for

the treatment effects within stage. However, neither approach is appropriate because of poor coverage probabilities in the presence of low response rates.

- Recalculate the confidence intervals using an approach that is appropriate for low response rates. Consider using Newcombe confidence intervals. The confidence intervals within Stage I need to be adjusted for multiplicity.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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KEVIN B BUGIN
06/07/2012



NDA 202-292

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Jennifer Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Crofelemer, 125 mg tablets.

We will be performing methods validation studies on Crofelemer, 125 mg tablets, as described in NDA 202-292.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

QCTP-234 Determination of Related Substances for Crofelemer Tablets, 125 mg and 250 mg

Samples and Reference Standards

100	Crofelemer tablets, 125 mg
250 mg	Crofelemer standard material
100 mg	caffeine reference material
25 mg	(b) (4) standard material
25 mg	(b) (4) standard material
25 mg	Catechin standard material
25 mg	Epicatechin standard material
25 mg	Epigallocatechin standard material
25 mg	Gallocatechin standard material
25 mg	Taspine standard material

Equipment

50	glass fiber filters, 25-mm, Whatman 0.7- μ m pore size
1	Waters Xterra 250-mm x 4.6 mm RP ₁₈ , 5- μ m particle size

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/05/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Clinical Pharmacology Information Request - May 23, 2012
Date: Wednesday, May 23, 2012 9:25:27 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer).

We are reviewing the clinical pharmacology sections of your submission and have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

- Crofelemer is a mixture of polymers containing various monomer units of catechin, epicatechin, gallo catechin and epigallocatechin. Studies NP-303-101 and CFFE1091 employed the most sensitive methodology (LC/MS) to assay human plasma samples. Please explain what the assay method in those two studies actually measured, including the molecular weight range of the polymers measured.

We request that you respond to this request by the end of June. If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
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KEVIN B BUGIN
05/23/2012



NDA 202-292

INFORMATION REQUEST

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Associate Director, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer 125 mg Tablets.

We also refer to your April 30, 2012 submission, containing a response to teleconferences between Salix and the FDA March 20, 2012, April 18, 2012 and April 26, 2012.

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

1. Regarding method QCTP-244 "Determination of Monomer Ratio, Average DP and Average Molecular Weight of Crofelemer Tablets" and related report ASRPT-117

a) [REDACTED] (b) (4)

b) Please provide comparative DP data for a single batch of drug substance [REDACTED] (b) (4)

2. Regarding the drug substance specification:

a) [REDACTED] (b) (4)

- b) Please add conversion yield to the drug substance specification. An acceptance range of (b) (4) is reasonable based on the clinical and stability batches.
- c) In view of all the uncertainties and deficiencies in characterizing your standards for (b) (4) please withdraw this method from the drug substance specification.
3. Please include the results of testing by method QCTP-244, as well as the oligomer composition, on the certificate of analysis for the reference standard.
4. While you have committed to improving your assay method for crofelemer (in drug substance and drug product) at a later time, please provide a timeframe within which you commit to do this.
5. While certificates of analysis for catechin, epicatechin, galocatechin, epigallocatechin, and taspine reference standards were submitted, as requested, the certificates for (b) (4) reference standards could not be found in the submission. Please provide these two certificates of analysis.
6. In the testing procedure for (b) (4) using (b) (4) QCTP-236) please clarify how the sample is prepared (b) (4)
7. A number of issues based on our previous information requests remain unresolved at the present time because the following information has not yet been submitted
- a. Validation report for determination of (b) (4) in the drug substance which you have committed to submit June 30, 2012.
- b. Justification of proposed process variables (b) (4)
You have committed to provide a comprehensive data set for historical by June 1, 2012 to justify the proposed ranges.
- c. Validation data for method QCTP-244 "Determination of Monomer Ratio, Average DP and Average Molecular Weight of Crofelemer Tablets, 125 mg (b) (4)", which you have committed to submit by June 30, 2012. Your proposal to submit linearity, precision, and solution stability information and omit accuracy and recovery studies is acceptable.
- d. Data to establish the oligomer composition and distribution in crofelemer batches used in clinical trials. Acceptance criteria should be added to the drug substance specification. You have committed to submitting this information by June 1, 2012.
- e. The HPLC testing procedure for related substances in the drug substance will be revised to (b) (4). You have committed to submitting these revisions by June 30, 2012.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE
05/18/2012
Chief, Branch IV

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Statistics Information Request - May 14, 2012
Date: Monday, May 14, 2012 3:24:36 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer).

We are reviewing Statistics sections of your submission and have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

- For ADVENT, please describe any algorithms that were used to automatically populate data fields in the eCRF and IVRS. In your response, identify the data sets and variables, if any, that are affected by the algorithms.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
05/14/2012



NDA 202292

GENERAL ADVICE

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Senior Manager, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer tablets, 125 mg.

We have reviewed the referenced material and have the following follow up comments for the Biopharmaceutics section of your April 3, 2012, response to the FDA's Information Request from March 20, 2012:

1.  (b) (4)
2. Please note that you should continue to obtain dissolution data and profiles using the proposed separate tests for release in acid and dissolution in buffer. This will allow us to link batches, and will support interim criteria until sufficient data are obtained at release and on stability to establish the final acceptance criteria for the USP<711>-based method. Establishment of the final dissolution acceptance criteria will likely be the subject of a post-marketing commitment.
3. Once the appropriate testing conditions (e.g., time in acid, paddle speed) for the USP<711>-based test are established, the procedure will need to be incorporated into ongoing and future stability studies. As noted, the current methods should continue to be used in parallel with the USP<711> test until such time that sufficient data are available to establish the final acceptance criteria for the USP<711> test.
4. The results presented in Table 12 (3.2.P.2, Dissolution Results for Crofelemer Tablets, ) indicate that  (b) (4) of drug was dissolved at the 0.5 hour time point. The original report was not clear on how the test samples were prepared. It is not clear why the results are reported as % Label Claim Dissolved since you were only trying to demonstrate the stability of crofelemer in acid (crofelemer drug substance could have been used).

Furthermore, it is not clear that a truly stability-indicating-method assay (or suitable combination of methods) was used. Please address our concerns with supportive data.

5. There is some information in the literature indicating that crofelemer is not completely stable in stomach acid (hence the original rationale for using an enteric coating). Furthermore, US Patent 7341744, assigned to the product's innovator, Napo Pharmaceuticals, describes the enteric formulation and includes data suggesting that crofelemer is, in fact, unstable in acid. Please re-evaluate the stability of crofelemer in stomach acid as this relates to the adequacy of controls for the enteric coating and performance of the drug product and submit the results of this evaluation.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE

04/26/2012

Chief, Branch IV



NDA 202292

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Salix Pharmaceuticals, Inc
Attention: Jennifer Richards
Sr. Manager, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated December 05, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crofelemer, 125 mg tablets.

On April 06, 2012, we received your April 06, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 05, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 08, 2012.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA

04/20/2012

Signing for Donna Griebel.

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 06, 2012
Meeting Time: 1:15 PM – 2:00 PM EST
Meeting Type: Teleconference
Applications: NDA 202292 Crofelemer tablets, 125 mg
Sponsor/Applicant: Salix Pharmaceuticals, Inc.
Meeting Chair: Marie Kowblansky, Ph.D.
Meeting Recorder: Kevin Bugin, M.S., R.A.C.

FDA ATTENDEES:

Office of Drug Evaluation III (ODE III)

Julie Beitz, M.D. Director

ODE III/Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D. Director
Anil Rajpal, M.D. Medical Team Leader
Wen-Yi Gao, M.D. Medical Reviewer
Sushanta Chakder, Ph.D. Pharmacology Team Leader
Sruthi King, Ph.D. Pharmacology Reviewer
Kevin Bugin, M.S., R.A.C. Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Kristina Estes, Pharm.D. Reviewer

Office of New Drug Quality Assessment

Marie Kowblansky, Ph.D. Chemistry Lead
Nina Ni, Ph.D. Chemistry Reviewer
Mark Seggel, Ph.D. Biopharmaceutics Reviewer
Terrance Ochletree, Ph.D. Director, DNDQAII

Office of Drug Evaluation IV/Botanical Review Team

Shaw T. Chen, M.D., Ph.D. Deputy Director

EXTERNAL CONSTITUENT ATTENDEES:

Salix Pharmaceuticals, Inc

William Forbes, PharmD, Executive Vice President Research and Development and Chief Development Officer
Craig Paterson, MD, Vice President, Medical and Clinical Development
Linda Young, Vice President, Regulatory
Enoch Bortey, Vice President Clinical Operations
Jody Lockhart, Associate Vice President, Pharmaceutical Development and Manufacturing
Steve Skiendzielewski, Executive Director Manufacturing
Holly Owens, Manager QC Analytical Science
Pam Golden, PhD, Executive Director, Nonclinical and Clinical Pharmacology
Chris Martin, Associate Director, QC Analytical Science
Jennifer Richards, Associate Director, Regulatory

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

BACKGROUND:

Reference is made to NDA 202292 Crofelemer Tablets dated December 5, 2011. On March 29, 2012, FDA requested a teleconference with Salix to discuss chemistry related deficiencies that may impact approvability of the application and the Sponsor's planned response along with timeline for submission of the response. The teleconference was scheduled for April 06, 2012. In preparation for the teleconference discussion, Salix provided the FDA with a submission with their proposed response and timeline.

TELECONFERENCE DISCUSSION:

[The Agency's CMC requests for information are in **bold font** with the Sponsor's response in normal typeface. Discussion from the meeting is captured in ***bold italic*** font.]

Drug Substance - Manufacturing Process

To ensure that the manufacturing process is adequately controlled, please provide:

1. **A description** (b) (4)

Salix is in the process of collecting this information and will provide it by April 30, 2012.

2. **Information regarding** (b) (4)

For any single lot of drug substance produced, (b) (4)

3. **Given the known carcinogenicity of** (b) (4) **which may be present as an impurity in** (b) (4) **its content should be controlled, either in intermediates or in the drug substance.**

Salix is in the process of collecting information on the controls for (b) (4) in the production of (b) (4) raw material, which will be provided by April 30, 2012.

If the (b) (4) manufacturer cannot demonstrate control of (b) (4) levels at or below the USP <467> requirements, appropriate measures will be put in place to control those levels at or below (b) (4) and will be described as appropriate.

4. **Your limits for process variables,** (b) (4) **, should be tightened to reflect ranges used in validation batches.**

Currently Salix is tabulating the information on the process variables from not only the validation batches but also from more than 200 drug substance batches manufactured for use in production of drug product, clinical trial materials, and stability lots. We will provide justification for the ranges for the process variables that are consistent with this comprehensive data set by June 1, 2012.

5. **Justify the wide range of [REDACTED] (b) (4)**
[REDACTED] **. They are not justified based on your**
validation process where the [REDACTED] (b) (4)
[REDACTED] **was specified.**

As described in the response to *Drug Substance - Manufacturing Process* Question 4 above, information from not only the validation batches, but also from more than 200 drug substance batches manufactured for use in production of drug product, clinical trial materials, and stability lots is being compiled. We will provide justification for the [REDACTED] (b) (4) based on this comprehensive data set, which will be provided by June 1, 2012.

6. **Given the possible [REDACTED] (b) (4) susceptibility of the drug substance, please justify (with data) the absence of procedures to exclude these from the manufacturing process.**

Salix is reviewing this issue and will provide a response by April 30, 2012.

Drug Substance - Characterization

1. [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

(b) (4)

Additional Discussion:

N/A

Drug Substance - Specification

- 1. You will need to narrow your (b) (4) assay limits. For five of the six validation batches of your drug substance, the assay range was (b) (4) only one batch (AA0068064) was (b) (4). These values do not justify your proposed broad limits.**

Salix is reexamining the specifications based on more than 200 lots of drug substance, material produced for use in clinical trials, for the production of drug product registration, and for stability lots, as described above. We intend to provide the data and calculations upon which the

proposed specifications were based. We have requested an opportunity to discuss the feasibility of tightening the assay acceptance criterion, in light of the botanical nature of crofelemer.

(b) (4)

For these reasons, the assay range is wider than is customary for most synthetic drug substances.

Additional Discussion:

The Agency noted that it will accept the (b) (4) assay limits but Salix will need to commit to improving the procedure or provide a data-based explanation why it is not possible to do so.

2. **Revise the drug substance specification to include controls for impurities with the (b) (4) or (b) (4) moiety, which you suggest may be present at levels up to (b) (4) or provide justification (with data) why such controls are not required.**

There is no “(b) (4) moiety in crofelemer. As described in the Quality Section of the NDA, structurally the visible data of crofelemer suggest the presence of a (b) (4)

(b) (4)

(b) (4)

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(b) (4)

Drug Product

- 1. Since the assay procedure is the same as the procedure for the drug substance, our questions regarding the stability indicating nature of the procedure are the same as discussed above. Assay acceptance criterion also needs to be tightened.**

See response to *Drug Substance – Specification* Request No. 4, above. Thirteen lots of drug product have been produced for use in clinical trials and for NDA stability studies. Salix will provide the data and calculations upon which the proposed specifications were based. We would like to discuss your request to tighten the assay acceptance criterion, in light of the botanical nature of crofelemer.

- 2. Only an abbreviated method validation report is provided for the HPLC determination of crofelemer related substances in tablets. Provide a full method validation report that includes forced degradation studies for this drug product procedure.**

Full method validation reports for the assay and related substances in tablets will be provided by April 30, 2012. These will include forced degradation studies for the drug product procedures

- 3.**

(b) (4)

Based on our discussion with FDA during the March 15, 2012 teleconference, Salix has chosen to print the tablet with an appropriate identifier for commercialization (b) (4)

The proposed commercial master batch record inclusive of the printing process will be provided along with technical information on the proposed black ink by April 30, 2012. We will also provide an updated regulatory specification to show the change in the identifier.

4. **Provide data to support your selected in-process controls and acceptance criteria (Table 1 in section 3.2.P.3.3). In particular, provide data to support the specified targets and ranges for core tablet hardness (b) (4) and for film coat weight (b) (4)**

Salix is currently tabulating the entire body of data associated with crofelemer drug product manufacturing. These data encompass the thirteen lots of drug product manufactured as both clinical trial materials and stability batches. Based on this review, we will provide data for core tablet hardness and film coat weight to justify the proposed target and range values for these attributes, which we will provide by April 30, 2012.

Biopharmaceutics

1. (b) (4)
- (b) (4)
- (b) (4)

Additional Discussion:

The Agency acknowledged Salix's acceptance to use USP <711> and encouraged the Sponsor to continue on this path.

2. **As an enteric coated formulation, crofelemer tablets should be tested in accordance with USP <711> Dissolution, Delayed-Release Dosage Forms. Dissolution profiles should be obtained at 50, 75, and 100 rpm to determine the most appropriate paddle speed. As noted in the 07-FEB-2012 communication, the acceptance criteria should**

be established in both acid stage and buffer stage using the same set of units, as follow:

- **Acid Stage:** no individual unit exceeds (b) (4) dissolved at 2 hours.
- **Buffer Stage:** the selection of the time point should be where $Q =$ (b) (4) dissolution occurs.

Please see the response to *Biopharmaceutics*, Request No. 1, above.

3. **Please account for the inter- and intra-lot variability in dissolution results for the primary stability batches at the six-month time point (3.2.P.2 Pharmaceutical Development, Sequence 0004), and describe the controls established to limit this variability. If available, please submit the dissolution profiles for uncoated tablets in the buffer stage. Similar variability is noted in Table 3 of Section 3.2.P.5.4 batch Analyses.**

Salix is currently evaluating all dissolution data available for the drug product, along with the data currently being generated in support of *Biopharmaceutics*, Requests Nos. 1 and 2, above. We will provide an evaluation of those data and our thoughts on the cause of the stated variability by June 1, 2012. At this time, no data are available comparing dissolution rates between uncoated cores and their respective coated tablets.

4. **Please submit the dissolution profiles obtained using the USP <711> 2-stage dissolution procedure for:**
- **All Phase III clinical trial materials, including the encapsulated beads.**
 - **The stability batches (including, but not limited to, the primary stability batches under long term and accelerated stability). We note that the six-month 25°C/60% RH data have been provided.**
 - **The validation batches, if available.**

(b) (4)

(b) (4)

(b) (4)

5. Please clarify how the data in Table 12 (3.2.P.2, Dissolution Results for Crofelemer Tablets, (b) (4) were obtained. The results indicate that (b) (4) was dissolved at the 0.5 hour time point.

The data in Table 12 of 3.2.P.2 represents a study to determine the stability of crofelemer in acidic conditions in the presence of tablet excipient materials. (b) (4)

(b) (4)

6. Please provide a tabulation of the quantitative compositions of all crofelemer formulations used in the clinical trials.

As discussed above, since Salix was not the originator of the product, we are currently reviewing the available information for the formulations used in clinical studies that were developed by the drug's prior sponsors. The quantitative compositions will be tabulated, as available, and will be submitted by June 1, 2012.

Additional Discussion:

The Agency clarified that the date for receiving additional information, July 30, 2012, will be a cut-off date. Given the uncertainty of resolving the pre-approval issues prior to the PDUFA date, the Agency offered a parallel activity or option to open a treatment IND. This could provide patients access to the drug, while the CMC issues are resolved.

Salix acknowledged the suggestion and would consider it.

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/s/

KEVIN B BUGIN
05/02/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Clinical Information Request - March 27, 2012
Date: Tuesday, March 27, 2012 10:35:56 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crofelemer.

In reviewing the clinical sections of your submission and we have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

In Studies 37544-209 and 37544-210, you have not provided subgroup analyses by concomitant protease inhibitor (PI) use. Provide a table for each study showing descriptive statistics for the following by treatment group in subgroups defined by concomitant PI use (≥ 1 PI and no PI):

- stool weight at baseline
- change in stool weight from baseline to the end of the inpatient treatment period

(The table for Study 37544-209 should look substantially like Table 10 on Page 36 of the 37544-209 Study Report except that the results are subgrouped by concomitant PI use. Similarly, the table for Study 37544-210 should look substantially like Table 12 on Page 46 of the 37544-210 Study Report except that the results are subgrouped by concomitant PI use.)

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

++++
If you are not the intended recipient you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2302 or by return e-mail.

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

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/s/

KEVIN B BUGIN
03/27/2012



NDA 202292

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Salix Pharmaceuticals, Inc
8510 Colonnade Center Drive
Raleigh, NC 27615

ATTENTION: Jennifer Richards
Sr. Manager, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated and received December 5, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Crofelemer Tablets, 125 mg.

We also refer to your December 21, 2011, correspondence, received December 22, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that this name is unacceptable for the following reasons:

1.

(b) (4)

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(b) (4)

We note that you have not proposed an alternate proprietary name in your submission dated December 21, 2011. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Kevin Bugin at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk
Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/20/2012



NDA 202292

INFORMATION REQUEST

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Senior Manager, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer) Tablets, 125 mg.

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

Drug Substance - Manufacturing Process:

To ensure that the manufacturing process is adequately controlled, please provide:

1. A description (including molecular weight cut-off), installation, and operation of (b) (4).
2. Information regarding the (b) (4).
3. Given the known carcinogenicity of (b) (4) which may be present as an impurity in (b) (4) its content should be controlled, either in intermediates or in the drug substance.
4. Your limits for process variables, such as (b) (4) should be tightened to reflect ranges used in validation batches.
5. Justify the wide range of (b) (4). They are not justified based on your validation process where the (b) (4) was specified.
6. Given the possible (b) (4) susceptibility of the drug substance, please justify (with data) the absence of procedures to exclude these from the manufacturing process.

Drug Substance - Characterization:

1. As requested by FDA, you have characterized your drug substance in terms of the (b) (4).

(b) (4)

Drug Substance - Specification:

1. You will need to narrow your (b) (4) assay limits. For five of the six validation batches of your drug substance, the assay range was (b) (4) only one batch (AA0068064) was (b) (4). These values do not justify your proposed broad limits.
2. Revise the drug substance specification to include controls for impurities with the (b) (4) or (b) (4) moiety, which you suggest may be present at levels up to (b) (4) or provide justification (with data) why such controls are not required.
3. Add optical rotation testing to the drug substance specification, with acceptance limits based on clinical batches.
4. The forced degradation study results show a significant increase in the crofelemer peak for samples subjected to (b) (4) this was evident in both your assay and related substance HPLC methods, indicating both methods are not stability indicating. You will need to revise both methods and reevaluate the stability of your drug substance with the new method.
5. Acceptance criteria for average molecular weight as determined from end-group analysis should be included in the drug substance specification. These should be based on clinical batches.
6. Your proposed limits of (b) (4) are too liberal when compared with the (b) (4) range for batches used in clinical trials. Please revise the limits to (b) (4).
7. Data to establish the oligomer composition and distribution in crofelemer batches used in clinical trials needs to be submitted. Acceptance criteria based on the clinical batches should be added to the drug substance specification.

Drug Product:

1. Since the assay procedure is the same as the procedure for the drug substance, our questions regarding the stability indicating nature of the procedure are the same as discussed above. Assay acceptance criterion also needs to be tightened.
2. Only an abbreviated method validation report is provided for the HPLC determination of crofelemer related substances in tablets. Provide a full method validation report that includes forced degradation studies for this drug product procedure.

3. (b) (4)

4. Provide data to support your selected in-process controls and acceptance criteria (Table 1 in section 3.2.P.3.3). In particular, provide data to support the specified targets and ranges for core tablet hardness (b) (4) and for film coat weight (b) (4)

Biopharmaceutics:

1. Your proposal (Response to FDA Request 5, 24-FEB-2012), (b) (4) is not acceptable. Also, your proposal of $Q =$ (b) (4) (where dissolution is $\geq$ (b) (4) for the buffer stage is not acceptable.
2. As an enteric coated formulation, crofelemer tablets should be tested in accordance with USP <711> Dissolution, Delayed-Release Dosage Forms. Dissolution profiles should be obtained at 50, 75, and 100 rpm to determine the most appropriate paddle speed. As noted in the 07-FEB-2012 communication, the acceptance criteria should be established in both acid stage and buffer stage using the same set of units, as follow:
 - Acid Stage: no individual unit exceeds (b) (4) dissolved at 2 hours.
 - Buffer Stage: the selection of the time point should be where $Q =$ (b) (4) dissolution occurs.
3. Please account for the inter- and intra-lot variability in dissolution results for the primary stability batches at the six-month time point (3.2.P.2 Pharmaceutical Development, Sequence 0004), and describe the controls established to limit this variability. If available, please submit the dissolution profiles for uncoated tablets in the buffer stage. Similar variability is noted in Table 3 of Section 3.2.P.5.4 batch Analyses.
4. Please submit the dissolution profiles obtained using the USP <711> 2-stage dissolution procedure for:
 - All Phase III clinical trial materials, including the encapsulated beads.
 - The stability batches (including, but not limited to, the primary stability batches under long term and accelerated stability). We note that the six-month 25°C/60% RH data have been provided.
 - The validation batches, if available.
5. Please clarify how the data in Table 12 (3.2.P.2, Dissolution Results for Crofelemer Tablets, (b) (4) were obtained. The results indicate that $\geq$ (b) (4) was dissolved at the 0.5 hour time point.
6. Please provide a tabulation of the quantitative compositions of all crofelemer formulations used in the clinical trials.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE

03/20/2012

Chief, Branch IV



NDA 202292

INFORMATION REQUEST

Salix Pharmaceuticals, Inc
Attention: Jennifer Richards
Sr. Manager, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer) tablets, 125 mg.

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

1. In Table 8 of the NP303-101 Study Report (Page 79), you have provided the number of patients by treatment group that were excluded from the PP population due to “Pathogen in stool related to diarrhea at screening,” but you have not provided the names of the pathogens. Provide the names of the pathogens in a data listing by subject identification number. Indicate the treatment group and Stage (1 or 2) for each of the patients.
2. In Table 10 of the NP303-101 Study Report (Page 83) and in Table 14.1.5.3 (Pages 88 to 105 of the demo.pdf document), you have provided descriptive statistics for the baseline number of daily watery bowel movements by treatment group and by Stage. We request that you provide a summary table showing the proportion of patients with baseline number of daily watery bowel movements > 2 and ≤ 2 by treatment group and by Stage. The table should look substantially like the following:

Baseline Number of Daily Watery Bowel Movements	Stage 1				Stage 2	
	125 mg (n=44)	250 mg (n=54)	500 mg (n=46)	Plac (n=50)	125 mg (n=92)	Plac (n=88)
> 2	a/44 (%)	b/54 (%)	c/46 (%)	d/50 (%)	e/92 (%)	f/88 (%)
≤ 2	g/44 (%)	h/54 (%)	i/46 (%)	j/50 (%)	k/92 (%)	m/88 (%)

Also submit an electronic dataset that includes the following fields (by subject identification number): (1) category of baseline number of daily watery bowel movements (>2 or ≤ 2); (2) baseline number of daily watery bowel movements; (3)

treatment group; and (4) stage. (Note that one electronic dataset may be submitted that includes the fields from tables in Items 2, 3, 4, and 5 of this Information Request Letter.)

3. In Table 22 of the NP303-101 Study Report (Page 98), you have provided a subgroup analysis by baseline number of daily watery bowel movements (> 2 and ≤ 2) for the 125 mg and placebo groups. However, you have not provided the results of this subgroup analysis by stage, and you have not included the other treatment groups. Provide a table showing the proportion of patients in clinical response by treatment group and stage in subgroups defined by baseline number of daily watery bowel movements (> 2 and ≤ 2). The table should look substantially like the following:

Clinical Response by Baseline Number of Daily Watery BM's						
Baseline Number of Daily Watery Bowel Movements	Stage 1				Stage 2	
	125 mg (n=44)	250 mg (n=54)	500 mg (n=46)	Plac (n=50)	125 mg (n=92)	Plac (n=88)
> 2	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
≤ 2	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)

Also submit an electronic dataset that includes the following fields (by subject identification number): (1) clinical response status; (2) category of baseline number of daily watery bowel movements (>2 or ≤ 2); (3) baseline number of daily watery bowel movements; (4) treatment group; and (5) stage.

4. In Table 13 of the NP303-101 Study Report (Page 86) and in Table 14.1.5.3 (Pages 88 to 105 of the demo.pdf document), you have provided descriptive statistics for the baseline CD4 cell count and you have provided the proportion of patients with baseline CD4 count < 404 cells/ μ L and ≥ 404 cells/ μ L by treatment group and by Stage. You have stated the number of patients with CD4 count < 200 cells/ μ L by treatment group on Page 93 of the Summary of Clinical Efficacy, but you have not provided a summary table by treatment group and Stage. We request that you provide a summary table showing the proportion of patients with baseline CD4 count < 200 cells/ μ L and ≥ 200 cells/ μ L by treatment group and by Stage. The table should look substantially like the following:

Baseline CD4 cell count [cells/ μ L]	Stage 1				Stage 2	
	125 mg (n=44)	250 mg (n=54)	500 mg (n=46)	Plac (n=50)	125 mg (n=92)	Plac (n=88)
< 200	a/44 (%)	b/54 (%)	c/46 (%)	d/50 (%)	e/92 (%)	f/88 (%)
≥ 200	g/44 (%)	h/54 (%)	i/46 (%)	j/50 (%)	k/92 (%)	m/88 (%)

Also submit an electronic dataset that includes the following fields (by subject identification number): (1) baseline CD4 cell count category (<200 cells/ μ L or ≥ 200 cells/ μ L); (2) baseline CD4 cell count [cells/ μ L]; (3) treatment group; and (4) stage.

5. Provide a table showing the proportion of patients in clinical response by treatment group and stage in subgroups defined by baseline CD4 cell count (< 200 cells/ μ L and ≥ 200 cells/ μ L). The table should look substantially like the following:

Clinical Response by Baseline CD4 Cell Count						
Baseline CD4 cell count [cells/ μ L]	Stage 1				Stage 2	
	125 mg (n=44)	250 mg (n=54)	500 mg (n=46)	Plac (n=50)	125 mg (n=92)	Plac (n=88)
< 200	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
$\geq$ 200	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)

Also submit an electronic dataset that includes the following fields (by subject identification number): (1) clinical response status; (2) baseline CD4 cell count category (<200 cells/ μ L or $\geq$ 200 cells/ μ L); (3) baseline CD4 cell count [cells/ μ L]; (4) treatment group; and (5) stage.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
03/12/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Clinical Information Request - February 29, 2012
Date: Wednesday, February 29, 2012 8:55:44 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer).

We are reviewing the Clinical sections of your submission and have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

In Table 11 of the NP303-101 Study Report (page 84), you have provided the proportions of patients that reported prior antidiarrheal medication (ADM) use by treatment group. However, you have not provided this information subgrouped by Stage (Stage 1 and Stage 2). Please provide a summary table showing the proportion of patients that reported prior ADM use by treatment group (similar to Table 11) except subgrouped by stage (Stage 1 and Stage 2). The table should look substantially like the following:

Prior ADM Use	Stage 1				Stage 2	
	125 mg (n=44)	250 mg (n=54)	500 mg (n=46)	Plac (n=50)	125 mg (n=92)	Plac (n=88)
Any ADM	a/44 (%)	b/54 (%)	c/46 (%)	d/50 (%)	e/92 (%)	f/88 (%)
Loperamide hydrochloride	a/44 (%)	b/54 (%)	c/46 (%)	d/50 (%)	e/92 (%)	f/88 (%)
Lomotil	a/44 (%)	b/54 (%)	c/46 (%)	d/50 (%)	e/92 (%)	f/88 (%)
Bismuth subsalicylate	a/44 (%)	b/54 (%)	c/46 (%)	d/50 (%)	e/92 (%)	f/88 (%)
Loperamide	a/44 (%)	b/54 (%)	c/46 (%)	d/50 (%)	e/92 (%)	f/88 (%)

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
02/29/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 Crofelemer - Statistics Information Request - February 28, 2012
Date: Tuesday, February 28, 2012 3:32:54 PM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer).

We are reviewing Statistics sections of your submission and have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

The following requests refer to NP303-101:

1. The meeting minutes from the Independent Analysis Committee that you submitted on February 14, 2012, (eCTD seq 0003) indicate (b) (4) submitted an additional note after the meeting. Please submit a copy of that note.
2. Confirm that these meeting minutes constitute the 'Dose Selection Report' that is described in the study protocol. If this is not the case, please submit the Dose Selection Report.
3. Provide a detailed discussion of the procedures and methodologies used to determine the use of prohibited medications, especially the use of anti-diarrhea medications or opiate pain medications. At a minimum, identify who reviewed the case report forms (CRFs), describe the standard operating procedures used for the reviews, describe whether the reviews were done prior to unblinding the study data, describe whether CRFs from unscheduled visits were included, identify and discuss the algorithms that were used to combine the data from the CRFs and the IVRS, and describe the role of the telephone contacts in determining the use of prohibited medications.

The reason for this request is that the study protocol and the clinical study report describe different approaches to capturing the use of prohibited medications. The estimates of response rates and treatment effects depend on the approach used. The protocol indicates the IVRS data would be used. Indeed, the clinical response endpoint used in the interim analysis was defined based on the IVRS data; see Sections 5.9.1 and 6.1.3 of the study protocol. However, the Clinical Study Report indicates the final analysis used a combination of data recorded on the CRFs and data captured by the IVRS, see Section 11.4.1.3 of the Clinical Study Report. The use of the data from the CRFs does not appear to have been pre-specified.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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F-301-796-9904

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/s/

KEVIN B BUGIN
08/15/2012



NDA 202292

FILING COMMUNICATION

Salix Pharmaceuticals, Inc
Attention: Jennifer Richards
Sr. Manager, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated December 05, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (crofelemer) 125 mg tablets.

We also refer to your submissions dated December 21, 2011, January 05, 2012, and February 14, 2012.

During our filing review of your application, we identified the following potential review issues:

1. (b) (4)
2. The certificate of analysis for crofelemer reference standard does not report the purity of this material. (b) (4)
(b) (4). Assay values that are reported throughout the submission should then be recalculated based on the purity of the reference standard that was used.
3. The (b) (4) used for determining molecular weights of the crofelemer drug substance suffers from a number of uncertainties. The two major issues are related to: (1) (b) (4)
(2) (b) (4)

To address our concerns, provide the following information:

- Data to establish the oligomer composition and distribution in crofelemer batches used in clinical trials. Based on literature reports for other procyanidins, HPLC/MS methods will likely be useful for this purpose.
 - Data from an independent determination of the number average molecular weight M_n (b) (4) for batches used in clinical trials. For this purpose, end group analysis would be acceptable. You may already have the raw data for this purpose from the (b) (4) experiments that were performed to determine the procyanidin/prodelphinidin ratio.
4. Limits for procyanidin/prodelphinidin ratio needs to be added to the drug substance specification.
 5. (b) (4)
your product is nonetheless a delayed-release dosage form. Drug release should therefore be determined using dissolution test conditions appropriate for a delayed-release dosage form. Refer to USP<711> Dissolution, Delayed-Release Dosage Forms. A single test with both acid stage and buffer stage should be developed. The acceptance criteria for your enteric coated product should be established in both the acid stage and the buffer stage as follows:
 - **Acid Stage:** No individual tablet exceeds (b) (4) dissolved at 2 hours.
 - **Buffer Stage:** The selection of the specification-time point should be where Q (b) (4) dissolution occurs.
 6. Data from a comparability study linking the current methods (acid resistance and dissolution) to the (b) (4) test will be needed to allow use of the batch release and stability data already submitted to the NDA. Acceptance criteria should be proposed.
 7. A dissolution development report documenting the justification of the selected test conditions should be provided. In order to establish acceptance criteria, complete dissolution profiles should be collected. Note that individual tablet results should be submitted.
 8. In order to allow us to fully interpret the dissolution data obtained at release and on stability testing using QCTP-235 and QCTP-238, and provided in the initial NDA submission, submit results for the individual tablet tested.
 9. Provide a more detailed and accurate map of the (b) (4) EcoGeographic Growing Regions (EGR) (with GPS coordinates, if possible).
 10. Provide a list of historic crofelemer (or similar products) and drug substance batches manufactured from CPL batches collected from EGRs (b) (4). Provide non-clinical and/or clinical data, if available, on products derived from BRM batches that are collected from EGRs (b) (4).

11. Compare the analytical data of representative batches of Crude Plant Latex (CPL) botanical raw material (BRM) from different EGRs to show levels of naturally occurring variations in their chemical profiles. Particularly, compare samples of CPL, drug substance and drug product from EGRs (b) (4) to the EGRs (b) (4).
12. Batches of BRM from different EGRs may need bridging data (CMC, non-clinical and/or clinical) to show that they are inter-changeable for clinical use.
13. Provide analytical data comparing representative batches of CPL from both wild grown and re-forested *Croton lechleri* tree to show levels of naturally occurring variations.
14. Clarify why one batch (No. RARM061378) of CPL contains crofelemer content at (b) (4), which is lower than the specification of NLT (b) (4). [see Section 3.2.S.2.3 Control of Materials, “Crofelemer Crude Plant latex - Botanical Raw Material Information”, Table 3 on page 24].

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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action. [See 21 CFR 201.57(a)(3)]
2. If a section or subsection is omitted from the full prescribing information (FPI) and table of contents (TOC), the heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
3. A horizontal line must separate the TOC and FPI.

We request that you resubmit labeling that addresses these issues by March 09, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
02/17/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 (b) (4) (crofelemer) - Quality (CMC, Biopharm, and Botanicals) Information Request - February 07, 2012
Date: Tuesday, February 07, 2012 10:11:48 AM

Hi Jennifer,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer).

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

1. (b) (4)
(b) (4)
(b) (4)
(b) (4)
2. The certificate of analysis for crofelemer reference standard does not report the purity of this material. (b) (4)
(b) (4)
(b) (4) Assay values that are reported throughout the submission should then be recalculated based on the purity of the reference standard that was used.
3. The (b) (4) used for determining molecular weights of the crofelemer drug substance suffers from a number of uncertainties. The two major ones are related to 1) (b) (4)
(b) (4)
(b) (4)
(b) (4).

To address our concerns, please provide the following information:

- Data to establish the oligomer composition and distribution in crofelemer batches used in clinical trials. Based on literature reports for other procyanidins, HPLC/MS methods will likely be useful for this purpose.
 - Data from an independent determination of Mn (b) (4) for batches used in clinical trials. For this purpose end group analysis would be acceptable. You may already have the raw data for this purpose from the (b) (4) experiments that were performed to determine the procyanidin/prodelphinidin ratio.
4. Please add procyanidin/prodelphinidin ratio to the drug substance specification.
 5. (b) (4) your product is nonetheless a delayed-release dosage form. Drug release should therefore be determined using dissolution test conditions appropriate for a delayed-release dosage form. Please refer to USP<711> Dissolution, Delayed-Release Dosage Forms. A single test with

both acid stage and buffer stage should be developed. The acceptance criteria for your enteric coated product should be established in both, acid stage and buffer stage as follow:

- **Acid Stage:** *No individual tablet exceeds (b) (4) dissolved at 2 hours.*
- **Buffer Stage:** *the selection of the specification-time point should be where Q (b) (4) dissolution occurs.*

6. Data from a comparability study linking the current methods (acid resistance and dissolution) to the (b) (4) will be needed to allow use of the batch release and stability already submitted to the NDA. Acceptance criteria should be proposed.
7. A dissolution development report documenting the justification of the selected test conditions should be provided. In order to establish acceptance criteria, complete dissolution profiles should be collected. Please note that individual tablet results should be submitted.
8. In order to fully interpret the dissolution data obtained at release and on stability using QCTP-235 and QCTP-238, and provided in the initial NDA submission, please submit results for individual tablet tested.
9. Provide more detailed and accurate map of the (b) (4) EcoGeographic Growing Regions (EGRs, with GPS locations, if possible).
10. Compare the analytical data of representative batches of Crude Plant Latex (CPL) botanical raw material (BRM) from different EGRs to show levels of naturally occurring variations in their chemical profiles. Particularly, CPL/drug substance/product samples from EGRs (b) (4) should be compared with the samples from EGRs (b) (4).
11. Provide analytical data of representative batches of CPL from cultivated and wild grown *Croton lechleri* tree to show levels of naturally occurring variations.
12. Provide a list of historic Crofelemer (or similar products) and drug substance batches manufactured from CPL batches collected from EGRs (b) (4). If some of the batches from EGRs (b) (4) have been tested in human clinical trials, provide summaries of safety and efficacy data and compare with the clinical data of the phase 3 trials.
13. Provide clarification why one batch (No. RARM061378) of CPL contains Crofelemer content at (b) (4) lower than the specification of NLT (b) (4) [Section 3.2.S.2.3 Control of Materials), "Crofelemer Crude Plant latex - Botanical Raw Material Information", Table 3 on page 24].

We request that you respond to these information requests by February 24, 2012. If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
02/07/2012



NDA 202292

PRIORITY REVIEW DESIGNATION

Salix Pharmaceuticals, Inc
Attention: Jennifer Richards
Sr. Manager, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated December 05, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (Crofelemer) 125 mg tablets.

We also refer to your submissions dated December 21, 2011, and January 05, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is June 05, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 08, 2012.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before February 17, 2012.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D. F.A.A.P., C.P.I.
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
02/03/2012

From: [Bugin, Kevin](#)
To: [Richards, Jennifer <Jennifer.Richards@salix.com>](#) ([Jennifer.Richards@salix.com](#))
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 (b) (4) (crofelemer) - Clinical, Statistics and Clinical Pharmacology Information Request - January 31, 2012
Date: Tuesday, January 31, 2012 3:22:10 PM

Hi Jennifer

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (crofelemer).

We are reviewing the clinical, statistics and clinical pharmacology sections of your submission and have the following comments and requests for information. We request prompt written response in order to continue evaluation of your NDA.

1. The proportion of patients achieving Clinical Response during the placebo-controlled (PC) phase of Study NP-303-101 is summarized by drug product lot number and treatment group in Table 26 (page 97) of the Summary of Clinical Efficacy (SCE).
 - a. Source data by individual patient were not provided. Provide a data listing with the subject identification number, drug product lot number, treatment group, Stage (1 or 2), and Clinical Response status. Please also submit an electronic dataset that includes each of these fields.
 - b. It is not clear if "Clinical Response" in Table 26 refers to the Primary Endpoint. Page 66 of the Protocol states "The primary efficacy endpoint is clinical response, defined as two or less watery bowel movements per week, during at least two of the four weeks of the 4-week efficacy assessment period of the placebo-controlled treatment phase in the ITT population." The text above the table states "Table 26 presents a summary of clinical response in the PC phase or PF phase of ADVENT during the PC phase by crofelemer drug product lot number and treatment group." (See Page 96 of the SCE.) Please clarify.
2. For Study NP-303-101, provide the adverse event "coding dictionary" consisting of a list of all investigator verbatim terms and the preferred terms to which they were mapped. Please submit this as a SAS transport file.
3. In Figure 9 of the NP-303-101 Study Report (page 108), it is not clear if the percentage of subjects with clinical response by week is for Stage 1, Stage 2, or combined Stage 1 and Stage 2. Please clarify. We request that you provide figures showing the percentage of subjects with clinical response by week for Stage 1, Stage 2, and combined Stage 1 and Stage 2.
4. In Table 12 of the NP-303-101 Study Report (page 85), you have provided the proportion of patients during the PC phase that received concomitant anti-diarrheal medications by treatment group. However, you have not provided this information by Stage (1 versus 2) and

you have not provided this information for the placebo-free (PF) phase. Please provide a summary table showing the proportion of patients that received concomitant anti-diarrheal medications by treatment group, phase (PC and PF), and stage (Stage 1, Stage 2, and combined). Please also submit an electronic dataset that includes each of these fields by subject identification number.

5. For Study NP-303-101, provide a summary table showing the duration (mean +/- SD, median, min, max) of concomitant anti-diarrheal medication use by treatment group, phase (PC and PF), and stage (Stage 1, Stage 2, and combined). Please also submit an electronic dataset that includes each of these fields by subject identification number.
6. Please identify the location of the minutes for the independent analysis committee meeting that was convened for Study NP-303-101. We note the submission contains an "Interim Analysis Report" in Appendix 16.1.9.4 of the NP-303-01 Study Report. However, we are looking for the minutes that describe the discussion surrounding the dose that was selected for the second phase of the study.
7. Provide the pharmacokinetic data in SAS transport (.xpt) format from Studies 37554-103 and NP-303-101.

We request that you respond to these information requests by February 17, 2012. If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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/s/

KEVIN B BUGIN
01/31/2012

From: [Bugin, Kevin](#)
To: ["Richards, Jennifer"](#)
Cc: [Bugin, Kevin](#)
Subject: NDA 202292 - Request for Carton and Container Labels - December 23, 2011
Date: Friday, December 23, 2011 9:02:27 AM

Hi Jennifer,

During the review of NDA 202292 for Crofelemer we have been unable to locate the carton and container labels for your finished product. These will need to be submitted for review. Also, we are aware of the recent request for proprietary name review. As part of the name review you will also need to submit the updated carton and container labels with the proposed name.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

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/s/

KEVIN B BUGIN
01/05/2012



NDA 202292

NDA ACKNOWLEDGMENT

Salix Pharmaceuticals, Inc
Attention: Jennifer Richards
Sr. Manager, Regulatory Affairs
8510 Colonnade Center Drive
Raleigh, NC 27615

Dear Ms. Richards:

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

Name of Drug Product: Crofelemer Tablets, 125 mg

Date of Application: December 05, 2011

Date of Receipt: December 05, 2011

Our Reference Number: NDA 202292

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 03, 2012, 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(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should 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 and Inborn Errors 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors 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/

KEVIN B BUGIN
12/16/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 51, 818

MEETING MINUTES

Salix Pharmaceuticals, Inc.
Attention: Gail Glifort
Associate Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Glifort:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Crofelemer (NP-303).

We also refer to the meeting between representatives of your firm and the FDA on May 24, 2011. The purpose of the meeting was to follow up on CMC questions from January 19, 2011 pre-NDA meeting and to review the status of crofelemer manufacturing development process.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cathy Tran-Zwanetz at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 24, 2011 at 10:00 AM
Meeting Location: FDA, White Oak, Building 22, Room 1417

Application Number: IND 51,818
Product Name: Crofelemer
Indication: The treatment of diarrhea in HIV-positive patients.
Sponsor/Applicant Name: Salix

Meeting Chair: Marie Kowblansky, Ph.D.
Meeting Recorder: Michael Folkendt

FDA ATTENDEES

Office of New Drug Quality Assessment

Marie Kowblansky, Ph.D., CMC Lead

Michael Folkendt, M.S., ADRA

Cathy Tran-Zwanetz, Regulatory Project Manager

Office of New Drug

Nancy Snow, M.D., Medical Officer

Erica Wynn, M.D., M.P.H., Medical Officer

Kevin Bugin, Regulatory Project Manager

Shaw Chen, Ph.D., M.D., Deputy Director, Office of Drug Evaluation IV, Botanical Review Team Leader

Jinhui Dou, Ph.D., Pharmacologist, Botanical Review Team

SPONSOR ATTENDEES

William Forbes, PharmD, Executive Vice President, R&D and Chief Development Officer

Joseph Lockhart, Associate Vice President, Pharmaceutical Development and Manufacturing

Steve Skiendzielewski, Executive Director, Manufacturing

Enoch Bortey, Vice President, Biostatistic

Pam Golden, Ph.D., Director, Nonclinical and Clinical Pharmacology, R&D

Christopher Martin, Associate Director, QC Analytical Science

Holly Owens, Manager, QC Analytical Science

Jennifer Richards, Senior Manager, Regulatory Affairs

Steven Smith, Regulatory Document Publisher

(b) (4)

(b) (4)

1.0 BACKGROUND

The purpose of the meeting is review Salix's responses to the Agency's CMC questions posed at the pre-NDA meeting held on January 19, 2011 and to review the status of the crofelemer manufacturing development program with the Division.

The specific objectives and outcomes expected from the meeting include the following:

- Review Salix's responses to the CMC questions posed by the FDA at the pre-NDA meeting held on January 19, 2011 and obtain concurrence that these responses provide the Agency with the information requested.
- Review and discuss the source, identification and harvesting of the starting material (*Croton lechleri* crude plant latex).
- Review and discuss the manufacturing and controls of the drug substance and obtain concurrence that the information to be provided in the NDA supports lot-to-lot consistency.
- Review and discuss the manufacturing and controls of the drug product (Crofelemer Tablets 125 mg) and obtain concurrence that the information to be provided in the NDA supports lot-to-lot consistency.

2. DISCUSSION

1. Salix has provided responses to the FDA's questions from the January 19, 2011 pre-NDA meeting (see Section 8.0). Do the responses provided, along with the Attachments to this document, sufficiently answer the questions posed?

FDA Response:

No, they do not. At the January 2011 meeting, FDA emphasized the need for setting specifications and controls that would ensure that the polymeric structure of the drug substance used to manufacture the commercial product would be consistently the same as was used in the clinical batches. Specifically, the need for controlling the ratio of the monomers that constitute the cofelemer copolymer was discussed.

(b) (4)

While we are not requesting that you determine the sequence of the monomers, you will need to include limits for the catechin/gallocatechin ratio as an identity test in your drug product specification. If you can demonstrate from clinical data that efficacy is not dependent on the monomer composition, this requirement can be waived.

Discussion:

- The above FDA response refers to the drug substance specification, not the drug product specification.
- FDA emphasizes that the catechin/gallocatechin ratio will need to be determined as an identity test. However, determination of the stereochemistry of the two monomers will not be required. Salix should evaluate the clinical effect of varying the monomer ratio as part of the current open-label study. Since the current protocol is an open-label safety study, Salix will add an efficacy component to this study, unless appropriate data can be provided from previous clinical trial material.
- FDA will give additional thought to whether the monomer ratio identity test can be dropped if the outcome from the clinical trial shows no correlation to the ratio.

Crude Plant Latex:

2. Does the Agency concur that:

a. The identification of the plant species, *Croton lechleri*, from which the CPL is extracted is adequate?

FDA Response:

Yes, the section 1.2 “Botanical identification and description of species (*Croton lechleri*)” in the meeting package provided adequate information.

Discussion:

Salix concurs with the FDA comments.

b. The collection process for the CPL is adequately described and controlled?

FDA Response:

Your field collectors of CPL are trained to identify *Croton lechleri* with leaves (glands on the petiole) and the miniature leaf-like stipules on the young stems. This approach appears simple and practical. Please comment on whether further training on the identification of the plant species by its flowers and fruits is needed.

We recommend that you establish minimum age of the tree (e.g., ≥ 7 years) or minimum size of the tree (e.g., diameter at breast height/DBH ≥ 10 cm) that is suitable for sustained collection of latex.

Currently, CPL is collected by first cutting down the tree of *Croton lechleri*. Please comment on the possibility of collecting CPL multiple times without cutting down the tree.

You will need to consult the Environmental Assessment staff regarding the environmental information that will need to be submitted with this NDA.

Discussion:

Salix will take the FDA suggestions in advisement and will be providing more details in the NDA. Some of the material used in clinical trials was wild and some was cultivated. For EA, Salix will provide information in the NDA on the sustainability and reforestation of the tree. Salix will also provide more info on how the tree is grown and on cultivator training in the NDA. Additional information on this topic may be found in FDA's ***Guidance for Industry: Botanical Drug Products***.

c. The methods used for quality control testing are reasonable and adequate to maintain lot-to-lot consistency?

FDA Response:

You have not submitted enough batch data to allow us to comment on the relationship between the raw material (CPL) specifications and the chemical profile of the drug substance, and thus we could not comment on whether the quality control of the CPL is adequate to maintain lot-to-lot consistency of the drug substance/product.

We recommend that you modify some of the specifications for the CPL, such as content of taspine, total phenolics, content of crofelemer, chromatographic purity, to include both the minimum and the maximum levels.

Discussion:

Salix agrees and will provide additional information, including ranges for the specifications.

Crofelemer Drug Substance:

3. Does the Agency concur that
a. the proposed manufacturing process is robust and well-controlled and adequate to maintain lot-to-lot consistency?

FDA Response:

It is not possible to comment on the adequacy of the manufacturing operation based on the limited information that has been provided in the briefing package. In the NDA submission you will need to describe in-process controls with acceptance criteria, why they are important to ensure a consistent drug substance, and show the effect of these controls on batch data.

Discussion:

Salix agrees with the comments and will be providing more extensive info in the NDA.

b. the proposed specifications and methods are appropriate?

FDA Response:

As discussed under item 1 above, the drug substance specification will need to include limits for the monomer ratio as an identity test. The (b) (4) limits for assay (b) (4) are unusually broad and will likely need to be narrowed. From the limited material in the briefing package it is not clear why such liberal limits are required: is it due to batch to batch variation, degradation with time, or is it due to poor accuracy or precision of the analytical method? It is not likely that any of these reasons will be acceptable to support such broad limits.

You have specified a range of (b) (4) daltons as the average molecular weight (b) (4) for the drug substance. You will need to define which molecular weight average you are reporting, the number average (Mn) or the weight average (Mw). Independent of which molecular weight average you plan to report, a three-fold range is not acceptable. For polymeric materials, both Mn and Mw are generally included in the specification.

(b) (4)

The (b) (4) range proposed for (b) (4) will need to be justified and consideration should be given to the fact that the level of (b) (4) at your proposed upper limit may promote (b) (4)

Discussion:

Drug substance batches used in clinical trials are prepared by (b) (4). FDA finds it reasonable to base drug substance specifications on (b) (4); (b) (4) will be considered in-process data. The final drug substance specifications will need to be based on the (b) (4) batches that were used in clinical trials.

Salix agrees with FDA's comments and will address these issues.

Crofelemer Drug Product

4. Does the Agency concur that
- the proposed manufacturing process is robust and well-controlled and adequate to maintain lot-to-lot consistency?

FDA Response:

It is not possible to comment on the adequacy of the manufacturing operation based on the limited information that has been provided in the briefing package. In the NDA submission you will need to describe in-process controls, with acceptance criteria, and why they are important to ensure a consistent drug product. You will also need to provide comparative batch data.

Discussion:

Salix will provide more detailed information in the NDA.

b. the proposed specifications and methods are appropriate for this category of product?

FDA Response:

The (b) (4) limits for assay are unusually broad and will likely need to be narrowed to the (b) (4) limits recommended for most drug products in USP.

The specification does not have a test for crofelemer molecular weight which would be used to monitor (b) (4) of the drug substance on stability testing.

We note that you are proposing a dissolution specification of Q= (b) (4) minutes for your product. Therefore, in the NDA submission you should provide data for the entire dissolution profile supporting the selection of the proposed dissolution specification.

Discussion:

Molecular weight determination will need to be added to the drug product specification and will need to be monitored in stability studies. FDA agreed that it will be acceptable to start measurement of this parameter at the 18 month point because the stability studies are already in progress. However, expiration dating will be problematic if molecular weight data at the 18 month point are significantly different from the initial value.

Salix agrees with the FDA comments regarding assay and dissolution.

Additional Biopharmaceutics Comments

We have the following advice comments regarding the dissolution information that should be provided in your NDA.

Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information: solubility data for the drug substance covering the pH range; detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters used to select the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable; provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

Dissolution Specification:

For the selection of the dissolution specification of your product, the following points should be considered:

- **The dissolution profile data from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution specification of your product (i.e., specification-sampling time point and specification value).**
- **The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.**
- **For immediate release product the selection of the specification time point should be where $Q = \text{(b) (4)}$ dissolution occurs.**

Note that the final determination on the acceptability of the proposed acceptance criteria for your product will be made during NDA review process based on the totality of the provided data.

Discussion:

Salix are taking these comments into consideration for their NDA submission.

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/s/

CATHERINE A TRAN-ZWANETZ
06/23/2011

MARIE KOWBLANSKY
06/24/2011

MOO JHONG RHEE
06/24/2011
Chief, Branch IV



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 051818

MEETING MINUTES

Salix Pharmaceuticals, Inc.
Attention: Jennifer Richards
Sr. Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Richards:

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

We also refer to the meeting between representatives of your firm and the FDA on January 19, 2011. The purpose of the meeting was to discuss plans for submitting a New Drug Application (NDA).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 19, 2011, 1:00 – 2:00 p.m. EST
Meeting Location: 10903 New Hampshire Avenue, White Oak Building 22,
Conference Room 1315, Silver Spring, Maryland 20903

Application Number: IND 051818
Product Name: Crofelemer
Indication: (b) (4)
Sponsor/Applicant Name: Salix Pharmaceuticals, Inc

Meeting Chair: Hugo Gallo-Torres
Meeting Recorder: Kevin Bugin

FDA ATTENDEES

Division of Gastroenterology Products

Donna Griebel, M.D., Director
Hugo Gallo Torres, M.D., Ph.D., P.N.S, Clinical Team Leader
Erica Wynn, M.D., Clinical Reviewer
Sushanta Chakder, Ph.D., Pharmacology Team Leader
Tamal Chakraborti, Ph.D., Pharmacology Reviewer
Wes Ishihara, Sr. Supervisory Regulatory Health Project Manager
Kevin Bugin, M.S., R.A.C., Regulatory Health Project Manager

Office of New Drug Quality Assessment

Marie Kowblansky, Ph.D., CMC Lead

Division of Botanical Drug Products

Jinhui Dou, Ph.D., Pharmacognosy Reviewer

Office of Translational Sciences

Mike Welch, Ph.D., Deputy Director, Division of Biometrics III
Lisa Kammerman, Ph.D., Biometrics Reviewer, Division of Biometrics III
Insook Kim, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III

Division of Regulatory Review Support (OPI/OBI)

Valerie Gooding, Regulatory Information Specialist

SPONSOR ATTENDEES

William P Forbes, Pharm.D., Executive Vice President, R&D and CDO

Jennifer Richards, Senior Manager, Regulatory Affairs

Pamela L Golden, Ph.D., Director, Development

Michelle Widman, Associate Director, Clinical Operations

Jeffrey Cohn, Ph.D., Associate Manager, Clinical Development

Rachel Ballard, Senior Clinical Project Manager

Enoch Bortey, Ph.D., Associate Vice President, Biostatistics, Data Management and
Programming

Shirley Huang, Ph.D., Principal Biostatistician

Krisann Spain, Regulatory Specialist

(b) (4)

Rodger MacArthur, MD, Professor of Medicine, Division of Infectious Diseases, Wayne State
University Director and Principal Investigator, HIV/AIDS Clinical Research Unit, Detroit
Medical Center

1.0 BACKGROUND

(b) (4)

(b) (4) Shaman (b) (4) in 2002 transferred IND 051818 to PS Pharmaceuticals, Inc, who later changed its name to Napo Pharmaceuticals, Inc. Finally, in 2008, ownership of 051818 was transferred to Salix Pharmaceuticals, Inc (Salix).

On October 12, 2010, Salix submitted a meeting request to discuss plans for submitting an NDA for Crofelemer. The meeting was granted on November 03, 2010 and preliminary comments were sent on January 18, 2011. The meeting was held in Silver Spring, MD as planned on January 19, 2011.

2. DISCUSSION

(Questions in the briefing package are shown in plain font. FDA's preliminary responses are shown in **boldface**. Salix's responses to FDA's preliminary responses are shown in *italics*. Discussion at the meeting is shown in ***bold italics***.)

Clinical / Statistical

Crofelemer tablets have been administered to approximately 70 healthy volunteers and approximately 1560 subjects with acute infectious diarrhea, traveler's diarrhea (TD), non-specific diarrhea, HIV-associated diarrhea, and d-IBS in 4 Phase 1 studies and 10 Phase 2-3 studies for up to 24 weeks of treatment.

Salix is proposing the following indication: (b) (4)

(b) (4)

Summaries of the clinical development program for crofelemer, including detailed summaries of the pivotal and supportive studies in patients with HIV/AIDS-related diarrhea (b) (4) are provided in Section 13.0.

1. *Does the Agency concur that the Phase 3 ADVENT study, along with the supportive HIV-associated diarrhea (b) (4) (b) (4) are sufficient for filing and review of an NDA submission for the proposed indication?*

FDA Response:

No, the Agency does not concur. The indication would need to reflect the specific patient population that was studied in the clinical trial based on the eligibility criteria. The adequacy of the eligibility criteria to define an appropriate population for product labeling would be a review issue. Whether a single clinical trial will constitute substantial evidence of efficacy will depend on whether the trial and its results meet requirements set for in the Guidance for Industry: “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.”

Salix Response:

In vitro and nonclinical in vivo studies demonstrate that crofelemer works through inhibition of the secretion of chloride through CFTR and CACC. Furthermore, a clinical study (37554-209) demonstrates the reduction of stool chloride following crofelemer treatment. Patients enrolled in ADVENT, 37554-209 and 37554-210 constitute a secretory diarrhea population who are HIV+, on concomitant antiretroviral therapy (ART) and devoid of known gastrointestinal infection. In these trials, changes in stool weight and/or stool consistency are consistent with this mechanism and the results support the purported mechanism of crofelemer’s action.

In addition, diarrhea in subjects entered into the ADVENT study was not the typical HIV-associated diarrhea seen in advanced HIV infection where there is blunting of the intestinal villi, malabsorption, and susceptibility to intestinal parasites. Rather, these subjects were otherwise healthy individuals with CD4+ cell counts above 100 cells/mm³.

[REDACTED] (b) (4)

In studies of diarrhea in [REDACTED] (b) (4) the following entry criteria for secretory diarrhea were met:

<i>Study Population</i>	<i>Diarrhea Entry Criteria</i>
<i>Diarrhea in HIV+ Patients</i>	<i>ADVENT: 5 out of 7 days of watery diarrhea Study 210: Stool weight ≥ 300 g for 24 hours Study 209: Stool weight ≥ 200 g for 24 hours and ≥ 3 liquid bowel movements</i>

(b) (4)

In addition, each of the conditions studied with crofelemer has a secretory pathophysiologic basis:

Diarrhea in HIV+ patients (ADVENT, 37554-209, 37554-210)

- *Mechanisms of ART-induced diarrhea:*
 - *Increased cell apoptosis, water/Na⁺/Cl⁻ secretion, intestinal permeability in vivo and in vitro¹*

¹Braga Neto , BMC Gastroenterology 2010

- *Disruption of epithelial barrier integrity in vivo*²
- *Altered ion secretion and barrier function in vitro*³

(b) (4)

(b) (4)

Salix will work with the Agency to determine the proper labeling to most accurately reflect crofelemer's mechanism of action and clinical utility.

Discussion:

The agency has no further comment.

2. (b) (4)

FDA Response:

(b) (4)

Salix Response:

(b) (4)

Salix would like to discuss this question further during the meeting.

² Wu , Gastroenterology 2010

³ Bode, Ann NYAS, 2000

(b) (4)

Discussion:

(b) (4)

However, Fast Track Designation does allow for a rolling review of portions of the submission prior to the start of the review clock.

Statistical analysis plans (SAP) were prepared for the ADVENT study detailing the statistical methods utilized for the analysis of the 4-week, placebo-controlled treatment phase, the 20-week placebo-free extension phase, and the pharmacokinetic (PK) analyses, respectively. The statistical methods for the interim analysis of the Stage I data for dose selection were included in the SAP for the 4-week, placebo-controlled primary efficacy analysis.

The original SAP for the placebo-controlled phase (Stages I and II) and the interim analysis of the ADVENT study was submitted to IND 51,818 on July 30, 2007 (S-039) and reviewed by the Agency under the SPA. The interim analysis SAP was revised and submitted to the FDA prior to the end of Stage I (IND 51,818; S-058). The SAP for analysis of the placebo-controlled phase was revised prior to completion of the placebo-controlled phase to add a hierarchical approach for testing the secondary endpoints (IND 51,818; S-077). This approach provides for proper control of Type I Error and does not affect the SAP or the conduct of the study as agreed upon under the SPA.

Copies of the SAPs for the final analysis of the 4-week efficacy assessment period of the ADVENT study is provided as an attachment to of this document (see Section 17.0).

3. *Does the Agency believe that the analyses described in the SAP are sufficient to support an NDA?*

FDA Response:

No.

In addition to the presentation of the overall results, we request that you report results separately for Stage I and for Stage II. Include a descriptive analysis and comparison of the baseline characteristics of the subjects enrolled in each stage.

Include exploratory analyses and a discussion that address:

- **why the Stage I clinical response for crofelemer 250 mg BID appears to differ from the clinical responses for 125 mg BID and for 500 mg BID, and**
- **why the Stage II treatment effect for crofelemer 125 mg BID is not statistically significant, while the Stage I treatment effect for crofelemer 125 mg BID is statistically significant. Explain why the combined p-value is statistically significant.**

All tables and text need to indicate the p-values are one-sided.

Salix Response:

Salix will include the requested information in the NDA.

Discussion:

The agency provided clarification to Salix.

Salix intends to submit an Integrated Summary of Efficacy (ISE) in Module 5. Salix is proposing to summarize the efficacy of crofelemer by each indication studied, providing side-by-side results for individual studies. The data will not be pooled across studies due to differences in study design, endpoints, and treatment duration. A Summary of Clinical Efficacy (SCE) will also be provided in Module 2.7.3.

4. *Does the Agency concur with the proposed presentation of efficacy data for an NDA submission?*

FDA Response:

Yes, we concur with the presentation of efficacy data.

Salix Response:

N/A

Discussion:

No further discussion.

Salix is planning to submit the NDA in the second quarter of 2011. At the time of the initial NDA submission, the safety database will include approximately 1600 subject exposures to crofelemer for up to 24 weeks.

The proposed safety database for the Integrated Safety Summary (ISS) will contain the following safety pools:

- Primary Safety Data Integration: HIV-Associated Diarrhea. Consists of approximately 695 unique subject exposures to crofelemer with approximately 350 unique exposures for up to 24 weeks
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

A copy of the ISS SAP is provided as an Attachment to this document (see Section 17.0).

Selected summaries of the integrated safety data for the safety data pools are provided in Section 13.3.1.

5. *Does the Agency concur that the proposed safety database and ISS analysis plan are sufficient to provide a substantive review of the NDA?*

FDA Response:

The pooling of clinical trials for the safety analysis appears appropriate. We suggest that you group trials of similar design, duration, population, and treatment exposures together in the Primary and Supportive Safety Population. Additionally you may consider an expanded safety population containing information from all trials.

Discussion:

No further discussion.

6. *Does the Agency concur with the proposed safety pools?*

FDA Response:

We concur; see response to question 5 above.

Salix Response:

N/A

Discussion:

No further discussion.

In a study to examine the effect of crofelemer on the hERG K⁺ channel, the mean IC₅₀ was 1.77 μM, or > 135-fold above the highest unbound plasma observed in a human PK study (37554-210-PK) and 1392-fold above the highest unbound plasma concentration observed in ADVENT. Based on these data, the absence of an effect on cardiovascular function in the conscious telemeterized dog model at doses up to 600 mg/kg, the absence of significant systemic exposure in humans, and lack of an adverse effect on QT interval in healthy volunteers and patients, Salix is intending to request a waiver of the requirement for a Thorough QT study (TQT). Relevant data supporting a waiver is summarized in Section 13.3.3 of this document. A formal request for a waiver with full supporting documentation will be submitted to the Agency prior to filing the NDA.

7.

(b) (4)

FDA Response:

No, we do not agree. We will need to consult with the QT-IRT team. Before we can do that, you will need to submit additional information on your clinical pharmacology studies; see answer to question 8, below.

Salix Response:

(b) (4)

Discussion:

No further discussion.

Clinical Pharmacology / Pharmacokinetics

At the End of Phase 2 (EOP2) meeting held in May 2004, the Agency requested that a mass balance study be conducted to establish the lack of significant systemic absorption. As described in the EOP2 meeting background document, attempts to radiolabel crofelemer failed, making a mass balance study unfeasible. The Agency agreed that a single dose PK study which relied on a sensitive assay at the highest dose would be an acceptable alternative to the mass balance study. Study CFFE1091 was conducted in response to this requirement. In addition, population PK samples were collected during the course of the ADVENT study. Results from CFFE1091 are summarized in Section 14.1.4 of this document.

8. *Does the Agency concur that the studies described establish the lack of significant systemic absorption and therefore preclude the necessity of a mass balance study?*

FDA Response:

Although it appears that the oral bioavailability of crofelemer is limited, we can not concur that the described studies confirm the lack of significant systemic absorption because it is unclear which component(s) were measured in PK studies given crofelemer is a mixture of polymers. Please, provide additional information about the in vivo pharmacokinetic studies and what was measured in plasma.

Please, clarify if ^{14}C -crofelemer was used in an in vitro study (page 175) in the meeting package) and if so why the same technique cannot provide radiolabeled crofelemer for a mass balance study.

Salix Response:

The design of in vivo pharmacokinetic studies and the sensitivity and specificity of the bioanalytical method will be described in detail in the NDA submission.

Regarding the study described on Page 175 of the briefing document, this study was conducted using a ^{14}C -methylated derivative of crofelemer, not crofelemer itself. Therefore, Salix believes that a mass balance study conducted with such a derivative may not accurately characterize the disposition of crofelemer in humans.

Discussion:

No further discussion.

A summary of relevant clinical pharmacology and PK data is provided in Section 14.0 of this document.

9. *Does the Agency concur that the clinical pharmacology and PK studies completed are sufficient to support an NDA submission?*

FDA Response:

It is unclear if you have adequately characterized single and multiple dose PK of crofelemer at the proposed dosage regimen i.e. 125 mg BID. We note that PK samples were collected during the ADVENT study; however, only at two time points i.e. 2 and 4 hours post-dose so do not consider it as adequate PK characterization.

We recommend that effects of crofelemer on the inhibition and induction of transporters e.g. p-glycoprotein and BCRP and on the induction of CYP enzymes be studied. You may conduct in vitro studies first to determine if in vivo drug interaction studies are necessary.

In vitro studies suggest that crofelemer inhibits CYP enzymes with an IC50 of less than 10 mcM SP-303. Since the concentration of crofelemer in the intestine would be about 174 mcM (according to your background package) in vivo effects of crofelemer on drug metabolized by those CYP enzymes should be addressed. This recommendation is based on the fact that CYP enzymes are present in the intestinal mucosa.

Please, also see response to question 8, above.

Salix Response:

The single-dose study in healthy subjects (CFFE1091) used an intense plasma sampling approach to characterize the entire pharmacokinetic profile over 48 hours following administration of a 500-mg crofelemer dose under fasted and fed conditions. Despite this intensive sampling approach, only 3 samples had quantifiable crofelemer plasma concentrations.

In the ADVENT trial, a population pharmacokinetic approach was used for sample collection following multiple crofelemer doses; population-based analysis of the analytical data, including plasma sampling times relative to dose administration, will be submitted with the NDA to demonstrate the ability of the sampling paradigm to characterize the multiple-dose PK profile.

Salix concurs with the Agency's recommendation regarding in vitro transporter interaction studies, and will submit the results of these studies with the NDA.

Discussion:

No further discussion.

Nonclinical

(b) (4)

10. Does the Agency concur that nonclinical studies of antiviral activity and those using an inhaled nebulized aerosol formulation are not required to be included in the NDA?

FDA Response:
Yes. We concur.

Salix Response:
N/A

Discussion:
No further discussion.

At the EOP2 meeting, the Agency requested that the following studies be conducted:

- A 6-month oral gavage toxicity study in rats using non-microencapsulated powder in aqueous vehicle
- Safety pharmacology studies to characterize the effects of the drug on the central nervous and respiratory systems.

These studies have subsequently been conducted. Summaries of these studies along with all of the nonclinical pharmacology, PK and toxicology studies supporting the use of crofelemer in the proposed indication are provided in Section 15.0 of this document.

In addition, the Agency agreed that non-clinical ADME studies conducted under IND (b) (4) were adequate to support the registration of crofelemer. Summaries of these studies are also provided in Section 15.0 of this document.

11. Does the Agency concur that the nonclinical program is complete for NDA submission and is adequate to support the proposed indication?

FDA Response:
Yes. Your nonclinical program appears to be complete for the NDA submission.

Salix Response:
N/A

Discussion:
No further discussion.

As agreed to in the EOP2 meeting, Salix intends to conduct 2-year carcinogenicity studies in mice and rats as a Phase 4 commitment.

12. Does the Agency concur that the prior agreements for the conduct of the 2-year carcinogenicity studies as a Phase 4 commitment remain effective?

FDA Response:
Yes. We concur.

Salix Response:

N/A

Discussion:

No further discussion.

Regulatory

The ADVENT study was conducted under an SPA. A summary of the negotiations and agreements under the SPA are as an attachment to this document (see Section 17.0).

13. Does the Agency concur that the agreements made under the SPA have been upheld and the ADVENT study was conducted in accordance with the SPA?

FDA Response:

No, we do not concur. Based upon our review of Version 4.0 of Protocol NP303-101 and correspondence referencing this protocol, it does not appear that a finalized agreement on the SPA was achieved.

In addition, per the Guidance for Industry “Special Protocol Assessment”, a special protocol assessment will not be provided after a study has begun. Furthermore, any disagreements regarding the study design should be resolved before starting the trial. It appears that the Sponsor initiated the study prior to their meeting request on January 29, 2008. Negotiations regarding the SPA continued through October of 2008 after the initiation of the trial. Any agreements reached regarding conduct of the ADVENT study are documented in correspondence and meeting minutes.

Salix Response:

In accordance with the Guidance for Industry “Special Protocol Assessment,” all substantive decisions regarding the protocol design, primary endpoint, study conduct, data analysis and potential labeling claims were agreed upon prior to the first patient entering the study in October 2007. In August 2008, the FDA requested clarification and refinements on minor issues, none of which affected the integrity or conduct of the study. The protocol was amended to reflect the Agency’s request (Version 3; Amendment 2) and the FDA subsequently confirmed via e-mail that the SPA review was complete but that no formal letter would be issued. Version 4.0 (Amendment 3) of the protocol was submitted by Salix in July 2009 and was comprised of administrative changes necessitated by the transfer of ownership of IND 51,818 from Napo to Salix, none of which changed the conduct of the study as agreed upon by the FDA under the SPA.

Based on the documentation of the SPA process, including FDA letters, e-mails and minutes from phone conferences, Salix believes that an SPA was achieved for the substantive aspects of the study and included all agreements in FDA correspondence dated 4-Dec-06, 9-Feb-07 and 21-Jun-07. Copies of this documentation can be made available upon request.

Discussion:

Salix and Agency agree that any agreements reached regarding the conduct of the ADVENT study are documented in correspondence and meeting minutes. The specifics of the agreements will be a review issue at the time of the NDA submission.

Fast track designation was granted for crofelemer for the treatment of diarrhea in patients with AIDS under IND (b) (4) and FDA subsequently agreed to transfer this agreement to IND 51,818 at the EOP2 meeting. A copy of this agreement is provided as an attachment to this document (see Section 17.0).

14. Does the Agency concur that the fast track designation is still applicable and the NDA will be considered for priority review in keeping with the fast track designation?

FDA Response:

Review priority will be assessed following the submission of the NDA and a priority review is not guaranteed by a Fast Track designation.

Per the Guidance for Industry, “Fast Track Drug Development Programs – Designation, Development, and Application Review,” the fast track development program must continue to demonstrate the potential ability to treat a serious or life-threatening condition and fulfill unmet medical needs. Your proposed indication does not match the indication that was subject to the original Fast Track designation review. If you wish to pursue this indication, you will need to submit a new Fast Track designation request.

Salix Response:

As agreed with the FDA in 2004, the ADVENT study fulfills the requirement for Fast Track Product Designation in the treatment of diarrhea in HIV infected patients. Salix understands that by maintaining this indication we will retain Fast Track designation.

As discussed in Question 1, Salix believes diarrhea in HIV+ patients taking ART is secretory and a serious condition that remains unaddressed by current treatments, none of which are approved for this indication.

In HIV+ patients, untreated diarrhea can lead to lack of adherence to, or discontinuation from, treatment regimens. Studies indicate that an adherence rate of greater than 95% is needed for optimal suppression of HIV RNA (less than 400 copies/ml).⁹ Diarrhea can significantly impact discontinuation of ART, leading to:

- increased risk of selecting for drug-limiting resistance mutations and*
- decreased future drug options as multiple ART are used due to side effects of previous regimens*

In addition, there are essentially no trials that have investigated the safety and efficacy of anti-motility agents for the treatment of diarrhea in patients with HIV/AIDS.¹⁰

⁹ Paterson, Ann Intern Med, 2000

¹⁰ Nwachukwu, Cochrane Rev, 2008

Successfully treating diarrhea leads to:

- *Improved adherence to ART regimens¹¹*
- *Improvements in quality of life^{12,13} including continence and decreased urgency, bloating and discomfort*
- *Decreased health care costs^{14,15,16,17}*

Discussion:

No further discussion.

At the EOP2 meeting, the Agency agreed that pediatric studies could be deferred provided a pediatric study plan is submitted with the NDA.

15. Does the Agency concur that pediatric studies will be deferred provided a pediatric study plan is submitted with the NDA?

FDA Response:

The deferral of pediatric studies is subject to review of your pediatric plan which should be submitted with the NDA. Please refer to the draft Guidance for Industry “How to Comply with the Pediatric Research Equity Act”.

Salix Response:

Salix will submit a pediatric plan with the NDA.

Discussion:

No further discussion.

Salix intends to file the NDA as an electronic Common Technical Document (eCTD). The Submission organization structure, nomenclature, and format will comply with the International Conference on Harmonization (ICH) Guidance on Organization of the CTD, Annex: Document Granularity. Additionally, the generation of XML document information files will be in accordance to CTD guidance documents. A summary of the specifications for the eCTD is provided in as an attachment to this document (see Section 17.0).

16. Does the Agency concur with the proposed eCTD submission strategy?

FDA Response:

Yes, we concur, however, you should prepare a sample submission to validate your eCTD specifications prior to submission of your application. This will avoid errors in submission

¹¹ Duran, HIV Clin Trials, 2001

¹² Tramarin, Quality of Life Research, 2004

¹³ Mannheimer, Clinical Infectious Diseases, 2008

¹⁴ López-Gigosos, BMC Infectious Diseases, 2009

¹⁵ Lundkvist, Journal of Travel Medicine, 2009

¹⁶ Reves, Arch Intern Med, 1988

¹⁷ Wang, Journal of Travel Medicine, 2008

acceptance. Contact esub@fda.hhs.gov for further information. We also recommend providing a Reviewer's Guide to provide an overview of the submission and facilitate the review team's access to key documents and files within the submission.

Please provide an adequate description of the datasets to be submitted to support review.

Salix Response:

N/A

Discussion:

No further discussion.

Additional requests and comments:

- 1. We have concerns that you may not have adequate documentation regarding your polymeric drug substance. Before you submit your NDA, you need to schedule a CMC-only meeting to discuss the specifications and manufacturing controls that you have in place. The specifications and controls need to ensure that you will be able to reproducibly manufacture a commercial drug substance and product that is the same as the product used in the pivotal clinical trials. Among issues that will need to be discussed is your ability to reproduce the catechin/gallocatechin monomer ratio from batch to batch, as well as the comparability of this ratio in clinical trial batches and in the to be marketed product.**

Salix Response:

Salix intends to schedule a CMC pre-NDA meeting prior to filing the NDA.

Discussion:

No further discussion.

- 2. No data regarding the relationship between plant age or season of collection and the latex composition have been provided. Since the chemical compositions of dragon's blood are expected to vary from batch to batch, knowledge of the important factors causing these variations would be very helpful for raw material quality control. It would also be helpful if you demonstrate that your purification process can effectively minimize chemical variations of different batches of the botanical raw material.**

Salix Response:

Salix intends to schedule a CMC pre-NDA meeting prior to filing the NDA.

Discussion:

No further discussion.

- 3. We recommend you establish Good Agricultural and Collection Practices (GACP) to assure the raw material quality and consistency.**

Salix Response:

Salix intends to schedule a CMC pre-NDA meeting prior to filing the NDA.

Discussion:

No further discussion.

4. **One important issue is how to prevent natural contamination from those easily confused plant species grown in the same area where the raw material is collected. Special attention should be given to related *Croton* species (and other species) that have been used to produce “dragon’s blood” for herbal medicine use.**

Salix Response:

Salix intends to schedule a CMC pre-NDA meeting prior to filing the NDA.

Discussion:

No further discussion.

5. **We recommend you provide a specification of the botanical raw material, dragon's blood, the latex of *Croton lechleri* Müll. Arg.**

Salix Response:

Salix intends to schedule a CMC pre-NDA meeting prior to filing the NDA.

Discussion:

No further discussion.

6. **The NDA needs to include the Interim Analysis Report and the Dose Selection Report, plus any minutes of the meeting held by the Interim Analysis Committee.**

Salix Response:

The NDA will include the Interim Analysis Report and the Dose Selection Report, plus any minutes of the meeting held by the Interim Analysis Committee.

Discussion:

No further discussion.

7. **When you submit data from a drug interaction study, please provide a ratio of AUC and Cmax and associated 90% confidence interval.**

Salix Response:

Agreed.

Discussion:

No further discussion.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

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

/s/

KEVIN B BUGIN
01/25/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,818

Napo Pharmaceuticals, Inc.
Attention: Kimberly Manhard
Regulatory Consultant
213 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Manhard:

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

We also refer to the meeting between representatives of your firm and the FDA on May 5, 2004. The purpose of the meeting was to discuss the continued development plan for Crofelemer in HIV-infected patients with diarrhea.

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 Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation 3
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

Memorandum of Meeting Minutes

Meeting Date: May 5, 2004
Meeting Time: 10:30-12:00 p.m.
Meeting Location: Teleconference

Application Number: IND 51,818
Drug Name: Croflemmer
Type of Meeting: EOP2
Meeting Chair: Joyce Korvick, M.D.
Meeting Recorder: Susan Daugherty, B.S.N.

BETWEEN:

Napo Pharmaceuticals Attendees:

Barry Quart, Pharm D., President, Chief Scientific Officer

(b) (4), Medical Consultant to Napo Pharmaceuticals, Inc.
(b) (4), Toxicology Consultant to Napo Pharmaceuticals, Inc.
(b) (4) Regulatory Consultant to Napo Pharmaceuticals, Inc.

(b) (4) Statistical Consultant to Napo Pharmaceuticals, Inc.
(b) (4)

AND

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

Joyce Korvick, M.D., M.S., Deputy Division Director
Robert Prizont, M.D., Medical Reviewer
Kenneth Hastings, Ph.D., Pharmacologist
Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist
Tamal Chakraborti, Ph.D., Pharmacology Reviewer
Susan Daugherty, B.S.N., Consumer Safety Officer
Monika Houstoun, Pharm. D., Regulatory Project Manager

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

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

Division of Biometrics II (HFD-715)

Stella Grosser, Ph.D., Biometrics Team Leader

PURPOSE: To discuss the continued development plan for Crofelemer in HIV-infected patients with diarrhea.

BACKGROUND:

(b) (4)

(b) (4)

IND 51,818 was transferred to PS Pharmaceuticals, Inc. effective April 23, 2002, and subsequently inactivated on May 15, 2002. PS Pharmaceuticals later changed their name to Napo Pharmaceuticals, Inc. and changed the product name from Provir™ to Crofelemer.

(b) (4)

This meeting request was transferred to DGCDP on March 29, 2004, under IND 51,818 and the sponsor requested reactivation of IND 51,818. The protocol was deemed safe to proceed by all disciplines.

FDA responses to questions from the sponsor were faxed to the sponsor on April 26, 2004. The sponsor subsequently requested that the meeting be held via teleconference.

DISCUSSION:

Response to questions from the firm

Clinical:

- a. Napo has designed the proposed phase 3 trial incorporating the previous advice of DSPIDP and the insight gained from an updated analysis of the previously conducted phase 3 study, 37,554-210. As described in Section 11.1 of the Background Document, Napo is proposing

a multicenter, randomized, out-patient, placebo-controlled, efficacy study (b) (4)
in patients with HIV-associated diarrhea. The study will include a (b) (4)

Does the Division agree that the study design for the proposed study as described in protocol concept NP-001 is an adequate and well-controlled trial for registration of crofelemer in the treatment of diarrhea in HIV-infected patients?

FDA Response:

We agree that the overall proposed design include appropriate adequacy for testing safety and efficacy of the test article. Patients who fail to treatment and require discontinuation should have stools re-tested for infectious organisms.

- b. At the Pre-NDA meeting with Shaman, the DSPIDP recommended one additional trial of crofelemer versus placebo or standard of care in at least 100 patients, focusing on sicker patients, to support approval as described in Section 11.2 of the Background Document. In the proposed placebo-controlled phase 3 trial, Napo proposes to include only patients with clinically significant diarrhea defined as patients (b) (4) during the one week Baseline Period.

- i. *Does the Division agree that the patient population of HIV-infected patients with clinically significant diarrhea as proposed for the placebo-controlled phase 3 trial (protocol concept NP-001) represents a suitable patient population to obtain approval of crofelemer for the treatment of HIV-associated diarrhea?*

FDA Response:

Agree with baseline assessment of (b) (4) Frequency of bowel movements per day, and overall daily stool consistency should also be assessed during the baseline run-in period. Baseline assessment should include use of OTC and/or prescription medications.

- ii. *Does the Division agree that the proposed trial meets the Division's request for an additional pivotal trial with supportive data from the previously conducted phase 2 and 3 studies in patients with AIDS-associated diarrhea to gain registration of crofelemer for the treatment of diarrhea in HIV-infected patients?*

FDA Response:

Agree

- c. The planned primary endpoint for the phase 3 study proposed by Napo is a "responder" endpoint with a responder defined as a patient with less than 2 watery stools in a week (see Section 11.1 of the Background Document). In the evaluation of studies 37,554-209 and 37,554-210 stool output, including stool frequency and stool weight, was highly variable on a daily basis; therefore, a weekly assessment was chosen. Weekly assessments have also

been used for endpoints for other gastrointestinal drugs for the treatment of chronic diarrhea such as Irritable Bowel Syndrome.

Does the Division agree with the proposed primary endpoint as described in protocol concept NP-001?

FDA Response:

We concur with the proposed endpoint. It is acceptable to define a responder as a patient with less than one watery bowel movement/week, as long as, there is adequate recording of daily stool consistency on each week, and there is a trend towards decrease of watery bowel movements on each tested month.

Sponsor Clarification Requested:

Unfortunately, the question we posed contained a small, but significant typographical error with respect to the number of watery stools in a week. As stated in Section 11.1 of the Background Document, “primary endpoint for the study will be watery stool responders, where a responder is a patient who has ≤ 2 watery stools in a week”, not less than 2 watery stools in a week as stated in the question. In addition, it is unclear if the FDA response also contains a typographical error since it states the endpoint is acceptable, but defines it as less than one watery bowel movement/week. Napo would like to obtain clarification and gain acceptance of the proposed endpoint as described in Section 11.1.

Additional Discussion

We agree with sponsor’s request for clarification, that the primary endpoint for a responder is 2 or less watery stools per week.

- d. On April 23, 1998, the DSPDIP gave Fast Track Product designation to crofelemer (SP-303) for the treatment of diarrhea in patients with AIDS. As discussed in section 11.3 of the Background Document, even in the era of highly active antiretroviral therapy (HAART) diarrhea remains an important problem in HIV-infected patients, significantly impairing their quality of life.¹ HIV treatments themselves contribute to the problem with secretory diarrhea being the most common dose-limiting adverse effect associated with protease inhibitors, such as nelfinavir.² There is currently no approved treatment for HIV-associated diarrhea and commonly prescribed anti-diarrheal treatments have undesirable side effects including constipation and addiction.

Does the Division agree that the proposed phase 3 trial fulfills the requirements for Fast Track Product designation for crofelemer in the treatment of diarrhea in HIV-infected patients?

FDA Response:

We agree

(b) (4)

¹ Siddiqui U, Bini EJ, Chandarana K, Ramsetty S, Poles MA. HIV-associated diarrhea in the era of HAART: still prevalent after all these years. Digestive Disease Week, May 2003 Abstract S1065.

² Rufo P, Lin PW, Andrade A, Flexner C, Jiang L, Alper SL, Lencer WI. Hiv-1 Protease Inhibitors Potentiate Muscarinic Stimulation of Cl- Secretion in Association with Increased and Prolonged Ca2+ Entry In T84 Cells. Digestive Disease Week, May 2003 Abstract S1051.

Clinical Pharmacology:

- e. As explained in Section 12.1.5 of the Background Document, Napo is working with non-profit organizations on the development of a pediatric formulation of crofelemer for the conduct of studies in HIV-infected children with diarrhea.

Does the Division agree that pediatric studies can be a post-approval commitment following the successful development of a pediatric formulation of crofelemer?

FDA Response:

You may defer pediatric studies provided a pediatric study plan is submitted.

- f. The DSPIDP stated at the Pre-NDA meeting with Shaman that the drug interaction information for crofelemer from study 37,554-103 was adequate. As discussed in Section 12.1.3 of the Background Document, due to the limited absorption of crofelemer, clinically relevant drug interactions are unlikely.

Does the Division agree that the drug interaction data remains adequate?

FDA Response:

You need to conduct a mass balance study to conclusively establish the lack of significant systemic absorption. Additional drug-drug interaction studies may be not be needed for an NDA submission if no significant systemic absorption occurs.

Sponsor Clarification Requested:

As explained in Section 13.2.3 of the Background Document, carbon-14 labeling was not possible because crofelemer is derived from a natural source (b) (4)

Therefore, due to the lack of radio-labeled drug and the inability to analyze the drug by mass spectrometry (GC/MS or LC/MS), Shaman was not able to conduct a mass balance study. Napo wishes to discuss the Agency's recommendation for the mass balance study.

Additional Discussion

As an alternative, a single dose PK study, relying on a sensitive assay at the highest dose to be studied, would be acceptable. Napo will supply additional data to be discussed in the future regarding which approach would be more appropriate understanding the difficulties with radiolabing the drug.

- g. The DSPIDP requested data from study 37,554-210 on food effect to determine if a food effect study would be needed. As discussed in section 12.1.4 of the Background Document, the potential effect of food on crofelemer pharmacokinetics in study 37,554-210 cannot be analyzed because the timing of meals relative to sample collection was not recorded on the Case Report Form or the source notes. (b) (4)

Does the Division agree that a food effect study will not be required for crofelemer?

FDA Response:

A delayed release oral formulation is generally more susceptible to food-effect relative to an immediate release oral formulation. Hence, a food-effect study is needed for an NDA submission.

Sponsor Clarification Requested:

Napo would like to clarify the goal of this study.

Additional Discussion

See response to question f, above.

Pharmacology/Toxicology:

- h. The DSPIDP stated at the Pre-NDA meeting with Shaman that the information regarding ADME of crofelemer summarized in Section 13.2 of the Background Document was considered adequate.

Does the Division agree that the ADME information remains adequate for registration of crofelemer?

FDA Response:

Yes.

- i. The DSPIDP stated at the Pre-NDA meeting with Shaman that the toxicology information on the product described in Section 13.3 to 13.9 of the Background Document was adequate. Since the meeting the results of the 9-month dog study (see Appendix D of the Background Document) have been evaluated and crofelemer exhibited neither cumulative nor unexpected toxicity in this study relative to the toxicity noted after one month of dosing in dogs.

- i. *Does the Division agree that the nonclinical toxicology information (other than the carcinogenicity data) remains adequate for registration of crofelemer?*

FDA Response:

Yes. However, we recommend that you conduct a 6-month oral gavage toxicity study in rats using non-microencapsulated powder in aqueous vehicle.

Sponsor Clarification Requested:

We apologize if this issue was not adequately discussed in the Background Document. As detailed in the original IND submission, the delayed-release formulation of crofelemer was developed to deliver the drug to the small intestine to by-pass degradation in the stomach. This was based on the results of an earlier in vitro study using crofelemer non-microencapsulated powder in solution (Shaman Report SP303-A008 19 June 1996; IND 51,818, S000, Volume 8, page 220) that demonstrated:

1. *Approximately 20% of SP-303 was changed or lost within 2 minutes in the presence of dilute hydrochloric acid (pH 1.7, 37°C) and approximately 25% was lost within 2 hours.*
2. *The addition of simulated gastric fluid showed precipitation of pepsin and approximately 30% loss within 2 minutes and approximately 50% loss within 2 hours.*
3. *No further significant reduction was seen when crofelemer solution in gastric juice was incubated with simulated intestinal fluid.*

Napo also considered the conduct of a 6-month toxicity study in rats using the non-microencapsulated powder in solution to overcome the problems associated with gavage administration of the microencapsulated beads. However, we believe that the conduct of a study in rats with the non-microencapsulated powder would not adequately expose the lower GI tract to the nondegraded and non-protein-bound drug and thus not be relevant to the conditions of human use. This is primarily based on 3 observations:

- *crofelemer is rapidly degraded in simulated gastric fluid,*
- *there is minimal systemic exposure in rats, and*
- *the lower gastrointestinal (GI) tract is where the clinical enteric-coated tablet formulation is delivered and is therefore the primary tissue of concern for toxicity assessment.*

In addition, because the dog is the more sensitive species to G.I. effects and has greater systemic exposure to the drug than the rat, we feel, as did the DSPIDP, that the 9 months of exposure in the more sensitive species to the clinically relevant formulation is adequate to demonstrate the safety of the compound for long-term human use. Napo would like to better understand the Division's rationale for requesting this study.

Additional Discussion

The sponsor agrees to conduct the study as the FDA has requested. However, they wish to disagree regarding the relevance of these studies to the final drug product.

- ii. *Does the Division agree with the proposal to conduct a gastrointestinal safety pharmacology study to further investigate the gastrointestinal toxicity of crofelemer?*

FDA Response:

We agree with your proposal to investigate the gastrointestinal toxicity of crofelemer. Additionally, please conduct safety pharmacology studies to characterize the effects of the drug on central nervous system and respiratory system.

Sponsor Clarification Requested:

Napo would like to confirm that the proposed safety pharmacology studies should be performed with the oral route of administration.

Additional Discussion

The FDA agrees with the sponsor's clarification.

- j. The DSPIDP also stated at the Pre-NDA meeting that carcinogenicity studies would be required and could be done as a post-marketing commitment. The Division further stated that transgenic models could be substituted for a mouse study and that alternative methods of administration could be discussed. Mortality and trauma associated with the gavage of microencapsulated material in rodents precludes the conduct of standard carcinogen bioassays or oral dosing in transgenic models. As discussed in Section 13.5 of the Background Document, Napo located a 1989 published reference documenting no carcinogenic potential or tumor promoter activity after 17 months of treatment with the latex from which crofelemer is isolated (6-10% dry weight of latex) in a 2-stage mouse skin carcinogenesis system.³ In addition, crofelemer was negative in all 3 genotoxicity tests including a test for gene mutation in bacteria, an in vitro test with cytogenetic evaluation of chromosomal damage in mammalian cells, and an in vivo test of chromosomal damage using rodent hematopoietic cells (see Section 13.4 of the Background Document). Since crofelemer is not systemically absorbed in humans and is not systemically toxic in animal species, the primary concern regarding potential for carcinogenicity relates to possible direct local effects within the gastrointestinal tract after oral administration. The lack of genotoxic activity of crofelemer and of carcinogenic activity of the latex from which crofelemer is derived indicates that this potential is negligible. Therefore, Napo does not believe a carcinogenicity study in rodents is feasible or necessary based on the available data for crofelemer and the latex.

Does the Division agree that the carcinogenic potential of crofelemer in rodents does not require further investigation?

FDA Response:

No. The cited study is not acceptable, as it is not a substitute for 2-year carcinogenicity studies. We stand by the Agency recommendation of January 9, 1998, End-of-Phase 2 meeting. Please conduct 2-year carcinogenicity studies in mice and rats with the non-encapsulated drug.

Sponsor Clarification Requested:

Napo wishes to confirm that the Division also agrees with the Agency recommendation of January 9, 1998 that "if required, these studies can be performed as a phase 4 commitment."

As explained in our requested clarification to Question i above, Napo also wishes to discuss the Division's recommendation to use the non-encapsulated powder in the proposed carcinogenicity studies in the rat and mouse since it does not appear to adequately represent the human clinical situation.

Additional Discussion

It is acceptable to conduct these studies as Phase 4 commitments.

³ Vasberg A, Milla M, Planas MdC, Cordova JL, Rosa de Agusti E, Ferreyra R, Mustiga MdC, Carlin L, Hammond GB. Taspine is the Cicatrizant Principle in Sangre de Grado Extracted from *Croton lechleri*. *Planta Medica* 1989; 55: 140-143.

The sponsor will consider the requested oral route with the non-encapsulated product and propose the study design for future discussion with the division.

The TGAC model has not turned out to be good for products other than those that are dermally applied. One full life span study is an option, but the data may be unsatisfactory at the end of the day.

The 6 month rat study will be useful for dose ranging for the carcinogenicity study.

CONCLUSION:

1. FDA agrees that the Fast Track designation can be carried over from the previous IND.
2. FDA agrees the primary endpoint for a responder is 2 or less watery stools per week.
3. FDA agrees that pediatric studies may be deferred, provided a pediatric study plan is submitted.
4. The sponsor agrees to conduct the 6-month oral gavage toxicity study in rats using non-microencapsulated powder in aqueous vehicle.
5. The sponsor agrees to conduct 2-year carcinogenicity studies in mice and rats with the non-encapsulated drug. FDA agrees that these studies may be conducted as Phase 4 commitments.

Minutes Preparer: _____
Susan Daugherty B.S.N.
Regulatory Project Manager

Chair Concurrence: _____
Joyce Korvick, M.D.
Deputy Division Director

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/s/

Joyce Korvick
6/1/04 03:43:28 PM
for Dr. Robert Justice