

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022205Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022205

SUPPL #

HFD #

Trade Name Giazo

Generic Name Balsalazide disodium

Applicant Name Salix Pharmaceuticals

Approval Date, If Known 02/03/2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3

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?

No

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# 020610

Colazal

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:

Study 2: BZUC3002

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

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

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

(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: 01/31/2012

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

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/

KEVIN B BUGIN
02/03/2012

DONNA J GRIEBEL
02/03/2012

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 22-205.



William P. Forbes, Pharm.D.
Vice President, Research and Development and
Chief Development Officer
Salix Pharmaceuticals, Inc.

7/13/07

Date

CONFIDENTIAL

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022205 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: GIAZO Established/Proper Name: balsalazide disodium Dosage Form: Tablet		Applicant: Salix Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Cycle 1: Heather Buck, Cycle 2: Roland Girardet, Cycle 3: Roland Girardet, Cycle 4: Kevin Bugin		Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p style="text-align: center;"><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p><u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 03, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None Complete Response 04/27/2010 Complete Response 12/22/2008; Approvable 5/16/2008

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.

<p>❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): type 3</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>Comments:</p>	
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes, date
<p>❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: Note: Orphan exclusivity for Colazal (“same drug” as Giazol under 21 CFR 316.3(b)(13)) expires 12/20/13; however, the sponsor of Colazal is the same sponsor as Giazol. Orphan designation is for the pediatric indication.
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below)</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

(Summary Reviews)).

- [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).

<p><i>If "No," continue with question (5).</i></p> <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	02/06/2012
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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>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval 02/03/2012 Complete Response: 04/27/2010 Complete Response: 12/22/2008 Approvable: 05/16/2008
---	--

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	02/03/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	07/17/2007
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Colazal 2006 Package Insert

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	04/14/2010
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	01/26/2012; 04/01/2010; 04/27/2009; 05/22/2008 04/13/2009; 05/20/2008
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 01/31/2008 <input checked="" type="checkbox"/> DMEPA (04/01/2010); 05/20/2008 <input type="checkbox"/> DRISK N/A <input checked="" type="checkbox"/> DDMAC 04/12/2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	04/17/2008
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> 02/03/2012
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>04/14/2010; 10/29/2008</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	01/30/2012; 01/17/2012; 11/01/2011; 09/15/2011; 09/09/2011; 04/26/2010; 04/23/2010; 04/19/2010; 04/14/2010; 04/13/2010;

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
 Version: 12/4/09

	04/06/2010; 11/10/2009; 03/13/2009; 03/02/2009; 01/29/2009; 01/15/2009; 01/14/2009; 07/31/2008; 05/29/2008; 05/27/2008; 05/27/2008; 05/22/2008; 03/11/2008; 02/12/2008; 01/31/2008; 12/20/2007; 11/19/2007; 09/26/2007; 07/27/2007
❖ Internal memoranda, telecons, etc.	03/29/2010; 03/23/2010; 11/13/2008
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	Not applicable N/A
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg: 03/16/2009; 06/09/2008
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 04/27/2007
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 08/08/2005
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02/03/2012; 04/27/2010; 12/22/2008; 05/16/2008
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02/03/2012; 04/27/2010; 12/21/2008
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None (3)
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	05/09/2008
• Clinical review(s) (<i>indicate date for each review</i>)	04/27/2010; 12/20/2008; 05/01/2008
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Located in Sec. 4.6, page 15, of Clinical Review dated 05/01/2008
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo (<i>indicate date</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A <input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 03/27/2009; 03/27/2009; 12/11/2008; 05/15/2008; 05/15/2008; 04/21/2008; 04/03/2008
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04/27/2010
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/21/2008; 05/15/2008; 09/05/2007
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Final 01/20/2012 (04/07/2010); 05/06/2008 (Filing Review located in Sec. 3.3, page 26, of Clinical Pharmacology Review dated 05/06/2008)
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 01/10/2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 01/09/2012; 04/14/2010; 11/21/2008; 04/24/2008; 08/28/2007
<ul style="list-style-type: none"> ❖ Microbiology Reviews <ul style="list-style-type: none"> <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> Not needed N/A N/A
<ul style="list-style-type: none"> ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Environmental Assessment (check one) (original and supplemental applications) 	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> 	Located in Sec. II.A., page 45, of CMC Review dated, 04/24/2008
<ul style="list-style-type: none"> <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> 	N/A
<ul style="list-style-type: none"> <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> 	N/A
<ul style="list-style-type: none"> ❖ Facilities Review/Inspection 	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: 01/09/2012 See Final CMC Review <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

KEVIN B BUGIN
02/07/2012

From: [Bugin, Kevin](#)
To: [Burgin, Benjamin \(Benjamin.Burgin@Salix.com\)](#)
Cc: [Bugin, Kevin](#)
Subject: NDA 22205 Giazio (balsalazide disodium) - Labeling and PMCs - January 30, 2012
Date: Monday, January 30, 2012 7:23:23 PM
Attachments: [NDA 22205 - August 2011 Resubmission - PI - FDA Revisions V2 - Tracked Changes - 30 Jan 2012.doc](#)

Hi Benjamin,

Attached please find the updated version of the PI which contains the FDA revisions from the last version and those up to date. Also, below please find the revised wording for the PMCs.

As we discussed in the TCON today, we look forward to receiving your comments on the label Wednesday, COB. And logistically, we need to keep in mind that the final labeling and PMCs that we agree on need to be submitted by Salix to the NDA by Friday in order for us to take action. If necessary, you can fax me a courtesy copy on Friday if we get to that point.

PMC 1627-1: A single- and repeated-dose pharmacodynamics, pharmacokinetic (b) (4) study of Giazio tablets administered orally to pediatric patients ages 12 to less than 17 years with mildly to moderately active ulcerative colitis to support pediatric labeling.

Protocol Submission: MM/YY
Study/Trial Start: MM/YY
Final Report Submission: MM/YY

PMC 1627-2: A placebo-controlled clinical trial in female active ulcerative colitis patients to assess the efficacy of an eight week course of Giazio therapy for the treatment active disease in this patient population (b) (4)

Protocol Submission: MM/YY
Study/Trial Start: MM/YY
Final Report Submission: MM/YY

PMC 1627-3: A pharmacokinetic study in patients to evaluate the effect of concomitant therapy with antibiotics commonly used in ulcerative colitis on the metabolism of balsalazide following administration of Giazio.

Protocol Submission: MM/YY
Study/Trial Start: MM/YY
Final Report Submission: MM/YY

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
01/31/2012

From: [Bugin, Kevin](#)
To: [Bugin, Benjamin \(Benjamin.Burgin@Salix.com\)](#)
Cc: [Bugin, Kevin](#)
Subject: NDA 22205: Draft Labeling and Draft PMCs
Date: Tuesday, January 17, 2012 10:12:40 AM
Attachments: [NDA 22205 - August 2011 Resubmission - PI - FDA Revisions - Tracked Changes.doc](#)

Hi Benjamin,

Please refer to your August 02, 2011, Class 2 Resubmission to your New Drug Application (NDA) for Giazio (balsalazide disodium) tablets, 1.1 g.

Please find attached an annotated WORD document containing FDA's revisions to your proposed labeling. Since the previous review there have been some changes to standards and requirements for labeling. For this reason another review was necessary and our revisions are a result. There are also a few comments where we look to you for assistance in confirming or completing some information. Also please note, the labeling is still draft and subject to final supervisory review and modification.

Additionally, we remind you that you will be responsible for the following Post Marketing Commitments (PMCs) and we will need Salix to reaffirm to these and provide updated dates for milestones:

PMC 1627-1: A single- and repeated-dose pharmacokinetic (b) (4) study of Giazio tablets administered orally to pediatric patients ages 12 to less than 17 years with mildly to moderately active ulcerative colitis, (b) (4) to support pediatric labeling (b) (4)

Protocol Submission: MM/YY
Study/Trial Start: MM/YY
Final Report Submission: MM/YY

PMC 1627-2: A placebo-controlled clinical trial in female active ulcerative colitis patients to assess the efficacy of an eight week course of Giazio therapy for the treatment active disease in this patient population. (b) (4)

Protocol Submission: MM/YY
Study/Trial Start: MM/YY
Final Report Submission: MM/YY

PMC 1627-3: A pharmacokinetic study in patients to evaluate the effect of concomitant therapy with antibiotics commonly used in ulcerative colitis on the metabolism of balsalazide following administration of Giazio.

Protocol Submission: MM/YY
Study/Trial Start: MM/YY
Final Report Submission: MM/YY

Regarding PMC 1627-1, while reviewing the statutes and laws applicable during this review, it was determined that PREA cannot be invoked on this application, due to the Orphan Designation granted to balsalazide disodium (Colazal) in pediatric ulcerative colitis. However, the Division feels strongly that the pediatric population planned for the study could benefit from this research and therefore requests Salix commit to this study. We understand this is new information and are open to discussing further with you at your convenience and as soon as possible.

If you have any questions or comments, 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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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
01/17/2012



NDA 020610
NDA 022205
NDA 022301

**ACKNOWLEDGE CORPORATE
ADDRESS CHANGE**

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, R.A.C.
Senior Manager, Regulatory Affairs
8510 Colonnade Center Dr.
Raleigh, NC 27615

Dear Mr. Burgin:

We acknowledge receipt on August 23, 2011, of your August 22, 2011, correspondence notifying the Food and Drug Administration that the corporate address has been changed from

Salix Pharmaceuticals, Inc.
1700 Perimeter Park Drive
Morrisville, NC 27560

to

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

for the following new drug applications:

NDA 020610 for COLAZAL, CAPSULES

NDA 022205 for GIAZO (balsalazide disodium), TABLETS

NDA 022301 for APRISO (mesalamine), CAPSULES

We have revised our records to reflect this change.

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

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

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

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/s/

KEVIN B BUGIN
11/01/2011



NDA 021881, 021892, 022205
NDA 022246, 022301, 022554
NDA 020610/S-016 and NDA 021361 (b) (4)

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Dear Applicant:

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

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Giuseppe Randazzo, M.S., Regulatory Scientist, at (301) 796-3277.

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/

GIUSEPPE RANDAZZO

09/15/2011

Signed for Dr. Donna Griebel



NDA 022205

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

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

Dear Mr. Burgin:

We acknowledge receipt on August 03, 2011, of your August 02, 2011, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GIAZO (balsalazide disodium) tablets, 1.1 g.

We consider this a complete, class 2 response to our April 27, 2010, action letter. Therefore, the user fee goal date is January 03, 2012.

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

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/s/

KEVIN B BUGIN
09/09/2011



NDA 022205

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

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

Dear Mr. Burgin:

We acknowledge receipt on August 03, 2011, of your August 02, 2011, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GIAZO (balsalazide disodium) tablets, 1.1 g.

This letter is to confirm that we consider this a complete, class 2 response to our April 27, 2010, action letter. This letter also corrects a prior communication regarding the user fee goal date. The user fee goal date for this resubmission is *February 03, 2012*.

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

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/s/

KEVIN B BUGIN
09/09/2011

Girardet, Roland

From: Girardet, Roland
Sent: Monday, April 26, 2010 9:48 AM
To: 'Burgin, Benjamin'
Subject: NDA 22205: additional Giazio labeling revision

Dear Mr. Burgin,

Based on the sodium content data provided in Section 11 (Description) of the Giazio label, it appears that 6.6 g of Giazio contains approximately 756 mg of sodium. As a consequence, we request the addition of the following statement as the third bullet point under Section 17 (Patient Counseling Information):

- Advise patients who need to control sodium intake that the recommended dosing of Giazio (6.6 g/day) provides about 756 mg of sodium per day.

If you have any questions regarding this request, please feel free to contact me at your earliest convenience.

Best Regards,

Roland Girardet, *MHS, MS, MBA*
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: (301) 796-3827
Email: roland.girardet@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22205

ORIG-1

SALIX
PHARMACEUTICA
LS INC

BALSALAZIDE DISODIUM
TABLETS

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/s/

ROLAND GIRARDET

04/26/2010

Girardet, Roland

From: Girardet, Roland
Sent: Friday, April 23, 2010 9:49 AM
To: 'Burgin, Benjamin'
Subject: NDA 22205: Giazio PI revisions
Attachments: Giazio PI 04_23_2010 clean.doc; Giazio PI 04_23_2010 tracked.pdf

Dear Mr. Burgin,

Attached please find the updated Giazio Package Insert (PI) which incorporates the latest FDA revisions to the PI submitted by Salix on April 21, 2010. The pdf file tracks the revisions which were made.

Please keep in mind that this is still draft labeling and additional edits may be requested.

If you have any questions, please feel free to contact me at your convenience.

Best Regards,

Roland Girardet, *MHS, MS, MBA*
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: (301) 796-3827
Email: roland.girardet@fda.hhs.gov

21 Page(s) of Draft Labeling have been Withheld in Full as
b4 (CCI/TS) immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22205

ORIG-1

SALIX
PHARMACEUTICA
LS INC

BALSALAZIDE DISODIUM
TABLETS

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/s/

ROLAND GIRARDET

04/23/2010

Girardet, Roland

From: Girardet, Roland
Sent: Monday, April 19, 2010 3:27 PM
To: 'Burgin, Benjamin'
Subject: NDA 022205: Giazio label as of 04_19_2010
Attachments: Giazio PI 04_19_2010.doc; Giazio PI 04_19_2010 - tracked.pdf

Dear Mr. Burgin,

Attached, please find the updated version of the Giazio package insert which includes FDA revisions to the package insert submitted by Salix on April 16, 2010. The Word file is a clean copy and the pdf file shows tracked changes.

Please keep in mind that this labeling is still considered draft and additional revisions may be forthcoming.

If you have any questions, please feel free to contact me at your convenience.

Best Regards,

Roland Girardet, *MHS, MS, MBA*
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: (301) 796-3827
Email: roland.girardet@fda.hhs.gov

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Application
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Submission
Type/Number

Submitter Name

Product Name

NDA-22205

ORIG-1

SALIX
PHARMACEUTICA
LS INC

BALSALAZIDE DISODIUM
TABLETS

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/s/

ROLAND GIRARDET

04/19/2010

Girardet, Roland

From: Girardet, Roland
Sent: Wednesday, April 14, 2010 2:25 PM
To: 'Burgin, Benjamin'
Subject: NDA 22205: Giazio draft PMCs

Dear Mr. Burgin,

Below, please find the draft Post Marketing Commitments (PMCs) for NDA 022205, GIAZO (balsalazide disodium) tablets, 1.1 g. Please keep in mind that these are draft and subject to final interdisciplinary and supervisory review and modification.

Please review and provide concurrence with milestone dates for both PMCs.

1. A placebo-controlled clinical trial in female active ulcerative colitis patients to assess the efficacy of an eight week course of Giazio therapy for the treatment active disease in this patient population. (b) (4)

[Redacted]

Final Protocol Submission: _____
Study Completion Date: _____
Final Report Submission: _____

2. A pharmacokinetic study in patients to evaluate the effect of concomitant therapy with antibiotics commonly used in ulcerative colitis on the metabolism of balsalazide following administration of Giazio.

Final Protocol Submission: _____
Study Completion Date: _____
Final Report Submission: _____

If you have any questions, please feel free to contact me at your earliest convenience.

Best Regards,

Roland Girardet, *MHS, MS, MBA*
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: (301) 796-3827
Email: roland.girardet@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22205

ORIG-1

SALIX
PHARMACEUTICA
LS INC

BALSALAZIDE DISODIUM
TABLETS

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/s/

ROLAND GIRARDET

04/14/2010

Girardet, Roland

From: Girardet, Roland
Sent: Tuesday, April 13, 2010 10:48 AM
To: 'Burgin, Benjamin'
Subject: NDA 22205: Giazo PI as of 04/13/2010
Attachments: Giazo PI 04_13_10.doc

Dear Mr. Burgin,

Attached, please find a clean Word copy of the Giazo package insert which includes the Division's most recent revisions. Please note that this is not a final version and that additional edits are likely, particularly in the Highlights section which may be effected by further edits to the Full Prescribing Information. Also, please note the yellow highlighted text which asks for information to be provided.

In Table 1, "2.7%" is highlighted to illustrate that this number does not conform with the title of the table.

If you have any questions, please feel free to contact me at your convenience.

Best Regards,

Roland Girardet, *MHS, MS, MBA*
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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Silver Spring, MD 20993-0002
Phone: (301) 796-3827
Email: roland.girardet@fda.hhs.gov

10 Page(s) of Draft Labeling have been Withheld in Full as
b4 (CCI/TS) immediately following this page

Application
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ROLAND GIRARDET

04/14/2010



NDA 022205

INFORMATION REQUEST

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

Dear Mr. Burgin:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Giazo (balsalazide disodium) tablets, 1100 mg.

We also refer to your February 16, 2010, submission, containing revised carton and container labeling.

We are reviewing 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.

A. GENERAL COMMENTS FOR ALL CONTAINER LABELS AND CARTON LABELING

1. As currently presented, the established name appears in a very thin font that is difficult to read. In accordance with 21 CFR 201.10 (g)(2), ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. The dosage form should be presented in the same font as the established name. Remove the bolding from "tablets" and match the font to that of the established name (see comment A.1 above).
3. The product strength is not easy to identify on the proposed labels and labeling. 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 net quantity statement.
4. Assure that there is a space between the numerical value and the unit of measure designation in the strength to avoid crowding and confusion (e.g. 1.1 g versus the current 1.1g).

B. PROFESSIONAL SAMPLE CARTON [REDACTED] (b) (4) (6 COUNT SAMPLE)

As currently presented, there are no directions of use for the [REDACTED] (b) (4). We request you include a statement that explains the intended use of the [REDACTED] (b) (4). If there is not enough room on the [REDACTED] (b) (4), consider printing this statement on the attached carton labeling. Ensure the statement does not distract from the proprietary name, established name, or strength presentation.

C. PROFESSIONAL SAMPLE CONTAINER LABEL (6 COUNT SAMPLE)

The 6 count sample is a unit-of-use package; therefore, include the following statement on the side panel to ensure patients self administer this medication correctly: "Take this medication with food." To provide room for this statement and to minimize crowding the side panel, remove the information regarding U.S. patent numbers.

D. RETAIL CONTAINER LABELS AND PROFESSIONAL SAMPLE CONTAINER LABELS (180 COUNT BOTTLES)

The 180 count bottle can be dispensed as a unit-of-use bottle. Please assure this bottle utilizes child-resistant closures to comply with the Poison Prevention Packaging Act of 1970.

E. RETAIL CONTAINER LABELS AND PROFESSIONAL SAMPLE CONTAINER LABELS (6 COUNT, 180 COUNT, AND 500 COUNT BOTTLES)

1. The [REDACTED] (b) (4) used to differentiate the net quantity on the principle display panel is inappropriately applied. As currently presented, the [REDACTED] (b) (4) affords the net quantity a greater prominence than the product name and strength. Remove the [REDACTED] (b) (4) on the principle display panel to allow room to address comment A.3 above. Once you remove the [REDACTED] (b) (4) change the white text to black to improve readability.
2. Minimize the manufacturer's name and logo on the principle display panel. As currently presented, this information is in larger font than that of the established name and strength presentation.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, M.B.A.
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

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Product Name

NDA-22205

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/s/

MATTHEW C SCHERER

04/06/2010

MEMORANDUM OF TELECON

DATE: March 29, 2010

APPLICATION NUMBER: NDA 022205

BETWEEN:

Name: Benjamin Burgin, RAC

Phone: 919-447-3404

Representing: Salix Pharmaceuticals, Inc.

AND

Name: Roland Girardet, Regulatory Project Manger

Division of Gastroenterology Products, HFD-180

SUBJECT:

Salix's decision to pursue male-only labeling for Giazio

Background:

On March 23, 2010, the Division of Gastroeneterology Products held a teleconference with Salix Pharmaceuticals to assess their interest in labeling Giazio for males-only and addressing the issue of lack of efficacy in females by conducting a post-marketing study. During the teleconference, Salix stated that they required some time to consider this option and would provide a response at a later date.

Discussion:

Salix stated that they were interested in pursuing male-only labeling and conducting a post-marketing study to address the issue of lack of efficacy in females. Salix stated they would submit revised labeling to reflect the gender-specific indication.

The call ended.

SIGNER'S NAME/TITLE

Application
Type/Number

Submission
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Submitter Name

Product Name

NDA-22205

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/s/

ROLAND GIRARDET

04/14/2010

MEMORANDUM OF TELECON

DATE: 03/23/2010

APPLICATION NUMBER: NDA 022205

BETWEEN:

Name: William P. Forbes, Pharm.D., Executive Vice President,
R&D and Chief Development Officer
Enoch Bortey, Ph.D., Associate Vice President,
Biostatistics, Data Management and Programming
Audrey Shaw, Ph.D., Director, Clinical Development
David Dobrowski, Director, Regulatory
Pam Golden, Ph.D., Director, Development
Benjamin Burgin, R.A.C., Senior Manager, Regulatory

Phone: 1-800-615-2830
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Joyce Korvick, M.D., M.P.H., Deputy Director for Safety,
Division of Gastroenterology Products
John Hyde, Ph.D., M.D., Medical Team Leader, Division of
Gastroenterology Products
Chris Leptak, M.D., Ph.D., Medical Reviewer, Division of
Gastroenterology Products
Mike Welch, Ph.D., Deputy Director, Division of
Biometrics III
Shahla Farr, Ph.D., Biostatistics Reviewer, Division of
Biometrics III
Insook Kim, Ph.D., Clinical Pharmacology Reviewer,
Division of Clinical Pharmacology III

Division of Gastroenterology Products (DGP), HFD-180

SUBJECT: Discussion of male only labeling with PMC for additional study

Background:

On October 26, 2009, Salix submitted a complete response to the complete response action issued by the Division of Gastroenterology Products on December 22, 2008. During the preliminary review of the resubmission, the FDA determined that Salix had not satisfactorily

addressed the outstanding issue of the high placebo response rate observed in female patients in study, BZUC-3002. However, given the significant treatment response observed males in this study, the Division would be willing to explore the option of labeling the product in male patients only since effectiveness in female patients was not demonstrated. The purpose of this teleconference was to discuss the current situation with Salix and to assess their interest in indicating Giazio for men (b) (4)

Discussion:

The FDA stated that in reviewing the totality of the information presented thus far, the issue of the differential gender response observed in study BZUC3002 was still unresolved. In attempting to understand this issue further, data from the Colazal application (NDA 20610) was reviewed and a similar, though less pronounced, trend towards a higher placebo response rate in women was also observed.

The FDA stated that it was currently exploring different options on how to use the information submitted in the Giazio application, given the lack of treatment effect shown in women. One option, which the FDA may be willing to consider, would be to review data from an additional clinical trial aimed at addressing the gender disparity issue and, in the meantime, using the information currently in the application to label product for men only.

Under this scenario, Salix would be required to make the following amendments to their proposed package insert:

- Amend the indication to reflect a male-only indication
- Add language which states that effectiveness in women had not been shown
- Separate safety information by gender
- Amend the Clinical Trials section (14.1) of the package insert to:
 - Include male only data
 - include separate bar graphs by gender for data from study BZUC3002
 - include information by gender on the secondary endpoints for data from study BZUC3002

Salix was asked to submit a commitment to perform an additional study to address the issue of effectiveness in women. The FDA recommended that in order to most completely address the agency's concerns regarding the lack of treatment effect in women, Salix should consider a three-armed study design comparing Giazio, Colazal and Asacol to placebo.

Also, in order to comply with the Pediatric Research Equity Act (PREA), should an approval action ultimately be taken on this application, Salix will be required to study Giazio in pediatric patients over the age of 12 years. As such, Salix should submit a pediatric plan for this study as soon as possible. This study should provide pharmacokinetic (PK) as well as safety data in pediatric patients.

Salix asked if the FDA intended to request any changes to the Colazal labeling in light of the

information observed in the Giazio trials. The FDA stated that, at this time, there was no plan to require amendments to the Colazal labeling.

Salix stated that they needed time to discuss how they wished to proceed with the application and would provide a response to the FDA after a decision had been reached. The FDA stated that, given the fast approaching PDUFA goal date of April 27, 2010, a response would be necessary very soon in order to complete the review of the application. Salix acknowledged the limited time frame and pledged to respond quickly.

The call ended.

Roland Girardet, Regulatory Project Manger
SIGNER'S NAME/TITLE

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22205

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/s/

ROLAND GIRARDET

04/26/2010



NDA 22-205

ACKNOWLEDGE CLASS 2 RESPONSE

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

Dear Mr. Burgin:

We acknowledge receipt on October 27, 2009, of your October 26, 2009, resubmission to your new drug application for Giazio (balsalazide disodium) Tablets, 1,100 mg.

We consider this a complete, class 2 response to our December 22, 2008, action letter. Therefore, the user fee goal date is April 27, 2010.

If you have any questions, call me at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Roland Girardet, M.H.S., M.S., M.B.A.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
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Submitter Name

Product Name

NDA-22205

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/s/

ROLAND GIRARDET

11/10/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-205

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

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for balsalazide disodium 1.1 g tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 16, 2009. The purpose of the meeting was to discuss the complete response action taken by the Division of Gastroenterology Products and to identify steps needed to address the deficiencies described in the Complete Response letter dated December 22, 2008.

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) 796-3827.

Sincerely,

{See appended electronic signature page}

Roland Girardet, M.H.S., M.S., M.B.A.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 16, 2009
TIME: 9:00-10:00 a.m. EDT
LOCATION: CDER White Oak, Bldg. 22, Rm. 1309
APPLICATION: NDA 22-205
DRUG NAME: (balsalazide disodium) delayed release tablets, 1.1 g.
TYPE OF MEETING: Type A

MEETING CHAIR: John Hyde, Ph.D., M.D., Clinical Team Leader

MEETING RECORDER: Roland Girardet, M.H.S., M.S., M.B.A.

FDA ATTENDEES:

Division of Gastroenterology Products

Donna Griebel, M.D., Director
John Hyde, Ph.D., M.D., Clinical Team Leader
Chris Leptak, M.D., Ph.D., Clinical Reviewer
Ruyi He, M.D., Acting Deputy Director
Mike Welch, Ph.D., Biometrics Team Leader
Shahla Farr, M.S., Biometrics Reviewer
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader
Insook Kim, Ph.D., Clinical Pharmacology Reviewer
Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

David Dobrowski, Director, Regulatory Affairs
Benjamin Burgin, R.A.C., Senior Manager, Regulatory Affairs
Bill Forbes, Pharm.D., Vice President

(b) (6)

Audrey Shaw, Ph.D., Director Clinical Development
Shirley Huang, Senior Biostatistician

(b) (6)

BACKGROUND:

On December 22, 2008, a Complete Response action was taken on NDA 22-205 concluding a second review cycle. The Complete Response letter described two deficiencies that needed to be addressed for future approval. The first deficiency was the inadequate justification of the (b) (4) non-inferiority (NI) margin selected by Salix for Study BZUC3003. The second deficiency related to the inability of the resubmission to adequately address the difference in

placebo response rates between genders, which led to the Approvable action on May 16, 2008, at the conclusion of the first review cycle.

On January 7, 2009, Salix requested a Type A meeting to discuss the Complete Response action. The Type A meeting was scheduled for February 5, 2009; however, due to a scheduling conflict on the part of Salix, the meeting was rescheduled for February 12, 2009. Due to another scheduling conflict on the part of Salix, this meeting was rescheduled for March 16, 2009. On February 3, 2009, Salix submitted the meeting background package, which was received by FDA on February 4, 2009. Preliminary responses were faxed to Salix on March 13, 2009. Salix submitted responses to FDA's preliminary responses via email on March 15, 2009. Because those materials were not submitted as part of the meeting package, they were not formally reviewed. They are included as an attachment to these minutes.

MEETING OBJECTIVES:

Salix's stated objectives for this meeting are listed below:

- Discuss the Division's decision to not approve NDA 22-205 despite the totality of the data provided in the application, including the demonstrated efficacy of balsalazide disodium in the two studies, BZUC3002 and BZUC3003.
- Gain clarification from the Division on the approval requirements for an NDA for a new formulation of an approved and marketed product.
- Gain clarification regarding how the Division determined the appropriateness of the non-inferiority margin and the specifics of the "Agency statistical practice" cited in the Complete Response letter dated December 22, 2008.
- Discuss the options available to Salix within the Agency to seek approval of the existing application.

DISCUSSION POINTS:

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

MEDICAL

- 1) Salix believes that the placebo response in females in study BZUC3002 does not preclude the Division from approving NDA 22-205. Salix is not aware of any reference that suggests that females with ulcerative colitis do not respond to 5-ASA agents including prodrug delayed or extended release formulations of 5-ASA products. Salix believes that the observed response in placebo-treated females was an anomalous finding. Additionally, a consistent efficacy response to balsalazide disodium is demonstrated across subgroups in studies BZUC3002 and BZUC3003. Is the Division aware of any data in 5-ASA products that would demonstrate the reproducibility of the observed placebo response in study BZUC3002?

FDA Response:

Study BZUC3002 lacked consistency of treatment effect between men and women, subpopulations that were equally represented in the study. A substantial therapeutic gain was demonstrated for men (37%), but a strikingly different result was found for women (-4%). Efficacy of balsalazide disodium (BD) tablets was not established in female patients.

Study BZUC3003 did not address the concerns that led to the first approvable action, which were stated in the first action letter. When a more appropriate non-inferiority (NI) margin is chosen, the efficacy of BD tablets was not demonstrated by a non-inferiority comparison to Asacol, thus providing no new support for the efficacy of BD tablets in this patient population and rendering the study unable to address the question of efficacy in females. The absence of a placebo arm further impaired the ability of the study to address the discrepancy in treatment effect between men and women that was found in the study BZUC3002.

Several of your referenced publications, as well as an additional one by Kane et al. (Reviews in Gastroenterological Disorders, 2003; 3(4), 210-218), have identified a wide range of placebo-response rates in UC clinical trials. Although a sub-analysis by gender was not included as part of the analyses in these publications, a survey of those studies that were placebo controlled showed placebo-response rates (including both male and female patients) approaching values as high as 75%. The studies varied greatly in their design, including duration of treatment; the data are therefore strictly intended only to give a reference range. The placebo-response rate in women in study BZUC3002 (58%) is within the range of published placebo-response rates. An effective product would still be expected to show a least a strong positive trend in a population with a large fraction of placebo responders. If there were not supporting evidence for a placebo-response rate as high as that seen in study BZUC3002, then we would be more inclined to question the importance of the finding and perhaps consider it to be a statistical anomaly in one study arm, as you suggest. However, the study findings from published literature do not compel that interpretation.

We also looked at the studies submitted under NDA 20-610, the original NDA for the approval of Colazal capsules, to determine if a gender disparity in treatment effect was found. We concluded that those data were unable to address the issue. The two main studies that led to the approval of Colazal capsules were of a non-inferiority design without placebo arms. The application did include one placebo-controlled, four-week study, CP069101, but none of the primary or secondary endpoints showed statistically significant differences between Colazal- and placebo-treated patients. It cannot be considered to be informative about gender differences in efficacy. (However, it is noteworthy that a subgroup analysis of the study by gender found that women had a greater placebo response than men in six of the seven endpoints, and the difference was pronounced.)

The totality of the evidence leaves open the question of whether there may, in fact, be a differential treatment effect of BD tablets between men and women with UC. The reasons for a potential gender disparity are unclear. However, until the question is resolved, such discrepancies need to be addressed adequately in an application before BD tablets are

approved. The results of the two studies submitted in support of your current NDA provided inadequate data to support labeling guidance to the medical community regarding the observed differential efficacy between men and women with UC.

Meeting Discussion:

Salix stated that it had done further sub-analyses of the data from Study BZUC3002 and focused on the endoscopic subscore as a more objective and widely recognized measure of clinical remission compared to other subscores such as rectal bleeding or stool frequency [see attached response of 3/15/09 from Salix]. Salix noted that an EMEA guidance on this subject supported the endoscopic subscore as a more reliable endpoint in ulcerative colitis. Salix felt that an improvement of two or more points in the endoscopic subscore was a more realistic measure of improvement. They further noted that a sub-analysis of this endpoint showed an improvement in both genders compared to placebo.

FDA stated that it was not possible to comment fully on the newly presented sub-analysis results provided by Salix, and could not, therefore, come to any final conclusions or agreements as to the appropriateness of this re-analysis at this time. Given the high variability in response rates seen in IBD studies, FDA emphasized that the most appropriate outcome measure of success is the one that was pre-specified prior to commencement of the study. Post-hoc analyses such as the ones being presented by Salix need to be interpreted with considerable caution.

Salix stated that if the study were judged solely on the original pre-specified endpoint of “all-patients” (regardless of gender), it would show that the drug was efficacious. Salix felt that the gender sub-analysis performed by FDA was exploratory and should not outweigh the results of the all-patients analysis. FDA stated that before Salix submitted their original NDA, they were advised that if only one Phase 3 study was submitted in support of its application, the results of this study would have to be both robust in meeting its primary endpoint and internally consistent. Since the original single study (BZUC3002) did not achieve a highly significant p-value and the gender sub-analysis showed a substantial difference in treatment effect between genders, the single study did not achieve this level of robustness. Additional data from BZUC3003 included as part of the NDA’s resubmission did not address the outstanding issues adequately to support approval.

FDA asked Salix what endpoints it thought drove the high placebo response rate in women. Salix responded that bowel frequency was largely responsible for the high placebo response rate. FDA asked Salix if a higher placebo response rate in females for bowel frequency has been observed in other inflammatory bowel trials. Salix stated that this phenomenon was common in IBS trials. FDA stated that it frequently observed variations in sub-analyses when reviewing studies; however, it was extremely unusual to see a difference in treatment effect between genders as large as that seen in study BZUC3002, and that a principal focus of the resubmission should have been to address this issue. FDA remarked that it might have been helpful if the types of analysis presented by Salix at the meeting had been provided in their resubmission.

Salix stated it felt that if the totality of the evidence, which included one placebo-controlled trial, one active-controlled trial, and PK study data, were taken into account, enough evidence was presented to support approval. Salix stated that since this application was for a “line extension” of a known drug, the standard of evidence required for single studies of new drugs did not apply. Salix stated that it noted that the Agency did not take into account the response rate of females in the second study (BZUC3003) which it felt helped to address the concerns from the first study. FDA stated that, without a placebo arm in BZUC3003, overall treatment effect (treatment response minus placebo response) could not be adequately determined.

Salix asked what would be an adequate package to address the concerns of the agency. FDA stated that additional clinical data with the drug would be best; however, Salix could also consider relying on additional external information from whatever sources it could find which could help explain the gender difference observed in BZUC3002. Also, it might be helpful to include data addressing whether there could be a difference between genders in the rate or extent of conversion of balsalazide to mesalamine. Any resubmission should be primarily focused on resolving the question about gender treatment effect differences, and it should be comprehensive. The onus was on Salix to convince the Division that the observed high placebo response rate was, in fact, spurious and that the data convincingly support a true treatment effect in women similar to that seen in men.

FDA added that the single trial in the first submission along with PK data might have been sufficient to warrant approval if the large gender treatment effect difference had not been present. The FDA felt the second study did not provide significant additional information because they did not view it as successful and it did not have a placebo arm as part of its design. Any future submission from Salix must address directly the gender treatment effect discrepancy.

- 2) By applying a ^{(b) (4)} methodology (Fisher et al [see Attachment 6]) to the efficacy results of the balsalazide tablets vs Asacol (BZUC3003) and the Asacol vs placebo trial (Sninsky - the data used by the Division to establish the non-inferiority margin) a statistical significance was obtained for balsalazide tablet vs placebo. A placebo arm was considered in the design in the BZUC3003 trial, but due to the reluctance of the medical community and IRBs, along with a required rescue for subjects, a placebo was not included in this trial. The ^{(b) (4)} analysis yielded an odds ratio of ^{(b) (4)} (95% confidence interval of ^{(b) (4)} demonstrating that balsalazide tablet is ^{(b) (4)} when compared with placebo. Therefore, we have demonstrated ^{(b) (4)} of balsalazide tablet to placebo in two adequate trials (BZUC3002 and BZUC3003). This finding reiterates Salix’s strong belief that the data in the NDA for balsalazide tablet should warrant approval. Does the Division concur with Salix’s assessment?

FDA Response:

We do not agree. Please refer to our response to Question 5.

Meeting Discussion:

Salix noted that FDA's response to Question 2 was to refer to Question 5, implying that the two issues were the same. Salix felt that the issue of (b) (4) and non-inferiority margin were distinct from each other. Salix explained the (b) (4) calculation methodology and stated that, while the non-inferiority paradigm was a more rigorous methodology, the analysis of the data in study BZUC3003 with a (b) (4) does show efficacy in both genders.

The FDA stated that it was familiar with the (b) (4) methodology, but from a regulatory standpoint, this method cannot be used to establish (b) (4) of the treatment to placebo, and the FDA considers this approach to be exploratory.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

- 3) The therapeutically active moiety responsible for topical activity and systemic toxicity, 5-ASA, meets the accepted criteria for bioequivalence when adjusting for the dosing interval (i.e., AUC₈ x 3 for the capsule and AUC₁₂ x 2 for the tablet). This suggests that dosing with the balsalazide tablet at a dose of 3.3 g bid or Colazal capsules at the current marketed dose of 2.25 g tid provides equivalent exposure to 5-ASA at steady state following multiple dosing over a 24 hour period (see Attachment 1, Question 1). Did the Division acknowledge this formulation equivalency in the decision to not approve NDA 22-205?

FDA Response:

The relative bioavailability of the BD tablet and Colazal capsules was not a factor for the Agency's decision. Because of differences in dosing regimens between your proposed product and the reference product, PK data are insufficient to infer efficacy. Therefore, clinical trial data are the basis for determining efficacy of your product.

Meeting Discussion:

FDA stated that PK data are of limited use in this case because the drug is locally acting and the change in the drug dosing regimen (BID vs. TID) prevented the PK data from being used to extrapolate efficacy. Salix replied that even if PK data were of limited use, it did provide an important component of the overall application and should be taken into consideration in the approvability. Salix further stated that based on the FDA's response to Question 3, it had the impression that PK was not taken into account in the totality of the data.

FDA responded that it did take the PK data into account, but that it did not help to resolve the deficiency concerns delineated in the Complete Response action letter. FDA further stated that this application involved a change in dosing regimen, and, for this type of change, PK data could not be relied upon to extrapolate drug efficacy.

- 4) Salix believes the similarity of the formulation performance characteristics of Colazal capsules and balsalazide tablets is demonstrated in multiple attributes. Both immediate release formulations of Colazal capsules and balsalazide disodium tablets have similar

performance characteristics including, but not limited to, product dissolution profiles which show complete drug availability for therapeutic effect well before introduction to the large intestine. In addition, the balsalazide tablet or Colazal capsules provides equivalent exposure to 5-ASA at steady state following multiple dosing over a 24 hour period. Salix believes there are no meaningful differences between the formulations. Can the Division provide any identified meaningful differences in the formulations?

FDA Response:

The relative bioavailability study (BZPK1003) in the original submission was not intended for demonstrating bioequivalence between the BD tablet and the Colazal capsule formulations. The study provided a descriptive summary of the effect of dosage form and dosing regimen on the PK of balsalazide and its metabolites in plasma based on 95% confidence intervals for the mean of each treatment.

In addition, it was noted that the C_{max} of balsalazide was significantly higher following a single dose of 2.25 g Colazal than after a single dose of 3.3 g BD tablet, despite a higher dose for BD tablet.

Please also see our response to Question 3.

Meeting Discussion:

No further discussion.

STATISTICAL

- 5) Salix is requesting the Division provide specific information regarding the “Agency statistical practice” cited in the Complete Response letter dated December 22, 2008. In addition, Salix is requesting the Division elaborate on the specific data used by the Division to determine the non-inferiority margin.

FDA Response:

Using the Sninsky publication data, an NI margin was calculated as follows (as previously discussed with you and referenced in the Complete Response letter):

Response Rate at Week 6		
Mesalamine (2.4 g) (95% CI)	Placebo (95% CI)	Difference (95% CI)
21/43=49% (33%, 65%)	10/44=23% (11%, 38%)	26% (6%, 45%)

The treatment difference was 26% with the lower limit of the 95% confidence interval (CI) at 6%. Applying a 50% discount to the lower confidence limit to establish the NI margin, the margin would be 3% for patients with mild to moderate UC treated for the duration of six weeks.

Meeting Discussion:

Salix argued that using only one study as a reference did not create a valid basis for establishing a non-inferiority (NI) margin. Salix stated that another study, (b) (4) study, was similar in design to the Sninsky study and could have also been used for comparison in calculating the NI margin.

FDA stated that they agree that basing an NI margin based on one small study may not establish the ideal NI margin. If, for example, two comparable studies were used to calculate a margin, then a more likely margin might have been 6%. FDA reemphasized that the NI margin is calculated using the lower bound of the confidence interval of the treatment effect size and preserving 50% efficacy. Even if the NI margin were increased to 6%, study BZUC3003 would still have not been determined to be successful. Salix stated that the true effect size was probably closer to 20% than to 6%. FDA stated that its approach is a conservative one and is done to guard against approval of a truly inferior drug product, but is a common practice for CDER statisticians. Regarding the (b) (4) study, FDA felt that the differences between this study and BZUC3003 were substantial enough to preclude using the (b) (4) data in calculating an appropriate NI margin. The FDA further stated that their procedure was consistent with ICH E10 guidelines.

REGULATORY

- 6) Salix considers the study information provided in the application for balsalazide tablets to be consistent with subsection 403(b)(2) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the May 1998 Guidance for Industry titled “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”. Salix believes the totality of the data submitted (clinical studies BZUC3002 & BZUC3003) within the NDA is sufficient to support approval of a reformulated marketed product. Salix requests the Division provide clarification on the specific approval requirements for a reformulation of an approved marketed product.

FDA Response:

Section II.C. of the May 1998 Guidance for Industry titled “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” describes the quantity of evidence to support effectiveness. This section states that “reliance on a single study of a given use ... leaves little room for study imperfections or contradictory (non-supportive) information.” The unexplained difference between genders in the treatment effect, accompanied by the high placebo-response rate in females, presented an important imperfection. The gender difference was numerically large, clinically significant, and associated with a small nominal p-value. While study BZUC3003 provided additional safety information, it did not adequately address the issue of treatment effect inconsistency between genders seen in study BZUC3002 to warrant marketing approval. The magnitude of the gender imbalance was inconsistent with other marketed 5-ASA drugs and should be addressed with evidence from additional clinical trial data.

Meeting Discussion:

No further discussion.

- 7) Salix requests the Division provide specific steps to be fulfilled, as cited in the complete response letter, in order that the application for balsalazide tablets may be approved.

FDA Response:

Approval of BD tablets for the treatment of mildly to moderately active UC would be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent findings across important subgroups, namely, males and females. Before initiating such a study, we recommend that you obtain input from FDA regarding the study design, including any use of non-inferiority comparisons.

Meeting Discussion:

No further discussion.

MEETING AGREEMENTS

No formal agreements were discussed or mutually endorsed. Additionally, FDA stressed that it was not possible at the time of the meeting to determine the acceptability of Salix's additional comments or analyses that were received on March 15.

ATTACHMENTS

Response from Salix submitted via E-mail on March 15, 2009.

Medical

1) Salix believes that the placebo response in females in study BZUC3002 does not preclude the Division from approving NDA 22-205. Salix is not aware of any reference that suggests that females with ulcerative colitis do not respond to 5-ASA agents including prodrug delayed or extended release formulations of 5-ASA products. Salix believes that the observed response in placebo-treated females was an anomalous finding. Additionally, a consistent efficacy response to balsalazide disodium is demonstrated across subgroups in studies BZUC3002 and BZUC3003. Is the Division aware of any data in 5-ASA products that would demonstrate the reproducibility of the observed placebo response in study BZUC3002?

FDA Response:

Study BZUC3002 lacked consistency of treatment effect between men and women, subpopulations that were equally represented in the study. A substantial therapeutic gain was demonstrated for men (37%), but a strikingly different result was found for women (-4%). Efficacy of balsalazide disodium (BD) tablets was not established in female patients.

Study BZUC3003 did not address the concerns that led to the first approvable action, which were stated in the first action letter. When a more appropriate non-inferiority (NI) margin is chosen, the efficacy of BD tablets was not demonstrated by a non-inferiority comparison to Asacol, thus providing no new support for the efficacy of BD tablets in this patient population and rendering the study unable to address the question of efficacy in females. The absence of a placebo arm further impaired the ability of the study to address the discrepancy in treatment effect between men and women that was found in the study BZUC3002.

Several of your referenced publications, as well as an additional one by Kane et al. (Reviews in Gastroenterological Disorders, 2003; 3(4), 210-218), have identified a wide range of placebo-response rates in UC clinical trials. Although a sub-analysis by gender was not included as part of the analyses in these publications, a survey of those studies that were placebo controlled showed placebo-response rates (including both male and female patients) approaching values as high as 75%. The studies varied greatly in their design, including duration of treatment; the data are therefore strictly intended only to give a reference range. The placebo-response rate in women in study BZUC3002 (58%) is within the range of published placebo-response rates. An effective product would still be expected to show a least a strong positive trend in a population with a large fraction of placebo responders. If there were not supporting evidence for a placebo-response rate as high as that seen in study BZUC3002, then we would be more inclined to question the importance of the finding and perhaps consider it to be a statistical anomaly in one study arm, as you suggest. However, the study findings from published literature do not compel that interpretation.

We also looked at the studies submitted under NDA 20-610, the original NDA for the approval of Colazal capsules, to determine if a gender disparity in treatment effect was found. We concluded that those data were unable to address the issue. The two main studies that led to the approval of Colazal capsules were of a non-inferiority design without placebo arms. The application did include one placebo-controlled, four-week study, CP069101, but none of the primary or secondary endpoints showed statistically significant differences between Colazal- and placebo-treated patients. It cannot be considered to be informative about gender differences in efficacy. (However, it is noteworthy that a subgroup analysis of the study by gender found that women had a greater placebo response than men in six of the seven endpoints, and the difference was pronounced.)

The totality of the evidence leaves open the question of whether there may, in fact, be a differential treatment effect of BD tablets between men and women with UC. The reasons for a potential gender disparity are unclear. However, until the question is resolved, such discrepancies need to be addressed adequately in an application before BD tablets are approved. The results of the two studies submitted in support of your current NDA provided inadequate data to support labeling guidance to the medical community regarding the observed differential efficacy between men and women with UC.

Salix Response:

Study BZUC3002 was an adequate well-controlled trial that was statistically significant in favor of balsalazide disodium vs placebo. There was a consistent treatment response for balsalazide subjects (male and female). In contrast, the placebo response rate in this trial was strikingly different between males and females. Placebo response rates from published literature, as noted by the Division, have been found to be highly variable and as high as 75%. This heterogeneity of placebo response rates across trials can also result in spurious results in subgroup analysis.

The definition of “clinical improvement” utilized in study BZUC3002 contributes to the high placebo response rate. A more stringent definition of “clinical remission” currently endorsed by regulatory authorities (endoscopy score 0 or 1 without rectal bleeding) results in a response rate in favor of balsalazide disodium (Tables 1, 2, 3, and 4).

Table 1 Endoscopy Score of 0 or 1 at EOT

Gender/ Time Point	Response	Balsalazide Disodium n (%)	Placebo n (%)	Difference in Proportions(3)	95% CI
Male		N=81	N=40		
Week 8/EOT	Yes	40 (49.4%)	7 (17.5%)	31.9%	15.8%,47.9%
	No	41 (50.6%)	33 (82.5%)		
Female					(b) (4)
Week 8/EOT					

Table 2 Endoscopy Score Improvement by 2 at EOT

Gender/ Time Point	Response	Balsalazide Disodium n (%)	Placebo n (%)	Difference in Proportions(3)	95% CI
Male		N=81	N=40		
Week 8/EOT	Yes	16 (20%)	0 (0%)	20%	11%, 28%
	No	65 (80%)	40 (100%)		
Female	(b) (4)				
Week 8/EOT					

Table 3 Rectal Bleeding of 0 at EOT

Gender/ Time Point	Response	Balsalazide Disodium n (%)	Placebo n (%)	Difference in Proportions(3)	95% CI
Male		N=81	N=40		
Week 8/EOT	Yes	37 (46%)	7 (17%)	28%	12%, 44%
	No	44 (54%)	33 (83%)		
Female	(b) (4)				
Week 8/EOT					

Table 4 Endoscopy Score of 0 or 1 and Bleeding of 0 at EOT

Gender/ Time Point	Response	Balsalazide Disodium n (%)	Placebo n (%)	Difference in Proportions(3)	95% CI
Male		N=81	N=40		
Week 8/EOT	Yes	28 (35%)	4 (10%)	24%	11%, 38%
	No	53 (65%)	36 (90%)		
Female	(b) (4)				
Week 8/EOT					

Our conclusion after examining these data is that more objective and reliable measures support efficacy in the treated females.

Furthermore, the treatment effect of females in study BZUC3002 is substantiated by the female response in BZUC3003. The females in BZUC3003 had a numerically greater response than males.

Additionally, the pharmacokinetic data from study BZPK1003 broken out by gender demonstrate females do not handle BD tablets appreciatively different in the rate and extent of converting balsalazide disodium to mesalamine. This is true whether looking at gender with BD tablets or looking between BD tablets and Colazal.

ATTACHMENT: Responses from Salix submitted via E-mail on March 15, 2009

2) By applying a (b)(4) methodology (Fisher et al [see Attachment 6]) to the efficacy results of the balsalazide tablets vs Asacol (BZUC3003) and the Asacol vs placebo trial (Sninsky - the data used by the Division to establish the non-inferiority margin) a statistical significance was obtained for balsalazide tablet vs placebo. A placebo arm was considered in the design in the BZUC3003 trial, but due to the reluctance of the medical community and IRBs, along with a required rescue for subjects, a placebo was not included in this trial. The (b)(4) analysis yielded an odds ratio of (b)(4) (95% confidence interval of (b)(4)) demonstrating that balsalazide tablet is (b)(4) when compared with placebo. Therefore, we have demonstrated (b)(4) of balsalazide tablet to placebo in two adequate trials (BZUC3002 and BZUC3003). This finding reiterates Salix's strong belief that the data in the NDA for balsalazide tablet should warrant approval. Does the Division concur with Salix's assessment?

FDA Response:

We do not agree. Please refer to our response to Question 5.

Salix Response:

The Agency's response to Question 5 provided specific information and elaboration for how the Division determined the non-inferiority margin that it considered appropriate but it did not address Question 2 which pertained to the (b)(4) that the sponsor showed through the method of Fisher, et al. A demonstration of (b)(4) is a demonstration of efficacy relative to (b)(4). Also, since the Sninsky, et al. article was used by the Division to establish the non-inferiority margin because it was considered by the Division to be comparable to BZUC3003 in terms of population and endpoint, it correspondingly provides a reasonable basis for an assessment of the (b)(4) of BD tablets to (b)(4) by the methodology in Fisher, et al.

Clinical Pharmacology and Biopharmaceutics

3) The therapeutically active moiety responsible for topical activity and systemic toxicity, 5-ASA, meets the accepted criteria for bioequivalence when adjusting for the dosing interval (i.e., AUC₈ x 3 for the capsule and AUC₁₂ x 2 for the tablet). This suggests that dosing with the balsalazide tablet at a dose of 3.3 g bid or Colazal capsules at the current marketed dose of 2.25 g tid provides equivalent exposure to 5-ASA at steady state following multiple dosing over a 24 hour period (see Attachment 1, Question 1). Did the Division acknowledge this formulation equivalency in the decision to not approve NDA 22-205?

FDA Response:

The relative bioavailability of the BD tablet and Colazal capsules was not a factor for the Agency's decision. Because of differences in dosing regimens between your proposed product and the reference product, PK data are insufficient to infer efficacy. Therefore, clinical trial data are the basis for determining efficacy of your product.

ATTACHMENT: Responses from Salix submitted via E-mail on March 15, 2009

Salix Response:

With the approval of generic balsalazide disodium products in December 2007, FDA set precedent that determined bioequivalence for balsalazide drug products is based upon two items: (1) Equivalent dissolution and (2) equivalent PK parameters. FDA determined that in vitro dissolution testing using GI mimicked conditions is an appropriate surrogate for in vivo dissolution testing. Additionally, in the FDA's response to citizen's petition docket no. 2005P-0146, demonstration of equivalent pharmacokinetic parameters of mesalamine assures us that balsalazide disodium reaches the colon and is converted to mesalamine at an equivalent rate for both the generic formulation and the reference listed drug.

Both Colazal and BD tablets meet USP <711> immediate release dissolution specification. In the relative bioavailability study BZPK1003, the therapeutically active moiety responsible for topical activity and systemic toxicity, 5-ASA, meets the accepted criteria for bioequivalence when adjusting for the dosing interval (i.e., $AUC_{8 \times 3}$ for the capsule and $AUC_{12 \times 2}$ for the tablet) and not by dose over 24 hours.

The dissolution data between these two immediate-release products coupled with the results of the relative bioavailability trial provide sufficient evidence that the BD tablet and Colazal capsules reach the colon and are converted to mesalamine to an equivalent extent.

Salix contends that the available dissolution and PK data are important data in the evaluation of balsalazide products and approval of BD tablets should be based primarily on the totality of the evidence provided by dissolution and PK and further substantiated by supportive clinical data.

4) Salix believes the similarity of the formulation performance characteristics of Colazal capsules and balsalazide tablets is demonstrated in multiple attributes. Both immediate release formulations of Colazal capsules and balsalazide disodium tablets have similar performance characteristics including, but not limited to, product dissolution profiles which show complete drug availability for therapeutic effect well before introduction to the large intestine. In addition, the balsalazide tablet or Colazal capsules provides equivalent exposure to 5-ASA at steady state following multiple dosing over a 24 hour period. Salix believes there are no meaningful differences between the formulations. Can the Division provide any identified meaningful differences in the formulations?

FDA Response:

The relative bioavailability study (BZPK1003) in the original submission was not intended for demonstrating bioequivalence between the BD tablet and the Colazal capsule formulations. The study provided a descriptive summary of the effect of dosage form and dosing regimen on the PK of balsalazide and its metabolites in plasma based on 95% confidence intervals for the mean of each treatment.

In addition, it was noted that the C_{max} of balsalazide was significantly higher following a single dose of 2.25 g Colazal than after a single dose of 3.3 g BD tablet, despite a higher dose for BD tablet.

ATTACHMENT: Responses from Salix submitted via E-mail on March 15, 2009

Please also see our response to Question 3.

Salix Response:

In the relative bioavailability study BZPK1003, the therapeutically active moiety responsible for topical activity and systemic toxicity, 5-ASA, meets the accepted criteria for bioequivalence when adjusting for the dosing interval (i.e., $AUC_{8 \times 3}$ for the capsule and $AUC_{12 \times 2}$ for the tablet) and not by dose over 24 hours.

Statistical

5) Salix is requesting the Division provide specific information regarding the “Agency statistical practice” cited in the Complete Response letter dated December 22, 2008. In addition, Salix is requesting the Division elaborate on the specific data used by the Division to determine the non-inferiority margin.

FDA Response:

Using the Sninsky publication data, an NI margin was calculated as follows (as previously discussed with you and referenced in the Complete Response letter):

Response Rate at Week 6		
Mesalamine (2.4 g) (95% CI)	Placebo (95% CI)	Difference (95% CI)
21/43=49% (33%, 65%)	10/44=23% (11%, 38%)	26% (6%, 45%)

The treatment difference was 26% with the lower limit of the 95% confidence interval (CI) at 6%. Applying a 50% discount to the lower confidence limit to establish the NI margin, the margin would be 3% for patients with mild to moderate UC treated for the duration of six weeks.

Salix Response:

Although the sponsor appreciates this explanation for how the Division determined the non-inferiority margin of 3%, it is puzzled as to how an effect size of 26% in the Sninsky, et al. article becomes translated to a seemingly worst case effect size of 6% from which the 50% discounting leads to 3%. The 26% effect size in the Sninsky, et al. article is compatible with an at least 20% effect size (D’Haens et al.) being the target of studies to establish clinically relevant superiority for indications like that addressed by study BZUC3003. The sponsor utilized the observed results from 12 studies that had a rational bridging relationship with BZUC3003 to determine the (b)(4) margin. The BZUC3003 study was a well designed study with an overall sample size of ~400 patients, and it provided a precise confidence interval for the difference between BD tablets and Asacol with the inclusion of this interval being within plus or minus (b)(4). That confidence interval well supports the efficacy of the BD tablet formulation through ruling out differences between the BD tablet formulation and Asacol of (b)(4) or more with this margin being less than half of the usual effect size of 20% or more in superiority studies

ATTACHMENT: Responses from Salix submitted via E-mail on March 15, 2009

with a bridging relationship to BZUC3003 and less than the 26% effect size in the Sninsky, et al. published data.

Regulatory

6) Salix considers the study information provided in the application for balsalazide tablets to be consistent with subsection 403(b)(2) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the May 1998 Guidance for Industry titled “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”. Salix believes the totality of the data submitted (clinical studies BZUC3002 & BZUC3003) within the NDA is sufficient to support approval of a reformulated marketed product. Salix requests the Division provide clarification on the specific approval requirements for a reformulation of an approved marketed product.

FDA Response:

Section II.C. of the May 1998 Guidance for Industry titled “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” describes the quantity of evidence to support effectiveness. This section states that “reliance on a single study of a given use ... leaves little room for study imperfections or contradictory (non-supportive) information.” The unexplained difference between genders in the treatment effect, accompanied by the high placebo-response rate in females, presented an important imperfection. The gender difference was numerically large, clinically significant, and associated with a small nominal p-value. While study BZUC3003 provided additional safety information, it did not adequately address the issue of treatment effect inconsistency between genders seen in study BZUC3002 to warrant marketing approval. The magnitude of the gender imbalance was inconsistent with other marketed 5-ASA drugs and should be addressed with evidence from additional clinical trial data.

Salix Response:

The efficacy and safety of BD tablets has not been established solely on a single clinical trial. The application includes important data from in vitro dissolution, in vivo PK, and 2 adequate well-controlled clinical trials. Salix believes that the difference in response rates by gender has been examined and explained in Question 1. The data from study BZUC3003 shows no treatment/gender interaction. Based upon the totality of the data provided (PK, dissolution, clinical), Salix believes there is sufficient evidence to approve BD tablets for the treatment of mildly to moderately active ulcerative colitis.

7) Salix requests the Division provide specific steps to be fulfilled, as cited in the complete response letter, in order that the application for balsalazide tablets may be approved.

FDA Response:

Approval of BD tablets for the treatment of mildly to moderately active UC would be dependent upon the review of additional efficacy data from an adequate and

ATTACHMENT: Responses from Salix submitted via E-mail on March 15, 2009

well-controlled study that would demonstrate substantial evidence of effectiveness and consistent findings across important subgroups, namely, males and females. Before initiating such a study, we recommend that you obtain input from FDA regarding the study design, including any use of non-inferiority comparisons.

Salix Response:

Additional placebo-controlled clinical trials in this indication have major ethical dilemmas and, in our opinion, are no longer in the best interest of patients. An additional non-inferiority clinical trial is inherently problematic because of uncertainty for the implications of an excessively small margin to prohibitively large sample size.

Salix contends that the available dissolution and PK data are important data in the evaluation of balsalazide products and approval of BD tablets should be based primarily on the totality of the evidence provided by dissolution and PK and further substantiated by 2 adequate and well-controlled clinical trials.

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/s/

Roland Girardet
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NDA 22-205

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

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

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) dated July 16, 2007, received July 17, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Tablets, 1.1 g.

We also refer to your September 8, 2008, correspondence, received September 9, 2008, requesting reconsideration of your proposed proprietary name, Giazio. We have completed our review of Giazio and have concluded that it is acceptable.

In addition, we have the following comments related to your carton and immediate container labels:

1. The size of the font used for the dosage form and strength should be the same as that which is used in the established name.
2. The strength "1.1g" should be located after the dosage form.

If **any** of the proposed product characteristics as stated in your July 16, 2007, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

NDA 22-205

Page 2

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.

Director

Division of Gastroenterology Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Donna Griebel

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DRAFT REVIEWERS' COMMENTS

NDA: 22-205

Product: Balsalazide Disodium Tablets, 1100mg

Sponsor: Salix Pharmaceuticals, Inc.

Indication: treatment of mild to moderately active ulcerative colitis in patients 18 years of age and older

Type of Meeting: Type A

Meeting Date: March 16, 2009

Introductory Comment:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 16, 2009, 9:00-10:00 a.m., CDER White Oak, bldg 22, Rm. 1309 between Salix Pharmaceuticals, Inc. and the Division of Gastroenterology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Roland Girardet, 301-796-3827). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecom). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan/the purpose of the meeting/to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact Roland Girardet to discuss the possibility of including these for discussion at the meeting.

Attachment is 5 duplicate pages from the Memorandum of Meeting Minutes dated March 16, 2009 that can be found in the Administration and Correspondence Review section of this Approved NDA.

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/s/

Roland Girardet
3/13/2009 03:52:30 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-205

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

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (Balsalazide Disodium) 1.1 g tablets.

We also refer to your January 7, 2009, correspondence, received January 8, 2009, requesting a meeting to discuss the regulatory action taken on December 22, 2008.

We further refer to the telephone conversation between yourself and Roland Girardet, Regulatory Project Manager, on February 10, 2009, in which you indicated that the revised meeting date of February 12, 2009, created another scheduling conflict for Salix. As agreed upon during this conversation, the meeting date has been changed as indicated below.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: March 16, 2009

Time: 9:00-10:00 a.m. EDT

Location: CDER White Oak, Building 22, Room 1309

CDER participants:

Donna Griebel, M.D., Director

John Hyde, Ph.D., M.D., Medical Team Leader

Christopher Leptak, M.D., Medical Reviewer

Mike Welch, Ph.D., Statistical Team Leader

Shahla Farr, M.S., Statistical Reviewer

Cristi Stark, M.S., Regulatory Project Manager

Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at

NDA 22-205

Page 2

roland.girardet@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Roland Girardet 301-796-3827; the division secretary, Deborah Ward, 301-796-4771.

If you have any questions, call me at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Roland Girardet
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Roland Girardet
3/2/2009 04:36:57 PM



NDA 22-205
Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (Balsalazide Disodium) 1.1 g tablets.

We also refer to your January 7, 2009, correspondence, received January 8, 2009, requesting a meeting to discuss the regulatory action taken on December 22, 2008.

We further refer to the telephone conversation between yourself and Roland Girardet, Regulatory Project Manager, on January 14, 2009, in which you indicated that the original meeting date of February 5, 2009 created a scheduling conflict for Salix. As agreed upon during this conversation, the meeting date has been changed as indicated below.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: February 12, 2009
Time: 3:00-4:00 p.m. EDT
Location: CDER White Oak, Building 22, Room 1419

CDER participants:

Donna Griebel, M.D., Director
Christopher Leptak, M.D., Medical Reviewer
Mike Welch, Ph.D., Statistical Team Leader
Shahla Farr, M.S., Statistical Reviewer
Cristi Stark, M.S., Regulatory Project Manager
Roland Girardet, M.H.S., M.S., M.B.A, Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at roland.girardet@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to

request an escort to the conference room: Roland Girardet 301-796-3827; the division secretary, Deborah Ward, 301-796-4771.

Provide the background information for this meeting (three copies to the NDA and five desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by January 30, 2009, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Roland Girardet
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Roland Girardet
1/29/2009 03:43:07 PM



NDA 22-205

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

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (Balsalazide Disodium) 1.1 g tablets.

We also refer to the FDA correspondence dated December 22, 2008, which constituted a complete response to your amendment dated June 30, 2008. It has come to our attention that, due to a typographical error, two number sets were inadvertently transposed on page number two of the complete response letter (Clinical and Statistical deficiencies, Section 1, third paragraph).

We have corrected the transposed number sets in the italicized paragraph below. The number sets of interest are underlined for identification purposes only:

The Sninsky article reports that the six-week combined treatment outcomes of patients classified as “in remission” or “improved” were: 21/43 (49%) patients in the Asacol 2.4 g/day treatment arm and 10/44 (23%) patients in the placebo treatment arm achieved clinical improvement (an endpoint similar to the primary efficacy endpoint assessment for Study BZUC3003).

We apologize for any confusion which might have resulted from this typographical error. Although the numbers in the complete response correspondence were transposed, the statistical analyses and conclusions were derived using the non-transposed number sets. The regulatory action stands as stated in the correspondence.

If you have any questions, call Roland Girardet, Project Manager, at 301-796-3827.

Sincerely,

{See appended electronic signature page}

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

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/s/

Donna Griebel

1/15/2009 06:31:24 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-205

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

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (Balsalazide Disodium) 1.1 g tablets.

We also refer to your January 7, 2009, correspondence, received January 8, 2009, requesting a meeting to discuss the regulatory action taken on December 22, 2008.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: February 5, 2009

Time: 4:00-5:00 p.m. EDT

Location: CDER White Oak, Building 22, Room 1309

CDER participants:

Donna Griebel, M.D., Director

Christopher Leptak, M.D., Medical Reviewer

Mike Welch, Ph.D., Statistical Team Leader

Shahla Farr, M.S., Statistical Reviewer

Cristi Stark, M.S., Regulatory Project Manager

Roland Girardet, M.H.S., M.S., M.B.A, Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at roland.girardet@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Roland Girardet 301-796-3827; the division secretary, Deborah Ward, 301-796-4771.

NDA 22-205

Page 2

Provide the background information for this meeting (three copies to the NDA and five desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by January 22, 2009, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Roland Girardet
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Roland Girardet
1/14/2009 11:28:04 AM

MEMORANDUM OF TELECON

DATE: November 13, 2008

APPLICATION NUMBER: NDA 22-205

BETWEEN:

Name: Bill Forbes, VP Research & Development and Chief Development Officer
David Dobrowski, Director, Regulatory Affairs
Benjamin Burgin, Senior Manager, Regulatory Affairs
Enoch Bortey, Executive Director, Biostatistics, Data Mgmt, &
Programming
Shirley Huang, Senior Biostatistician
Audrey Shaw, Director, Clinical Development
Shadreck Mareya, Manager, Clinical Development
Phone: 1-800-910-2586 Passcode: 967430
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Donna Griebel, M.D., Director
John Hyde, Ph.D., M.D., Medical Team Leader
Christopher Leptak, M.D., Ph.D. Medical Reviewer
Shahla Farr, Ph.D., Biostatistical Reviewer
Maria Ysern, Ph.D., Chemistry Reviewer
Roland Girardet, Regulatory Project Manager
Representing: Division of Gastroenterology Products, HFD-180

SUBJECT: Communication of deficiencies that preclude the Division of Gastroenterology Products from entering into labeling negotiations at this time.

As part of Good Review Management Practices (GRMP), which state that the FDA should advise Applicants of the deficiencies that preclude entering into labeling discussions when those discussions will not begin six weeks before the PDUFA goal date, the Division of Gastroenterology Products (DGP) held a teleconference with Salix Pharmaceuticals, Inc., (Salix) to convey two deficiencies that currently preclude the Division from beginning labeling negotiations.

The following two deficiencies were communicated to Salix:

1. The choice of (b) (4) as the non-inferiority (NI) margin for BZUC3003, the new active-controlled study included in Salix's resubmission of NDA 22-205, was not appropriate. As discussed in ICH E10, DGP stressed that the choice of an appropriate NI margin should be pre-specified, evidence-based, and determined based upon placebo-controlled studies of the active comparator (Asacol 2.4 g/day). Those placebo-controlled studies of the active comparator should have an analogous study design to the study of interest,

including similar patient populations, inclusion/exclusion criteria, treatment duration, and efficacy endpoints. In order to calculate the appropriate non-inferiority margin, FDA referred to the original studies submitted in support of Asacol's FDA approval and the Sninsky publication from 1991 that the Applicant included as part of the NDA 22-205 resubmission. FDA calculated the 95% CI for the treatment difference between Asacol and placebo. Applying a 50% discount to the lower confidence limit, which is the Agency's procedure for margin selection, FDA determined that the margin should not exceed 3%. (b) (4)

2. The concern of gender disparity of treatment effect remains as an unresolved deficiency. BZUC3002 was the only clinical study in the original submission of NDA 22-205 on July 16, 2007. In the placebo-controlled treatment arm of BZUC3002, female patients had a much higher placebo response than male patients. This differential placebo response lead, in part, to a lack of demonstrated treatment effect in women with UC on balsalazide disodium therapy. This disparity was a reason for an approvable regulatory action being taken for NDA 22-205's original submission, and the deficiency was included in the Approvable Letter dated May 16, 2008. Although FDA acknowledged that BZUC3003 did include a sub-analysis by gender, the lack of a placebo arm in the active-controlled study did not address nor clarify the high placebo response rate found in female patients in BZUC3002. As discussed, FDA is unable to know how to reflect this disparity of treatment effect in men and women in product labeling to appropriately advise the medical community.

FDA stressed that the NDA was still under review and that should additional deficiencies be identified, those concerns would be shared with Salix as well.

Salix asked if there was any more information that it could submit to help the Division in completing its review. FDA stated that it is not currently requesting any additional information to complete its review.

No agreements were discussed or mutually supported by both Salix and the FDA.

Roland Girardet, RPM
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Roland Girardet
12/17/2008 05:21:24 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-205

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

Dear Mr. Dowbrowski:

We acknowledge receipt on June 30, 2008, of your June 30, 2008, resubmission to your new drug application for Balsalazide Disodium Tablets, 1100 mg.

We consider this a complete, class 2 response to our May 16, 2008 action letter. Therefore, the user fee goal date is December 31, 2008.

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

If you have any question, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Cristi L. Stark, M.S.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Cristi Stark

7/31/2008 12:03:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-205

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

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Tablets, 1100 mg.

We also refer to the meeting between representatives of your firm and the FDA on June 9, 2008. The purpose of the meeting was to discuss your plans for a complete response to our approvable letter sent to you May 16, 2008, as well as the trade name.

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) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, M.S., M.B.A.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 9, 2008
TIME: 1:00 PM – 2:00 PM EST
LOCATION: FDA CDER WO 1309 conf rm Bldg22 - AR
APPLICATION: NDA 22-205
DRUG NAME: Balsalazide Disodium Tablets, 1100 mg
TYPE OF MEETING: Type A: Post-Action

MEETING CHAIR: Ruyi He, M.D.

MEETING RECORDER: Heather Buck

FDA ATTENDEES:

Joyce Korvick, M.D., M.P.H., Division Director, Division of Gastroenterology Products
Ruyi He, M.D., Medical Team Leader, Division of Gastroenterology Products
Fathia Gibril, M.D., Medical Officer, Division of Gastroenterology Products
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, Office of New Drug Quality
Assessment
Maria Ysern, M.Sc., Chemistry Reviewer, Office of New Drug Quality
Assessment
Mike Welch, Ph.D., Deputy Director, Division of Biometrics 3
Shahla Farr, Ph.D., Statistical Reviewer, Division of Biometrics 3
Denise Toyer, Pharm.D., Deputy Director, Division of Medical Error Prevention (DMEP)
Diane C. Smith, Pharm. D., Safety Evaluator, Division of Medical Error Prevention
Heather Buck, M.S., M.B.A., Regulatory Project Manager, Division of Gastroenterology
Products

SALIX PHARMACEUTICALS ATTENDEES:

William P. Forbes, PharmD., VP R&D and Chief Development Officer
Enoch Bortey, Ph.D., Executive Director, Biostatistics, Data Management and Programming
David Dobrowski, Director, Regulatory Affairs
Benjamin Burgin, RAC, Senior Manager, Regulatory Affairs

BACKGROUND:

On May 16, 2008, we sent an approvable letter to your NDA submitted on July 16, 2007.

On May 19, 2008, you submitted a meeting request and intent to file an amendment.

On June 2, 2008, we received preliminary questions for the present meeting, to which we sent preliminary responses on June 5, 2008.

MEETING OBJECTIVES:

The meeting objective is to discuss your plans for a complete response to our approvable letter sent to you May 16, 2008, as well as the trade name.

DISCUSSION POINTS:

Note: Sponsor questions are in plain text, FDA responses are in **bold** text, and meeting discussion is in *bold italics*.

Question 1

In the approvable letter dated May 16, 2008, the Division cited two items needed to complete the review of balsalazide tablets; namely:

- a. Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.
- b. The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis.

Salix proposes that reference to the 120-day safety update, submitted November 16, 2007, which contains a full integrated clinical trial report for clinical study BZUC3003 will constitute a complete response to the approvable letter dated May 16, 2008 and that no additional clinical efficacy data or study is required. Clinical Study BZUC3003 is a comparator study of balsalazide tablets and Asacol. Does the Division concur that this study constitutes a complete response and is sufficient in providing the relevant data to resolve the issues stated in the approvable letter, e.g. a lack of consistency of treatment effect between men and women and demonstration of a persuasive finding of treatment effect?

FDA Response:

Your second study (BZU3003) appears to be an adequate and well controlled study and would constitute a complete response to the approvable letter dated May 16, 2008. However, the adequacy of efficacy data from this study cannot be determined without comprehensive review. Please clarify if subgroup analyses including demographic and baseline disease characteristics, and analysis by center, have been performed.

We cannot locate the efficacy dataset in your 120-day safety update submitted November 30, 2007. Please submit the efficacy datasets for your second study (BZU3003) in your complete response.

Meeting Discussion:

Salix claimed that all of the efficacy data was submitted via 3 CDs with the 120-day safety update on November 16, 2007. Additional data was then submitted

on November 30, 2008. The Division said they did not have the previously submitted efficacy data and that Salix would need to resubmit it with the complete response. The Division asked that all study documents and data relating to Study BZU3003 be resubmitted in the complete response, regardless of what was previously submitted in either 120-day safety update submission.

Salix asked how the Division preferred the efficacy data subgroup analyses. The Division reiterated that the gender subgroup data would not be interpreted in a confirmatory manner, but should be consistent with results based on the entire study population. If center enrollments are very small, it is sufficient to combine data from the centers by region to explore any differences in regional effects. The Division is also interested in the derivation and justification for Salix's non-inferiority margin; adequacy of the margin will be a review concern.

Question 2

Salix proposes that previously submitted 120-day safety update (dated November 16, 2007) is sufficient to fulfill the request for a safety update in the approvable letter. The 120-day safety update includes the clinical study report for BZUC3003, an updated ISS, ISE, product label, and updated CTD summaries. There are no additional safety data or safety findings at this time. Does the Division concur that no additional safety update is needed in order to complete the review of NDA 22-205?

FDA Response:

Your proposal is not acceptable. You need to provide an updated ISS. We understand that you have an ongoing long-term, open-label safety study, and you need to provide updated available safety data.

Meeting Discussion:

The timeframe covered by the next 120-day safety update was clarified. The Division will expect two submissions: a cumulative safety data including any new data from the time of the last 120-day submission in November, 2007, to now (this includes an updated ISS), and another 120-day safety update from the date of the complete response.

Question 3

Salix believes that the use of the trade name "Colazal" for balsalazide tablets will lead to increased confusion and medication errors. Salix is aware of the potential of medication errors between Colazal capsules and Clozaril tablets (see attached article) and that this issue was mitigated by the difference in dosage form (capsules vs tablets). Salix proposes that a different trade name is justified for the balsalazide tablet in order to minimize the potential for medication errors. Does the agency concur?

FDA Response:

Salix concludes that if balsalazide tablets are marketed under the proprietary name Colazal, there will be an increased potential of confusion with Clozaril because they share the tablet dosage form and have orthographic similarity. We believe that the Applicant's conclusions are flawed for the following reasons.

We note the article erroneously refers to both Colazal and Clozaril as tablets. However, it does not make reference to any differences in dosage form (i.e., capsule vs. tablets) as a mitigating factor to minimize error. We acknowledge that the article states that Colazal and Clozaril share orthographic similarity and the potential for confusion increases when "orders for Clozaril 75 mg [are] written improperly with a terminal zero (75.0 mg)." The proposed dose for the tablet formulation is 1.1 grams or 1100 milligrams which is higher than the maximum dose of Clozaril which is 900 milligrams per day, Thus the likelihood of confusion between Clozaril and Colazal (Balsalazide) 1.1 grams (i.e., 1100 mg) is minimal.

We believe that the safest way to minimize medication errors is to manage both balsalazide 1.1 grams and balsalazide 750 mg under one proprietary name, Colazal.

Meeting Discussion:

Salix does not want to use the name "Colazal" because it is 'genericized', i.e., when a prescription is written for Colazal, the patient could get one of five different drugs on the market. The Colazal brand is not strong enough, and its future is not certain. The Division believes that Salix did not submit a strong enough argument to support this. The FDA-conducted (Failure Mode Effect Analysis) FMEA showed that use of two names resulted in more errors, mainly the likelihood of concomitant therapy. Use of one name resulted in less errors. The Division recommended that Salix conduct their own FMEA using one, then two proprietary names, and analyze results on both sides of the test. It is recommended that Salix submit this data along with their argument for a trade name. Either this data will be sufficient enough to support the use of a second trade name, or Colazal will be the accepted trade name. Salix should plan for the trade name review to take 90 days, and should submit new draft labeling.

Question 4

Salix proposes to submit updated drug product stability data as part of the complete response. This will include three bulk tablet lots each packaged into both 6-count and 500-count HDPE bottles with 24 months of real-time data. One of those bulk tablet lots is also packed in (b) (4) HDPE bottles with 18 months of real time data. Salix believes that this updated data is sufficient to support a proposed 36 month expiry for balsalazide tablets. Does the Division concur with Salix's proposal to submit updated stability data in the complete response?

FDA Response:

We will accept updated stability data with the complete response. The data will be reviewed to determine if it supports your new proposed expiry date.

*Meeting Discussion:
No further comments.*

*Additional Discussion:
Salix plans to submit their complete response to the approvable letter the first week of July 2008.*

DECISIONS (AGREEMENTS) REACHED:

N/A

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

N/A

ACTION ITEMS:

N/A

ATTACHMENTS/HANDOUTS:

Salix distributed copies of the approvable letter issued by the Division (not attached as can be found in DFS).

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/s/

Heather G Buck
6/18/2008 10:32:41 AM

Ruyi He
6/18/2008 10:58:31 AM

From: [Buck, Heather](#)
To: ["david.dobrowski@salix.com"](mailto:david.dobrowski@salix.com); ["Burgin, Benjamin"](#);
CC:
Subject: 22-205 Type A Meeting Revision
Date: Thursday, May 29, 2008 10:41:30 AM
Attachments:

This email is to confirm that our scheduled meeting for June 9, 2008 at 1:00 pm EST is now face-to-face rather than via phone as requested. Please find revised meeting details below. Let me know if you have questions.

Phone Arrangements: (b) (4)

Please have all your attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at heather.buck@fda.hhs.gov so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Heather Buck x. 61413; Doris Garrison x. 60896.

Thanks,

Heather Buck, M.S., M.B.A.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
(301) 796-1413
fax (301) 796-9905
Heather.Buck@fda.hhs.gov

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/s/

Heather G Buck
5/29/2008 10:45:58 AM
CSO



NDA 22-205

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

Dear Mr. Burgin:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Tablets, 1100 mg.

We also refer to your correspondence received May 19, 2008 requesting a meeting to discuss your plans for a complete response to our approvable letter sent to you May 16, 2008. We further refer to our discipline review letter regarding your proposed trade name Giazo, sent to you May 22, 2008. Per email correspondence between Benjamin Burgin and Heather Buck on May 23, 2008, we understand you wish to also discuss the trade name.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: June 9, 2008

Time: 1:00 PM – 2:00 PM EST

Phone Arrangements:

(b) (4)

CDER Participants:

- Donna Griebel, M.D., Division Director, Division of Gastroenterology Products
- Ruyi He, M.D., Medical Team Leader, Division of Gastroenterology Products
- Fathia Gibril, M.D., Medical Officer, Division of Gastroenterology Products
- Sue-Chih Lee, Ph.D., Clinical Pharmacology Leader, Division of Clinical Pharmacology 3
- Insook Kim, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
- Sushanta Chakder, Ph.D., Supervisory Pharmacologist, Division of Gastroenterology Products
- Ke Zhang, Ph.D., Pharmacology Reviewer, Division of Gastroenterology Products
- Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, Office of New Drug Quality Assessment
- Maria Ysern, M.Sc., Chemistry Reviewer, Office of New Drug Quality Assessment
- Mike Welch, Ph.D., Deputy Director, Division of Biometrics 3
- Shahla Farr, Ph.D., Statistical Reviewer, Division of Biometrics 3

- Todd Bridges, R.Ph., Team Leader, Division of Medication Error Prevention
- Cheryle Milburn, R.N., Regulatory Project Manager, Office of Surveillance and Epidemiology
- Heather Buck, M.S., M.B.A., Regulatory Project Manager, Division of Gastroenterology Products

As discussed, we will not be expecting a background package for this meeting. We do, however, ask that you provide a list of questions prior to the meeting. Please email these questions to heather.buck@fda.hhs.gov at least 1 week prior to the meeting (by June 2, 2008).

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

Sincerely,

{See appended electronic signature page}

Heather Buck, M.S., M.B.A.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Heather G Buck

5/27/2008 02:31:49 PM



NDA 22-205

DISCIPLINE REVIEW LETTER

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

Dear Mr. Burgin:

Please refer to your July 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Giazio (balsalazide disodium) Tablets 1100 mg.

We also refer to your submission dated August 16, 2007 proposing the trade name Giazio, and to our approvable letter sent to you on May 16, 2008.

We have completed our review of your proposed trade name, Giazio, and labeling.

We do not recommend the use of the trade name, Giazio. The results of the Proprietary Name Risk Assessment found that the proposed name, Giazio, is confusing and misleading because the product may be concomitantly ordered and administered with the currently marketed product Colazal. Rather than use a dual trade name, we recommend the use of a single trade name, Colazal, for all balsalazide disodium products that you market.

We also have the following labeling recommendations.

Carton and Container Labels, Including the Sample Carton

1. Relocate the dosage form to ensure it immediately follow the established name (e.g., balsalazide disodium tablets).
2. Relocate the net quantity to the lower third of the container label and ensure the prominence is less than the product strength.
3. Revise to include a statement noting the “new strength” and “dosing interval”. This statement should not appear on the labeling for a period to exceed 6 months.
4. Revise the color scheme for the proprietary name so that the entire name is presented in one color font and font type.
5. Ensure that the established name is at least ½ the size of the proprietary name and the strength is proportional to the proprietary and established name.
6. Relocate the dosage form to ensure it immediately follows the established name (e.g., balsalazide disodium tablets).

7. Increase the size and prominence of the product strength.
8. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207-35(b)(3)(i).

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Heather G Buck
5/22/2008 08:43:27 AM



NDA 22-205

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

Dear Mr. Burgin:

Please refer to your new drug application (NDA) dated July 16, 2007, received July 17, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Giazio (balsalazide disodium) Tablets, 1100 mg.

We acknowledge receipt of your submissions dated August 16, September 21, November 16, November 21, November 30, and December 22, 2007, and February 15, February 20, March 6, March 10, March 20, and March 24, 2008.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to resolve the following:

Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.

The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Gastroenterology Products to discuss what steps need to be taken before the application may be approved.

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Donna Griebel

5/16/2008 04:31:38 PM



NDA 22-205

INFORMATION REQUEST LETTER

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

Dear Mr. Burgin:

Please refer to your July 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Giazio (balsalazide disodium) Tablets 1100 mg.

We also refer to your responses received November 21, 2007, December 22, 2007, and February 21, 2008 to our initial Information Requests dated November 19, 2007, December 21, 2007, and February 12, 2008 respectively.

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

1. For the Phase 3 trials, was the drug administered with or without food?
2. For the study BZPK1003, please provide the relative BA information after multiple dosing based on "AUC_{tau} multiplied by the dosing frequency in a day" without dose-normalization. In other words, the comparison is between AUC_{8 x 3} for the capsule and AUC_{12 x 2} for the tablet. Both the point estimate for the ratio and its 90% CI should be provided.
3. Regarding Question 1 of your February 21, 2008 response:
 - a. In your explanation for the high placebo response rates for females, you claim that females with baseline MMDAI score ≥ 9 had a larger placebo response, and no placebo males with severe baseline disease responded. We do not believe this is a sufficient explanation. In fact, the response rates for females with baseline MMDAI ≥ 9 was 13/20 (65%) and was similar to that for females with MMDAI < 9 : 12/23 (52%). For treated females, the response rates were (b) (4) for the high and low baseline categories, respectively.

- b. While subjects who have severe disease measured at baseline may typically regress to the mean" without treatment, your explanation does not address why a high placebo response rate was not observed for males.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Brian Strongin
3/11/2008 03:27:09 PM



NDA 22-205

INFORMATION REQUEST LETTER

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

Dear Mr. Burgin:

Please refer to your July 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Giazio (balsalazide disodium) tablets 1100 mg.

We also refer to your 4-Month Safety Update submitted November 16, 2007, as well as your November 21, 2007 and December 22, 2007 responses to our Information Requests dated November 19, 2007 and December 21, 2007 respectively.

We are reviewing the Clinical, Statistical, and Chemistry, Manufacturing, and Controls (CMC) sections 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. Our preliminary review of the efficacy data indicates that there is a significantly higher placebo response rate in females than in males for study BZUC3002. Please provide explanations for the discrepancy in placebo response rates between males and females.
2. Please add an acceptance criterion for [REDACTED] (b)(4) to the drug product specification.
3. Your dissolution profile is unique for an immediate release dosage form in that it takes [REDACTED] (b)(4) to achieve complete dissolution, with approximately [REDACTED] (b)(4) dissolved in [REDACTED] (b)(4). To ensure batch-to-batch consistency for your product and consistent efficacy, we recommend that you add a dissolution acceptance criterion at 30 minutes, in addition to the 90 minute requirement that you proposed, unless you can provide acceptable justification as to why this is not required.
4. The first paragraph of Page 1510 of Vol. 21, Section 3.2.1 of your submission states that "any missing responses (scores) will be replaced with the average of the non-missing scores to calculate the component score, this rule applies to total score as well." However, in other sections you have stated that "for any missing score, the last

observation was carried forward.” It is not clear as to which one of these methods you have used. Please clarify your method of imputation.

5. We have not yet received replies to the following requests in the Information Request letter dated November 19, 2007.
 - a. In addition, please refer to Page 1524 of Vol. 21, Section 4.9 under the heading “Handling of Dropouts or Missing Data.” In the first paragraph of this section, you state that “Subjects who terminate early will be classified as treatment failures.” However, in the next paragraph you state that “for subjects who terminated early, the data from last treatment visit were collected on the EOT case report forms.” For the primary ITT analysis, if you are carrying forward the data from last visit to EOT, explain if these subjects are considered as dropouts and coded as “failures.” Please clarify your definitions of treatment success and treatment failure.
 - b. There is a discrepancy in the number of subjects for the ITT population in the two efficacy datasets you have submitted. For example, in dataset DEFFDIAR, data was available for a total of 246 subjects (165 in balsalazide and 81 in placebo) in the ITT group, however, there are a total of 249 subjects in the dataset DEFFDAI (166 in balsalazide and 83 in placebo). There should have been 250 subjects in each of these studies. Please explain this discrepancy.
 - c. Please provide a description of the method of randomization. Were subjects randomized by center, by region, or by some other factor?

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Brian Strongin
2/12/2008 12:43:46 PM



NDA 22-205

INFORMATION REQUEST LETTER

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

Dear Mr. Burgin:

Please refer to your July 16, 2007 new drug application (NDA) submitted under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for balsalazide disodium tablets. The labeling text for this pending NDA was submitted in Structured Product Labeling (SPL) format, along with the proposed package insert in Physician's Labeling Rule format (PLR) on July 16, 2007.

Please also refer to your 4-Month Safety Update containing updated labeling information submitted November 16, 2007.

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

1. Highlights

- a **Initial U.S. Approval** - The verbatim statement "Initial U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity....
 - The active ingredient balsalazide disodium was first approved as Colazal NDA 20-610 on July 18, 2000¹.
- b Font is currently in 10 point font but must be in 8 point font.
 - Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11 paper, single spaced, 8 point type with ½ inch margins on all sides, in a two-column format)

¹ http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020610&TABLE1=OB_Rx

- c Inconsistent bulleting under headings. Because each heading only contains one item, no bullets are needed; either choose to bullet every subheading or remove bullets.
- If there are multiple subheadings, each subheading must be preceded by a bullet point. [Best Practices].

2. Table of Contents

- Change 13.2 subsection title from "Animal Toxicology" to "Animal Toxicology and/or Pharmacology".

3. Full Prescribing Information

- Remove bold from body systems in subsection 6.1, and from subsection 16. All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly; and use another method for emphasis such as italics or underline. [Best Practices].
- In subsection 6.1 Clinical Studies Experience, include the following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice." (Word copy only; SPL format contains this statement).

Please address the identified deficiencies/issues and re-submit labeling by February 22, 2008. This updated version of labeling will be used for further labeling discussions.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Brian Strongin
1/31/2008 04:57:53 PM



NDA 22-205

INFORMATION REQUEST LETTER

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

Dear Mr. Burgin:

Please refer to your July 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Giazio (balsalazide disodium) Tablets, 1100 mg.

We also refer to your submission dated November 16, 2007.

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. Please provide a safety summary table that includes individual symptoms related to GI events as well as infestation and infectious events for females versus males for pivotal study BZUC3002 (see Table 2.7.4-30).
2. Please identify subjects in both treatment arms that withdrew from the study due to abnormal lab tests and state the abnormal laboratory tests that led to their discontinuation from pivotal study BZUC3002. In addition, help us locate the narrative summary for these subjects in the document submitted.
3. We received the summary table we requested in our information request letter dated November 19, 2007. However, the mean (SD), median, minimum, and maximum for age, BMI, and baseline MMDAI score for each gender that we requested are missing from the tables you provided. Please provide this information.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Brian Strongin
12/20/2007 05:01:41 PM



NDA 22-205

INFORMATION REQUEST LETTER

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

Dear Mr. Burgin:

Please refer to your July 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Giazio (balsalazide disodium) Tablets, 1.1 gm.

We are reviewing the clinical, clinical pharmacology, and statistical sections of your submission and have the following comments and information requests. Except as noted below, questions pertain to your phase 3 study BZUC3002. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please refer to your statistical analysis plan, "Handling of Dropouts or Missing Data" (Vol. 21, Section 4.9, page 1524). It states that "Subjects who terminate early will be classified as treatment failures." However, in the next paragraph it states "for subjects who terminated early, the data from last treatment visit were collected on the EOT case report forms." Please clarify the imputation method applied in your primary ITT analysis; subjects who discontinued early should have been classified as treatment failures, as stated in your study protocol.
2. Regarding the ITT population, dataset DEFFDIAR shows a total of 246 subjects (165 in the balsalazide arm and 81 in the placebo arm), however, in dataset DEFFDAI, there is a total of 249 subjects (166 balsalazide and 83 placebo). Please explain this discrepancy.
3. Please clarify the method of randomization applied in your study. It is not clear if subjects were randomized by center, region, or some other factor.
4. Please provide an additional analysis dataset according to the following requirements:
 - One record (observation) per subject
 - The data should not be imputed (use only observed data)
 - The dataset should include the following variables:
 - Patient
 - Site (do not pool sites)
 - Treatment arm

Gender
Age
Race
Baseline bowel frequency
Baseline bleeding
Baseline physician's global assessment
Baseline endoscopy/sigmoidoscopy
Bowel frequency at each visit
Bleeding at each visit
Physician's global assessment at each visit (if available) and
Endoscopy/sigmoidoscopy result at the end of the study
MMDAI at baseline
MMDAI at the last visit

5. Please provide a summary table of baseline characteristics similar to your Table 2.7.3-9 in Module 2 (page 18) for each gender. Please also include mean (SD), median, minimum and maximum for age, BMI, and baseline MMDAI score for each gender.
6. For Studies BZPK1002 and BZPK1003, please provide the SAS datasets for the human pharmacokinetic studies.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Brian Strongin

11/19/2007 12:10:54 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-205

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

Dear Mr. Burgin:

Please refer to your July 16, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Giazo, (balsalazide disodium) Tablet, 1100 mg.

We also refer to your submission dated August 16, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 15, 2007, in accordance with 21 CFR 314.101(a).

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

At the August 8, 2005, End of Phase 2 meeting and the August 27, 2007, pre-NDA meeting, you were advised that two adequate and well-controlled studies were recommended and that if a single study were submitted, it would be expected to show substantial evidence of efficacy. The level of evidence and data quality will be a review issue; it will be expected that efficacy results across centers, subgroups and other factors, and multiple secondary endpoints demonstrate consistent findings. Other review issues may include sensitivity of results to dropouts, imputation, and center-pooling strategies.

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.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Julieann DuBeau
9/26/2007 02:16:03 PM

August 16, 2007

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

**Subject: Proposed Trade Name
NDA 22-205
Balsalazide Disodium Tablets, 1100 mg**

Dear Dr. Shames:

Please note the above referenced pending New Drug Application (NDA) for balsalazide disodium tablets submitted July 16, 2007 in accord with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older.

Additional reference is made to the pre-NDA meeting with the Division on April 27, 2007 and the proposal by Salix to provide a new trade name and separate package insert for the tablet dosage form of balsalazide disodium. Salix proposes the following trade name for consideration:

Proposed Trade Name: Giazio (pronounced "jē-Ā-zō")

Further reference is made to the draft package insert text provided in Module 1.14.1.3 of the pending NDA for balsalazide disodium tablets. Salix requests a separate package insert for the tablet dosage form based on the following rationale:

1. A separate package insert would minimize potential consumer confusion between the capsule and tablet dosage forms. Important differences between the dosage forms include:
 - Different dosing regimens (3 capsules 3 times a day vs 3 tablets 2 times a day).
 - Different active amounts per unit (750 mg balsalazide disodium per capsule vs 1.1 g balsalazide disodium per tablet).
 - Different total daily doses (6.75 g per day for capsules vs 6.6 g tablets per day for tablets)

Based on the dosing regimen and active amount of each dosage form, confusion between the capsule and tablet could lead to incorrect administration of up to 9.9 g balsalazide disodium per day (tablet taken on capsule regimen) or as little as 4.5 g balsalazide disodium per day (capsule taken on tablet regimen).

2. In the case of Visicol[®] (NDA 21-097) and OsmoPrep[™] (NDA 21-892), the Division allowed separate package inserts when the active amounts were identical (1.5 g sodium phosphate per tablet) and the dosing regimens were different (40 Visicol[®] Tablets vs 32 OsmoPrep[™] Tablets).



We look forward to your review of our request for a new trade name and separate package insert for the tablet dosage form of balsalazide disodium. If there are any questions concerning this submission, please do not hesitate to contact Benjamin Burgin at (919) 447-3404, by fax at (919) 447-3410, or by email at Benjamin.Burgin@salix.com.

Sincerely,
Salix Pharmaceuticals, Inc.

Jill Kompa for JK

Jill Kompa, M.S., RAC
Director, Regulatory Affairs

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/s/

Kristen Everett
8/16/2007 04:46:57 PM



NDA 22-205

NDA ACKNOWLEDGMENT

Salix Pharmaceuticals, Inc
Attention: Jill Kompa, M.S., RAC
Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Kompa:

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

Name of Drug Product:	Tradename (balsalazide disodium) Tablets, 1100 mg
Review Priority Classification:	Standard (S)
Date of Application:	July 16, 2007
Date of Receipt:	July 17, 2007
Our Reference Number:	NDA 22-205

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 September 15, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 17, 2008.

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

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

NDA 22-205

Page 2

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Kristen Everett
7/27/2007 11:40:24 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Pre-NDA

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 38,492

Salix Pharmaceuticals, Inc.
Attention: Jill Kompa, M.S., RAC
Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Kompa:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for balsalazide disodium tablets, 1.1g.

We also refer to the meeting between representatives of your firm and the FDA on April 27, 2007. The purpose of the meeting was to discuss your proposed NDA submission for balsalazide disodium tablets.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 27, 2007
TIME: 11:00 am – 12:00 pm
LOCATION: FDA, White Oak Campus, Building 22, Conference Room 1309
APPLICATION: IND 38,492
DRUG NAME: balsalazide disodium tablets
TYPE OF MEETING: Type B: Pre-NDA

MEETING CHAIR: Fathia Gibril, M.D., M.H.Sc., Acting Medical Team Leader

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

FDA ATTENDEES:

Joyce Korvick, M.D., M.P.H., Acting Director, Division of Gastroenterology Products
Fathia Gibril, M.D., M.H.Sc., Acting Medical Team Leader, Division of Gastroenterology Products
Keith St. Amand, M.D., Medical Officer, Division of Gastroenterology Products
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, Office of New Drug Quality Assessment
Maria Ysern, M.S., Chemistry Reviewer, Office of New Drug Quality Assessment
Abimbola Adebowale, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3
Mike Welch, Ph.D., Acting Biometrics Team Leader, Division of Biometrics 2
Kristen Everett, R.N., Regulatory Project Manager, Division of Gastroenterology Products

SALIX PHARMACEUTICALS, INC. ATTENDEES:

William P. Forbes, PharmD, Vice President, R&D and Chief Development Officer
Jill Kompa, M.S., RAC, Director, Regulatory Affairs
Benjamin Burgin, RAC, Senior Manager, Regulatory Affairs

(b) (4)

Jody Lockhart, M.B.A., Executive Director, Pharmaceutical Development and Manufacturing
Michael Getter, M.S., Associate Director, Statistical Programming
Michael Jiroutek, DrPH, Senior Biostatistician
Shirley Huang, Senior Biostatistician
Scott Lyman, M.S., PMP, Associate Director, Project Management

BACKGROUND:

On February 16, 2007, Salix submitted a Type B Pre-NDA meeting request to discuss their proposed NDA submission for balsalazide disodium tablets.

On March 29, 2007, Salix submitted the background package for the meeting which contained the information and questions for discussion.

On April 26, 2007, the FDA faxed the preliminary responses to the questions contained in the March 29, 2007, background package.

MEETING OBJECTIVES:

Salix identified the following objectives for this meeting:

- To identify and discuss any unresolved issues.
- To identify the adequate and well-controlled study on which Salix is relying to establish the effectiveness of the balsalazide disodium tablets.
- To discuss the proposed statistical analysis plan.
- To obtain agreement on the PREA exemption for the NDA.
- To acquaint the FDA reviewers with the general information to be submitted in the NDA.
- To discuss the data presentation and formatting of the NDA.

DISCUSSION POINTS:

The questions contained in the March 29, 2007, background package are in plain text, the preliminary responses faxed to Salix are in **bold text**, and the meeting discussion from the April 27, 2007, meeting is in ***bold italics***.

Medical Reviewer

1. During the August 8, 2005 EOP2 meeting, Salix and the Division agreed that the submission of a single adequate and well controlled study with the new balsalazide disodium dosage form and strength would be adequate to allow filing of the marketing application in conjunction with certain pharmacokinetic studies. Salix is requesting concurrence with the previously agreed upon strategy.

Response:

In the EOP2 meeting, you were informed that the standard recommendation for approval is 2 adequate and well-controlled clinical trials, unless the results from a single study are robust (or adequate justification is provided as to why two studies are not necessary). It was further clarified that approvability of your new dosage form will ultimately be based on the robustness of the data and the consistency of effect seen in the primary and secondary endpoints. You may file your application with only one trial and our review of the data will determine approvability.

2. The submission will include safety data from approximately 240 patients (randomized 2:1, balsalazide disodium tablet to placebo) enrolled in study BZUC3002 and available long-term exposure data from the on-going open-label Study BZUC3005. Does the FDA agree that the proposed safety database is adequate to support filing of the marketing application?

Response:

Yes, we agree that this safety database, along with the Integrated Summary of Safety (ISS), which will include all safety information related to your product in all dosage forms (i.e., capsule and tablet), is adequate to support filing of your application. However, adequacy of the safety database for approval is a review issue.

3. Since effectiveness is derived from a single adequate and well-controlled study Salix proposes to include the efficacy summary only in Module 2.7.3, Summary of Clinical Efficacy [Note: a complete Clinical Study Report for the single trial would be included in Module 5.3.5, Reports of Efficacy and Safety Studies]. A separate Integrated Summary of

Efficacy (ISE) document will not be prepared and the corresponding efficacy section in Module 5.3.5.3.1, ISE, will refer the reviewer to Module 2.7.3. Does the FDA agree with this proposal?

Response:

We note that a Phase 3 study (BZUC3003) is ongoing and that safety data will be submitted as part of the 120 day safety update. Please clarify when this study is expected to be completed, and if the efficacy data will be submitted as part of your NDA. We require that a separate ISS/ISE be presented under section 5.3.5.3, as the contents of Module 2 are meant to summarize an analysis that is discussed at length in Module 5. Please refer to the following websites for more information:

[http://www.fda.gov/cder/regulatory/ersr/ISS ISE clarification.htm](http://www.fda.gov/cder/regulatory/ersr/ISS%20ISE%20clarification.htm)

<http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>

Meeting Discussion:

If only one study is submitted, then an ISE is not required. However, if additional efficacy data from other studies is included, then an ISE would need to be included in this submission.

4. Long-term safety data from patients enrolled in Study BZUC3002 who participate in the open-label rollover study, Study BZUC3005, will be included in the Integrated Summary of Safety (ISS) and Module 2.7.4, Clinical Safety Summary, but no separate interim study report for BZUC3005 will be included in the marketing application. Does the FDA agree with this approach?

Response:

No. Please submit full safety data for BZUC3005 in Module 5 of your NDA.

Meeting Discussion:

Salix states that they plan to submit an interim safety report of the study. We advised Salix to refer to the Guidance for Industry: The extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions (ICH-E1A, March, 1995). We further explained that although the indication is for 8 weeks of treatment, ulcerative colitis is a relapsing/remitting disease, therefore patients may very well take the medication on a chronic basis. Salix stated that they plan to rely on the Colazal safety data. We agreed that this would be supportive data; however, the capsules are administered three times/day, while the proposed dosing of the tablets is two times/day, thereby exposing the patient to higher doses at each administration. Salix stated that their pharmacokinetic (PK) data will provide information concerning the exposure, and that the preliminary data show the exposure is similar to that of the capsule dosage form.

5. Salix proposes to submit CRFs for patients who discontinued due to adverse events or died during the study as hard copies in an appendix to the final clinical study report. Does the FDA agree with this approach?

Response:

No. Please submit CRFs for patients who discontinued for any reason.

Meeting Discussion:

Salix requested the rationale for submitting CRFs for all patients that discontinued the study and we stated that, although it is not a requirement, we would like to know the reason for each patient that was discontinued from the study.

Statistical Reviewer

6. Does the FDA have any comments on the Statistical Analysis Plan (SAP) for BZUC3002, the summary plan for Module 2.7.3, or the ISS SAP?

Response:

Statistical methods should have been detailed in the study protocol at the design stage. A detailed review of the SAP will be done during the NDA review process. However, it is noted that the SAP states that no adjustments for multiple comparisons will be made. You should be advised that control of Type I error and appropriate adjustment methods are necessary for any secondary endpoints that might be intended for labeling purposes. Otherwise, the secondary analyses will be considered to be for exploratory purposes. Also, since study BZUC3002 is intended to be a single principle study for efficacy, results are expected to be internally consistent and robust, demonstrating substantial efficacy with a p-value considerably smaller than .05.

Meeting Discussion:

We stated that the primary and secondary endpoints should be clearly defined and that introducing new endpoints at this time could be concerning. Salix stated that the protocol has completed enrollment, but that the study had not yet been unblinded.

7. Salix intends to provide summary tables for comparative safety data from the marketed balsalazide disodium capsule formulation to support the safety of balsalazide tablets in patients with mild to moderate ulcerative colitis. The summary tables will be included in the final ISS and are outlined in the ISS SAP. Does the Division have any comments regarding the presentation of the marketed balsalazide capsule safety data in the marketing application?

Response:

Yes, your proposal appears to be acceptable.

8. Salix intends to provide paper copies of the Case Report Tabulations (CRTs) in the domain profile format, commonly referred to as patient data listings as part of the clinical study report. The electronic datasets will be provided in SAS Xport Version 8.2 and Salix is not planning to provide data in the patient profile format. Does the FDA agree with this approach?

Response:

No. SAS Xport data sets should be in V5 format. Please see data specifications under <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>.

Pharmacology Reviewer

9. Does the FDA agree, as discussed during the August 8, 2005 EOP2 meeting, that the nonclinical data that supported the approval of the capsule dosage form is adequate to

support the tablet dosage form and that no additional information is necessary for submission in the tablet marketing application?

Response:

Yes, we agree.

10. For Module 2.4, Module 2.6, and Module 4, Salix proposes to incorporate by cross-reference the nonclinical data submitted under NDA 20-610. Does the FDA agree with this approach?

Response:

Yes, we agree.

Meeting Discussion:

We clarified that a summary of all the non-clinical studies should be included in Module 2 in this NDA submission. Salix stated that this would involve a significant amount of research and information that will need to be gathered from the original 1997 NDA submission. Salix stated that they will provide a summary in this NDA submission.

Chemistry Reviewer

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

Response:

Preparation of an environmental assessment is required unless the proposed action qualifies for exclusion under 21CFR 25.30 or 21 CFR 25.31. An NDA would not qualify for categorical exclusion if FDA's approval of the application increases the use of the active moiety and the estimated concentration of the substance at the point of entry into the aquatic environment will be 1 ppb or greater.

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

Response:

The submission of only one executed drug product batch record will be adequate if it is representative of the commercial manufacturing process.

13. Does the Division have guidance on the content and/or format of the information that will be included in Module 3?

Response:

To ensure that all the needed information is included, we recommend that you refer to *Guidance for Industry: M4Q: The CTD (Common Technical Document for the Registration of Pharmaceuticals for Human Use)-Quality*, which may be found on the FDA website.

Regulatory

14. Salix will be submitting a paper submission in the CTD format [Note: the required SAS datasets will be provided in SAS Xport Version 8.2 and labeling components will be submitted electronically]. Does FDA have any comments concerning the proposed Table of Contents?

Response:

We have no comments regarding the TOC. XPT files should be submitted in SAS version 5, which is our current standard. SPL files should be submitted in a separate folder marked SPL.

15. In accord with FDA's August 2001 guidance, Submitting Marketing Applications According to the ICH-CTD Format – General Considerations, we propose to submit a paper CTD with page numbering at the document level and not at the volume or module level. A document is defined as a set of pages, numbered sequentially and divided from other documents by a tab, in accord with ICH guidance. Therefore, any cross-reference to other items in the NDA will cite a tab identifier (including name and section reference) and document page number. Does the FDA agree with this approach?

Response:

This approach is correct. According to guidance, you should reference documents by volume, CTD module, tab identifier, and page number.

16. On August 12, 2005 balsalazide disodium was granted orphan drug designation for the treatment of ulcerative colitis in pediatrics. Since balsalazide disodium has orphan drug designation for the proposed tablet indication, does FDA agree that Salix is exempt from the Pediatric Research Equity Act (PREA) requirements?

Response:

No. The orphan drug designation for your product is “the treatment of pediatric patients with ulcerative colitis.” For your new dosage form, your proposed indication is “the treatment of mildly to moderately active UC in subjects 18 years and older.” PREA exemptions only apply to the orphan indication, so your new product will trigger PREA. However, you may request a waiver of PREA obligations for balsalazide tablets for any of the following reasons:

- **necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed); OR**
- **there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; OR**
- **the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.**

If you wish to request this waiver of PREA obligations, the request should be submitted with your NDA and should include your justification why the waiver should be granted.

17. Salix will be proposing a new trade name and separate package insert for the tablet dosage form. Does FDA have any comments on this approach?

Response:

We do not have a definitive response for this question at this time. We will review your request at the time that it is submitted and have the appropriate individuals provide input.

Additional Comment:

We acknowledge your proposal to include the following studies in the NDA as discussed at the EOP2/Pre-Phase 3 meeting held with the Agency on August 8th, 2005:

- **A single-dose and multiple-dose relative bioavailability study comparing the proposed drug product to Colazal Capsules and,**
- **A single-dose study evaluating the bioavailability of the proposed drug product following administration with a high-fat meal.**

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

None

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

/s/

Kristen Everett
5/22/2007 10:29:48 AM

Keith B St.Amand
5/22/2007 01:31:58 PM
I am signing as the acting team leader for
Fathia Gibril who is unavailable to sign at
this time.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

EOP-2

IND 38,492

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

Dear Mr. Kashiwase:

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

We also refer to the meeting between representatives of your firm and the FDA on August 8, 2005. The purpose of the meeting was to discuss the proposed Phase 3 development plan to support registration of the tablet form.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 8, 2005
TIME: 2:00 pm – 3:00 pm
LOCATION: Potomac Conference Room, Parklawn Building, Rockville, MD
APPLICATION: IND 38,492
DRUG NAME: Colazal (balsalazide disodium)
TYPE OF MEETING: Type B Meeting: EOP 2/Pre-Phase 3
MEETING CHAIR: Ruyi He, M.D., Medical Team Leader
MEETING RECORDER: Kristen Everett, R.N., Regulatory Project Manager

BETWEEN:

Salix Pharmaceuticals, Inc

Christopher Warner, Ph.D., Executive Director, Clinical Research
David N. Taylor, M.D., Chief Medical Officer
Robert Haake, Ph.D., Executive Director, Biostatistics and Data Management
Catherine Maher, Ph.D., Sr. Manager, Regulatory Affairs

(b) (4)

William Forbes, Pharm.D., VP R & D and Chief Development Officer
Angela Barnes, Regulatory Specialist

(b) (4)

Jody Lockhart, Executive Director, Manufacturing and Process Development
Lorin Johnson, Ph.D., Chief Scientist

AND

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

Brian E. Harvey, M.D., Ph.D., Division Director
Ruyi He, M.D., Medical Team Leader
Lolita A. Lopez, M.D., Medical Officer
Maria E. Ysern, Ph.D., Review Chemist
Ke Zhang, Ph.D., Pharmacologist
Kristen Everett, R.N., Regulatory Project Manager
Monika Houstoun, Pharm. D., Regulatory Project Manager

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

Suliman Al Fayoumi, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics II, HFD-715

Stella Grosser, Ph.D., Statistics Team Leader

PURPOSE:

To discuss the proposed Phase 3 development plan to support registration of the tablet dosage form.

BACKGROUND:

On May 25, 2005, Salix Pharmaceuticals, Inc. submitted a Type B Meeting Request for an End of Phase 2/Pre-Phase 3 meeting. On July 8, 2005, a subsequent background package was submitted.

The Division sent pre-meeting responses to Salix Pharmaceuticals, Inc. on August 4, 2005.

DISCUSSION:

Responses to questions posed by the sponsor.

Questions for the FDA, Grouped by Discipline

Medical Reviewer

- 1) In accordance with subsection 403(b)(2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products, and the May 1998 Guidance for Industry, titled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", Salix plans to conduct a single adequate and well-controlled study in patients with mildly to moderately active ulcerative colitis to support marketing approval of the tablet formulation. Does the Agency agree that a single clinical study, if successful, will be adequate to provide substantial evidence of the efficacy of balsalazide disodium tablets for the intended indication? [please refer to Section 9.3.5 and Attachment 4]

FDA Response:

In general, two adequate and well-controlled clinical efficacy trials are recommended, unless results from a single study are robust (or adequate justification is provided as to why two studies are not necessary).

The Agency clarified that a single study is not a filing requirement. Approvability will be based on robustness of the data and consistency of effect seen in primary and secondary endpoints.

- 2) The proposed dose for balsalazide disodium tablets is three 1.1g tablets two times a day, for a total daily dose of 6.6 grams. The recommended dose in the approved product labeling for Colazal Capsules is three 750 mg capsules three times a day, for a total daily dose of 6.75 grams. Does the Agency agree with the selection of the 3.3 g BID dose (6.6 gram daily dose) for the registration study?

FDA Response:

The proposed treatment with 3.3 g BID appears acceptable as long as adequate safety and efficacy can be demonstrated using this new dose and dosing regimen.

- 3) The proposed Phase 3 study includes an eight week treatment duration [refer to Attachment 4], however, Salix is considering reducing the length of treatment (e.g., to 2, 4, or 6 weeks), can the Division advise if this treatment duration change to the proposed single efficacy study is acceptable?

FDA Response:

We recommend a treatment duration of 8 weeks, which is similar to those studies that led to approval of the original NDA Colazal capsules. We are concerned that it will be difficult to compare the results of shorter duration clinical trials with the outcomes that led to the finding of safety and efficacy. In addition, patients should be assessed at least 2 weeks after the last day of study drug treatment.

- 4) Does the Division have any comments with respect to the proposed Phase 3 registration study design such as choice of comparator, choice of primary and secondary endpoints, and frequency of safety and laboratory assessments? [please refer to Attachment 4]

FDA Response:

(a) Although your choice of placebo control is acceptable, we recommend adding a third arm to your study. This could consist of a currently approved dosing regimen of Colazal capsules or other approved comparator drug in a non-inferiority or a superiority design.

(b) If you intend to label this product for patients 12 to ^(b)₍₄₎ years old, an adequate number of pediatric patients should be included in the study to demonstrate that the drug is safe and effective for this age group.

(c) At screening visit, a stool culture, stool c. difficile, and stool ovum and parasite (O&P), and other appropriate stool studies should be performed to rule out infectious etiology of colitis.

(d) In general, the primary and secondary endpoints appear acceptable.

(e) Patients should be assessed at least 2 weeks after study drug treatment.

- 5) Salix is also considering alternative Phase 3 study designs such as use of an active comparator control (e.g., Asacol(mesalamine) Delayed-Release Tablets) or a dose comparison (e.g., 1.1 g vs. 3.3 g balsalazide disodium BID) does the Division agree that these study designs are, in principle, acceptable as the single study to support the efficacy of balsalazide disodium tablets?

FDA Response:

See response to question 4 (a).

If Asacol is used as a comparator drug, clarify the study design and dose regimen that will be used.

- 6) Salix intends to utilize the existing acute UC treatment safety data from Colazal Capsule studies in which patients received a daily balsalazide disodium dose of 6.75 g/day in conjunction with tablet Phase 3 study data for the tablet safety database. Is the proposed size and exposure within the combined tablet and capsule safety database adequate to support the planned NDA? [please refer to Section 9.3.4]

FDA Response:

Although the total daily dose for the approved capsule form and the proposed tablet form are similar, the amount of drug per dose in the proposed tablet form is 50% more (1.05 g). Therefore, the current safety database from the capsule form may not be adequate to support the tablet form, but will be supportive.

Sponsor will provide information from their long term safety database at 6 and 12 months and Agency will review.

- 7) Does the Division agree that no additional pediatric studies are necessary for the proposed indication? [please refer to Section 9.3.6]

FDA Response:

The tablet form has a different formulation and dosing schedule from the capsule form; therefore, under the Pediatric Research Equity Act (PREA), a pediatric study plan should still be submitted. You should propose a pediatric study plan for this application and provide a rationale for your plan. You may request a waiver, partial waiver or deferral for pediatric studies and provide a justification as to why you think pediatric studies should be waived, partially waived or deferred for your product. If you request a waiver, it is required at the time of NDA submission.

Biopharmaceutical Reviewer

- 8) Does the Division agree that for the tablet NDA the proposed pharmacokinetic studies are adequate to support the proposed indication? [please refer to Section 9.2 and Attachment 2]

FDA Response:

No. You additionally need to conduct the following studies prior to NDA submission:

- A relative bioavailability study comparing the proposed drug product to Colazal
- A study evaluating the multiple-dose PK of the proposed drug product at the proposed dosing regimen

Sponsor proposes to conduct a single and multiple dose relative bioavailability crossover study with balsalazide tablets and capsules for one week.

- 9) Since balsalazide is locally active and relatively non-absorbed, in the absence of renal impairment information, can the Division provide comment on the necessity to further investigate this area? [please refer to Section 9.2]

FDA Response:

You need to submit a formal response to the Phase 4 commitment related to evaluation of balsalazide PK in renal impairment for Agency review and comment.

Statistical Reviewer

- 10) Does the Division agree with the statistical considerations for the Phase 3 registration study? [please refer to Attachment 4, protocol section 7]

FDA Response:

Yes. The statistical approaches outlined are acceptable.

Pharmacology and Toxicology Reviewer

- 11) Does the Division agree that for the tablet NDA the proposed pharmacology and toxicology studies are adequate to support the proposed indication? [please refer to Section 10 and Attachment 6]

FDA Response:

Yes, we agree.

Chemistry Reviewer

- 12) Does the Division have any comments concerning the CMC data on the tablet dosage form? [please refer to Section 11]

FDA Response:

The company has provided a succinct description of the drug product section. We recommend referring to the *Guidance for Industry: M4Q: The CTD (Common Technical Document for the Registration of Pharmaceuticals for Human Use)-Quality*, to ensure that all the needed information is included such as, but not limited to, process controls, detailed manufacturing process, any reprocessing operations. An End of Phase II CMC meeting is also recommended, if needed.

Minutes Preparer: _____

Kristen Everett, R.N.
Regulatory Project Manager

Chair Concurrence: _____

Ruyi He, M.D.
Medical Team Leader

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

/s/

Kristen Everett
8/31/2005 01:42:16 PM

Ruyi He
8/31/2005 02:43:46 PM