CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205613Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205613 SUPPL # na HFD #

Trade Name Uceris

Generic Name budesonide

Applicant Name Salix

Approval Date, If Known 10/7/14

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2), original NDA

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:

NA

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☒ NO ☐

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

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#	21324	Entocort EC (budesonide)
NDA#	21949	Pulmicort Flexhaler (budesonide)
NDA#	20746	Rhinocort (budesonide)
NDA#	20929	Pulmocort Respules (budesonide)
NDA#	203634	Uceris (budesonide)
NDA#	21929	Symbicort (budesonide; formeterol fumarate dihydrate)

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:

BUCF3001
BUCF3002

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

BUCF3001
BUCF3002

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

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 104725 YES ☒ ! NO ☐

! Explain:

Investigation #2 !
!
IND # 104725 YES ☒ ! NO ☐
! Explain:

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

Investigation #1 !
!
YES ☐ ! NO ☒
Explain: ! Explain:
no other studies essential to approval were conducted by the applicant

Investigation #2 !
!
YES ☐ ! NO ☒
Explain: ! Explain:
no other studies essential to approval were conducted by the applicant

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kelly Richards
Title: Regulatory Project Manager
Date: 9-2-14

Name of Office/Division Director signing form: Andrew E Mulberg
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

KELLY D RICHARDS
10/07/2014

ANDREW E MULBERG
10/07/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205613 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Uceris rectal foam Established/Proper Name: budesonide Dosage Form: foam		Applicant: Salix Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Kelly Richards		Division: DGIEP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 10/7/14

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 15, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None TA 9-15-14
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received (N/A)
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type III
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type-Pediatric	☐ No ☒ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Version: 2/7/2014

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Final Approval, 10/7/14; Tentative Approval, 9/15/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	4/10/14 4/9/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ 1/28/14 DMEPA: ☐ 6/24/14 DMPP/PLT (DRISK): 8/14/14 ☐ OPDP: ☐ 8/14/14 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	RPM Filing Review/Memo of Filing Meeting 1/28/14 ☐ Not a (b)(2) 10/6/14, 9/2/14
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC If PeRC review not necessary, explain: The product will receive orphan designation, PREA does not apply.	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	8/13/14
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 7/23/13
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 9/15/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 9/15/14
PMR/PMC Development Templates *(indicate total number)*	☐ None 9/10/14 (1)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	8/4/14, 12/16/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	8/4/14. Refer to section 3.3 of the clinical review.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	None None ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 8/25/14
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 8/5/14, 1/8/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 8/18/14, 1/14/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 8/25/14, 1/8/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None n/a
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ None
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/3/13, 1/17/14, 8/19/14, 9/4/14
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 12/3/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 6/13/14 (CDRH), 3/4/14 (CDRH)
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/5/14
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection: Pending—expected week prior to action	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 1/13/14, 9/4/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

KELLY D RICHARDS
10/08/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 13, 2014

Application Number: 205613
Product Name: budesonide rectal foam
Sponsor/Applicant Name: Salix

Subject: Sponsor Notification of 505(b)(2) Determination of Application

FDA Participants
Andrew E. Mulberg, MD, FAAP, CPI, Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Anil Rajpal, MD, MPH, Clinical Team Leader, DGIEP
Kelly Richards, RN, MSN, Regulatory Project Manager, DGIEP
R. Wesley Ishihara, Chief, Project Management Staff, DGIEP
Sushanta Chakder, PhD, Nonclinical Team Leader, DGIEP
Dinesh Gautam, PhD, Nonclinical Reviewer, DGIEP
Sue Chih Lee, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III
Dilara Jappar, PhD, Clinical Pharmacologist, OCP, DCPIII
Maria Walsh, RN, MSN, Associate Director for Regulatory Affairs, Office of Drug Evaluation III (ODEIII)
Marie Kowblansky, PhD, Quality Team Leader, Office of New Drugs Quality Assessment (ONDQA)

Sponsor/Applicant Participants

Craig Paterson, MD, MBA	Vice President, Medical and Clinical Development
Enoch Bortey, PhD	Vice President, Clinical Operations and BioMetrics
Linda Young, RPh, JD	Vice President, Regulatory
Pam Golden, PhD	Associate Vice President, Nonclinical and Clinical Pharmacology
Robert Rolleri	Executive Director, Clinical Development
Tom Walton	Executive Director, Quality
Jennifer Richards	Associate Director, Regulatory

1.0 BACKGROUND:

On November 15, 2013, the applicant submitted their New Drug Application (NDA) as a 505(b)(1) submission. Upon further review, it was noted that there was reliance on published literature necessary for approval for nonclinical. And the annotated labeling references Uceris (which Salix owns) and Entocort (which Uceris relied upon) in six sections including section 12.3 PK.

2.0 DISCUSSION:

Maria Walsh notified the applicant that they relied on published literature necessary for approval for nonclinical and the annotated labeling references Uceris and Entocort in six sections. The applicant was notified that they will have to identify their application as a 505(b)(2) and submit a new FDA form 356 to the NDA. She further explained to the applicant that in lieu of providing the results of a relative bioavailabilty study, they can submit a scientific justification as to why FDA can rely on our findings of safety and efficacy for Entocort to approve their proposed product.

Maria Walsh then explained to the applicant the following options:

- Submit a paragraph iii patent certification to Entocort and FDA can take a tentative approval. When the patent expires, Salix can resubmit and we can approve the application at that time.
- Submit a paragraph iv patent certification to Entocort. The applicant will need to notify the NDA holder and patent owner and submit proof of notification (registered mail receipt). The NDA holder/patent owner then has 45 days to file suit. If they provide written documentation before the PDUFA date that the NDA holder/patent owner will not file suit, we can take an approval action. If they do not provide written documentation, a tentative approval action could be taken. If the NDA owner/patent holder does NOT file suit within 45 days from notification, Salix can resubmit and we can approve the application at that time
- If the NDA owner/patent holder DOES file suit within 45 days of notification, then a 30-month stay of approval is in place

The applicant acknowledged the need to identify their application as a 505(b)(2) and the options they have available as explained by Maria Walsh. At this time, the applicant intends on updating the label based on their own work and literature and that they intend on submitting data for review by FDA. They further indicated that they would discuss their available options and notify FDA as soon as possible of their intended plan.

3.0 ACTION ITEMS:

No action items were identified.

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/s/

KELLY D RICHARDS
08/25/2014

From:	Richards, Kelly
To:	"Richards, Jennifer"
Cc:	Richards, Kelly
Subject:	NDA 205613 Budesonide Rectal Foam- Request for Information-CMC-August 18, 2014
Date:	Monday, August 18, 2014 11:43:00 AM

Dear Jennifer,

Please refer to your New Drug Application (NDA) submitted on November 15, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Budesonide Rectal Foam.

We have the following request for additional information:

1. According to the FDA Blue Book Memorandum #G95-1, entitled Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.", your rectal applicator is considered limited surface contacting. We recommend cytotoxicity, sensitization, and irritation / intracutaneous reactivity tests per FDA's recognized standards to 2-117: AAMI / ANSI / ISO 10993-3:2003/(R) 2009.

Please provide this information as soon as possible.

Please let me know if you have additional questions.

Best regards,

Kelly

Kelly Richards, RN, MSN
Captain, U.S. Public Health Service
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
Phone: 240-402-4276

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/s/

KELLY D RICHARDS
08/18/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205613

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Jennifer Richards
Associate Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) dated and received November 15, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Budesonide Rectal Foam, 2 mg.

We also refer to:

- Your correspondence, dated and received February 18, 2014, requesting review of your proposed proprietary name, Uceris.
- Your amendment to your request dated and received March 26, 2014.

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

If any of the proposed product characteristics as stated in your February 18, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact Kevin Bugin, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2303.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205613

NDA ACKNOWLEDGMENT

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

Dear Ms. Richards:

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

Name of Drug Product: Budesonide 2 mg, Rectal Foam

Date of Application: November 15, 2013

Date of Receipt: November 15, 2013

Our Reference Number: NDA 205613

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 January 14, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Senior 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
11/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104725/NDA 205613

ADVICE/INFORMATION REQUEST

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

Dear Ms. Richards:

Please refer to your Investigational New Drug (IND) application for Budesonide 2 mg Rectal Foam.

We further refer to the meeting request submitted to NDA 205613 on May 24, 2013, and the meeting briefing package submitted on June 26, 2013. The following are additional comments from the Biostatistical reviewers regarding questions 9 and 10.

9. Does the Agency believe that there are analyses beyond those described in the SAP that need to be addressed by Salix in the planned submission?

FDA Response:

a. Logistic Regression
You applied logistic regression methods to analyze the primary efficacy endpoint (clinical remission at Week 6/withdrawal) and key secondary efficacy endpoints with response as variable. These model-based methods, however, usually require additional non-statistical arguments to justify assumptions, such as the study data are a statistically random sample.

On the basis of randomization, the design-based methods have the advantage of requiring minimal assumptions. Fisher's exact test, chi-square test (without stratification), and Cochran-Mantel-Haenszel (CMH) test (with stratification) are more appropriate statistical methods for analyzing binary data, and we recommend that these methods be used.

Analyses based on the CMH test should be the primary analyses for the primary endpoint and key secondary endpoints. The analyses based on logistic regression will be considered as supportive analyses.

b. LOCF Analysis for the Primary Efficacy Endpoint

For addressing the issues of missing data for the primary efficacy endpoint, you performed a LOCF analysis, a worst case analysis, and an observed case analysis. If a subject had less than three diary entries prior to each respective visit, the subject was to be considered as a "non-responder" at the specific visit.

We recommend that your sensitivity analyses for the primary efficacy endpoint also include the following:

- Complete case: exclude subjects from the analysis at all time points if they had insufficient data at any of the time points of analysis.
- Worst case: subjects receiving placebo with missing observations at any of the time points of analysis are assumed to be a responder, and subjects receiving budesonide 2 mg rectal form with missing observations at any of the time points of analysis are assumed to be a non-responder.
- A multiple imputation method

c. Analysis of Secondary Efficacy Endpoints

For key secondary efficacy endpoints and other efficacy secondary endpoints, you proposed to perform LOCF analyses. Please also perform "observed case" analyses of key secondary efficacy endpoints and other efficacy endpoints with no imputation. An observed case analysis is defined as one which excludes subjects from the analysis at a specific time point if the patient has any missing data at that time point.

d. Analysis of MMDAI Subscale Three key secondary efficacy endpoints were added in the SAP.

- Proportion of subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of 6 weeks of treatment.

- Number of assessments subjects achieved a rectal bleeding MMDAI subscale score of 0 during the treatment phase.

- Proportion of subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of 6 weeks of treatment

(1) The 2nd key secondary endpoint (number of assessments subjects achieved a rectal bleeding MMDAI subscale score of 0 during the treatment phase) result might be difficult to interpret since this measure does not address time of onset and whether the effect is sustained. For this reason, we do not recommend you include this endpoint as a key secondary endpoint.

Furthermore you use the proportional odds method to assess this endpoint. We recommend that you use the generalized CMH chi-square test for ordinal data with stratification.

(2) For the Analysis of the Number of Time Points/Weeks with Rectal Bleeding Responder Classification, you performed the analysis of the number of time points/weeks with rectal bleeding as a responder classification (binary endpoint) using the proportional odds model for ordinal outcome with fixed effects: treatment arm and country. A more appropriate statistical method for the efficacy analysis of rectal bleeding during the 6-week study period is an analysis that addresses onset and sustained effect of rectal bleeding. This analysis should utilize the patterns of response during the entire 6 weeks of the study. This method would weigh responses in the order of both optimal outcome for the patients, as well as mechanistic plausibility. This ranking rewards early and durable response (e.g., response with responder at all time points having the highest rank; response with no responder at all time points having lowest rank).

(3) Regarding, the analysis of proportion of patients achieved an MMDAI rectal bleeding score of 0 by week (Table 48), also perform an observed case analysis of proportion of patients who achieved an MMDAI rectal bleeding score of 0 by week. (See item c, above for definition of observed case analysis.)

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

FDA Response:
See response to Question 9

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

  If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

DONNA J GRIEBEL
09/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205613

MEETING MINUTES

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

Dear Ms. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Budesonide 2 mg Rectal Foam.

We also refer to the meeting between representatives of your firm and the FDA on July 23, 2013. The purpose of the meeting was to discuss the status of the development program for budesonide 2 mg rectal foam and plans for submitting an NDA based on the results of two Phase 3 clinical studies and other supportive clinical trials completed to date.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	July 23, 2013 from 11:00 AM to 12:00 PM, ET
Meeting Location:	10903 New Hampshire Ave White Oak Building 22, Conference Room 1421 Silver Spring, MD 20903
Application Number:	NDA 205613
Product Name:	Budesonide 2 mg Rectal Foam
Indication:	(b) (4)
Sponsor/Applicant Name:	Salix Pharmaceuticals, Inc.
Meeting Chair:	Anil Rajpal
Meeting Recorder:	Kevin Bugin

FDA Attendees:

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, MD, Director
Joyce Korvick, MD, MPH, Deputy for Safety
Anil Rajpal, MD, MPH, Clinical Team Leader
Aisha Peterson Johnson, MD, MBA, Clinical Reviewer
Dinesh Gautam, PhD, Nonclinical Reviewer
Kevin Bugin, MS, RAC, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology
Dilara Jappar, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics III
Milton Fan, PhD, Statistics Reviewer

Office of New Drug Quality Assessment
Marie Kowblansky, PhD, Quality Team Leader
Zhangfang Ge, PhD, Quality Reviewer

Office of Scientific Investigations

Khairy Malek, MD, Clinical Reviewer

Division of Medication Error Prevention and Analysis
Lisa Khosla, MD, Clinical Reviewer

Sponsor Attendees:
William P. Forbes, Pharm.D. Executive Vice President, Medical, R&D and Chief Development Officer
Enoch Bortey, Ph.D. Vice President, Clinical Operations
Craig Paterson, M.D. Vice President, Medical and Clinical Development
Linda G. Young, R.Ph., J.D. Vice President, Regulatory Affairs
Joseph Lockhart Associate Vice President, Pharmaceutical Development and Manufacturing
Bob Rolleri, Pharm.D. Executive Director, Clinical Development
Pam Golden, Ph.D. Executive Director, Nonclinical and Clinical Pharmacology
Christopher Martin Associate Directory, Technical Operations
Jing Yu Associate Director, Biostatistics
Jennifer Richards Associate Director, Regulatory Affairs
Holly Owens Manager, Manufacturing

1.0 INTRODUCTION

On May 24, 2013, Salix Pharmaceuticals submitted a correspondence requesting a Pre-NDA meeting to discuss the status of the development program for budesonide 2 mg rectal foam and plans for submitting an NDA based on the results of two Phase 3 clinical studies and other supportive clinical trials completed to date.

The meeting was granted and took place as scheduled on July 23, 2013.

2.0 DISCUSSION

QUALITY

Question 1
Does the agency concur with the proposed documentation to be provided to support the drug substance and drug product in the NDA filing?

FDA Response:
In addition to the information you propose to submit, you will also need to provide data from extractable/leachable testing for all the primary container/closure components in contact with the drug product as required in USP<661>. The extraction solvents used in these studies should be relevant to the proposed formulation.

Salix Response:
Data is currently available from applicable extractable/leachable testing. Those data will be presented in the NDA.

Question 2
Does the agency concur with the proposed drug product specifications?

FDA Response:
Your proposed specification is reasonable, but we have the following comments:

A. **The limit for one of the impurities is given at NMT (b) (4)%. Since this exceeds ICH recommendations, you will need to conduct toxicology studies to qualify this level or provide justification why such studies are not necessary.**

Salix Response:
Salix believes the specification of NMT (b) (4)% for (b) (4) is consistent with the qualification thresholds provided in the ICH guidance. The maximum daily

dose for budesonide foam is not more than 4 mg. Per ICH Q3A, the qualification threshold for such a dose is 1.0% or 50 µg. The proposed specification of NMT [redacted] (b) (4)% ([redacted] (b) (4) ug) is below the ICH qualification threshold.

Discussion:
The Agency agrees.

B. You will need to include limits for the number of actuations per container and initial prime.

Salix Response:
Limits for the number of actuations per container will be provided in the NDA. There is no [redacted] (b) (4) for budesonide foam drug product. As such, those specifications are not applicable.

C. Your "Assay per Actuation for Budesonide" should comply with USP <905> Content Uniformity and should be conducted with full, half, and minimally filled containers. This assay should be conducted not only at release, but as part of stability studies as well.

Salix Response:
Salix would like to gain an understanding as to why the Agency believes the requirements described in USP <905>, Uniformity of Dosage Units are applicable.

Budesonide foam is a metered dose topical aerosol and as such, Salix believes that delivered-dose uniformity requirements described in USP <601>, Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers, are the appropriate measures for dosage uniformity. For release testing, Salix proposes to follow the USP <601> procedures for delivered-dose uniformity including those over the entire contents of the can. For stability testing, Salix is proposing to conduct delivered dose uniformity testing across the entire contents of a single can as described in USP <601>.

To date, release and stability testing has been conducted where three actuations (the 2nd, 7th, and 13th) from three separate cans for a total of nine actuations are assayed for budesonide content. These data will be presented in the NDA along with assay data from the entire contents of individual cans. Salix believes these data provide evidence of dosage uniformity as is currently acquired. Salix will make necessary changes to release testing monographs to immediately implement the 10-unit and 10-dose uniformity requirements presented in USP <601>. For stability testing, this will be implemented at the next stability time point (12 months).

Discussion:
The Agency finds the Sponsors proposals to use USP <601> acceptable as noted above.

For release testing, the Sponsor will evaluate the uniformity between separate cans of product.

For stability testing, the Sponsor will evaluate the top, middle and bottom of a single can. The Sponsor agrees that the first actuation and last actuation will be included in the evaluation.

The inter-can testing should be implemented immediately for all release batches and should be submitted in the NDA. For the primary batches which are already on stability testing, the intra-can testing will be started at the 12 month time point as described above.

D. Weight loss needs to be monitored as part of the stability studies.

Salix Response:
Weight loss is currently being monitored as part of the registration stability studies. Those data will be provided in the NDA.

Question 3
Does the Agency agree that the NDA can be filed with 9 months of stability data?

FDA Response:
We will not accept any application with less than 12 months of long term stability data and 6 months of accelerated data for three batches of product. All data will need to be provided at the time of submission.

Salix Response:
Salix would like to discuss further.

Discussion:
The Office of New Drug Quality Assessment current policies require that 12 months of long term stability is provided at the time of submission. The Agency agreed with the Sponsor's proposal to submit 9 months of stability data at the time of initial submission with a commitment of submitting 12 month data within 30 days of the receipt of the application.

As an additional comment, the stability studies need to include testing of the container stored in both the upright and inverted positions.

Salix Response:
Registration batch stability includes both upright and horizontal positions. Both sets of data will be provided in the NDA.

NON-CLINICAL

Question 4
Does the Agency concur that the carcinogenicity profile of budesonide has been established and no further carcinogenicity studies are required?

FDA Response:
Yes, we concur.

Salix Response:
No comment

Question 5
Does the Agency concur that the nonclinical and toxicology package adequately supports an NDA submission?

FDA Response:
Yes, the nonclinical and toxicology studies support your NDA submission.

Salix Response:
No comment

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Question 6
Does the Agency concur that the clinical pharmacology and pharmacokinetic data adequately support an NDA submission?

FDA Response:

A. The clinical pharmacology component of the NDA appears to be adequate. Please clarify in the NDA which drug-transporters and enzymes you have evaluated to assess the potential drug interactions of budesonide.

Salix Response:
Salix will clarify in the NDA which drug-transporters and enzymes we have evaluated to assess the potential drug interactions of budesonide.

B. Regarding the ACTH test result, please report the percent of the patients who had normal and abnormal response to the ACTH stimulation test according to the Cosyntropin injection label [normal response defined as: (1) control plasma cortisol > 5 µg/dL; (2) 30-minute (post-injection) level should be at least 7 µg/dL above basal level; and (3) 30-minute (post-injection) level should exceed 18 µg/dL] based on the individual patient level.

Salix Response:
Salix will report the percent of patients who had normal and abnormal responses to the ACTH stimulation test according to the Cosyntropin injection label and per protocol.

C. In the NDA, please compare the adverse event profiles of patients with impaired renal and hepatic functions to patients with normal renal and hepatic functions.

Salix Response:
The pivotal protocols excluded subjects with creatinine > 2 mg/dL and ALT, AST, alkaline phosphatase or total bilirubin > 1.5 X ULN.

Salix proposes classifying renal impairment in accordance with FDA Draft Guidance for Industry "Pharmacokinetics in Patients with Impaired Renal Function" as shown in the table below.

Stage	Description	CLcr (mL/min)
1	Control (normal) GFR	≥90
2	Mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis
		Requiring dialysis

Given the exclusion criteria for subjects with hepatic function tests as noted, how does FDA propose Salix define hepatic impairment in order to provide the requested analysis?

Discussion:
The Agency agrees with the Sponsors proposes for classifying renal impairment by creatinine clearance strata.

The Sponsor clarified that the eligibility criteria will preclude enrollment of patients with moderate to severe hepatic impairment. In light of that, the Agency agreed that it would be unlikely that the application will contain adequate numbers of Child-Pugh B and C category patients to perform the recommended analysis.

CLINICAL / STATISTICAL

Question 7
Does the Agency concur that the results from the pivotal Phase 3 studies, along with the supportive studies are sufficient to support an NDA submission for the proposed indication?

FDA Response:
Yes, we agree that the top-line results from your studies appear to support an NDA submission. It is premature for us to come to an agreement regarding an indication statement before fully reviewing your NDA submission.

Salix Response:
No comment

Question 8
Does the Agency concur that the clinical studies completed to date and the on-going open label study provide sufficient patient exposures to support the intermittent use of budesonide 2 mg rectal foam?

FDA Response:
In general, the size of your premarket safety database appears reasonable. However, the final determination regarding the adequacy of the safety database will be determined during the NDA review process. The appropriate size of a safety database supporting a new product depends on the novelty of the treatment, availability of alternative therapies and the relative safety of those alternatives, the intended population and condition being treated and the intended duration of use.

Salix Response:
No comment

Question 9
Does the Agency believe that there are analyses beyond those described in the SAP that need to be addressed by Salix in the planned submission?

FDA Response:
The safety analyses described in the SAP appear reasonable, and no additional analyses are requested by the Agency at this time. However, during the course of our review of your NDA, additional analyses may be requested.

We request that you provide in your NDA post hoc exploratory analyses based on the following four endpoint definitions:

(a) Endoscopy subscore = 0, Rectal Bleeding subscore = 0, and Stool Frequency subscore decreases or no change from Baseline (all assessed at Week 6)

(b) Endoscopy subscore ≤ 1, Rectal Bleeding subscore = 0, and Stool frequency subscore = 0 (all assessed at Week 6)

(c) Endoscopy subscore ≤ 1, Rectal Bleeding subscore = 0, and Stool frequency subscore = 1 (all assessed at Week 6)

(d) Endoscopy subscore ≤ 1, Rectal Bleeding subscore = 0, Stool Frequency subscore decreases or no change from Baseline, and Total score ≤ 1 (all assessed at Week 6)

Salix Response:
Salix will provide post hoc exploratory analyses based on the endpoints described above.

Question 10
Does the Agency concur with the proposed presentation of efficacy data for an NDA submission?

FDA Response:
The proposed presentation of efficacy data for your NDA appears reasonable.

Salix Response:
No comment

Question 11
Does the Agency concur with the proposed safety pools?

FDA Response:
It appears that you are proposing the following safety pools:

(1) "RCT Study Population": pooled data from BUCF3001 and BUCF3002

(2) "All Budesonide Safety Population": pooled data from BUCF3001, BUCF3002, and BFPS3073

(3) Individual Study Summaries: data presented separately from BUCF3001, BUCF3002, BFPS3073, BUF-6/UCA, and BUF-9/UCA.

We agree with your proposal for the "RCT Study Population" safety pool and individual study summaries.

However, we request that you revise the "All Budesonide Safety Population" as follows:

- **Define the "All Budesonide Safety Population" as pooled data from BUCF3001, BUCF3002, BFPS3073, BUF-6/UCA, and BUF-9/UCA.**
- **Define an additional safety pool "All Salix Budesonide Safety Population" as pooled data from BUCF3001, BUCF3002, and BFPS3073**

Salix Response:
Salix will revise the "All Budesonide Safety Population" as described above.

Question 12
Does the Agency concur that the proposed safety database and ISS analysis plan are sufficient to provide a substantive review of the NDA?

FDA Response:
Your proposed safety database and ISS analysis plan appear sufficient to begin a substantive review of the NDA.

Salix Response:
No comment

Question 13
Does the Agency agree that a TQT study is not required for the NDA approval of budesonide foam?

FDA Response:
In your NDA, you should submit your rationale for not conducting a Thorough QT (TQT) study to evaluate the effects of your product on QT prolongation. During the review of

your NDA, we will consult the QT Interdisciplinary Review Team (QT-IRT) to determine if a TQT study is required for the evaluation of QT prolongation potential of your drug.

Salix Response:
No comment

Question 14
Does the Agency agree with the proposed partial waiver and deferral?

FDA Response:
(b) (4)

Salix Response:
(b) (4)

3.0 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP). The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

6.0 ATTACHMENTS AND HANDOUTS

See attached CDER GCP Site Selection Tool Release Notice – 7/16/2013

GCP Release Notice 7/16/2013:

An updated version of the CDER GCP Site Selection Tool was released along with an updated User Guide. This Notice summarizes the new features available:

1. NEW TAB – CI CROSS REF

   The CI Cross Ref tab can be accessed directly by clicking the tab or from the Risk Ranking tab by clicking the number of studies for the Site ID in the Multiple column. The new tab, CI Cross Ref, provides:

   1. Summary information for all studies within the application that a given Clinical Investigator (CI) participated in.
   2. Within the new tab, CIs may be sorted based on their participation in only one study, or by those participating in multiple studies. [See filter available on the CI Cross Ref tab to fill the select list with all CIs (All) or only CIs assigned to more than one study (>1 Studies)].
   3. Summary information included within the tab includes the CI's location and information about their inspectional history, as well as by study enrollment, screening, discontinuation, death, protocol violation, and SAE data for the CI. In addition, efficacy outcome data for each study, by treatment arm, are displayed.
      - The data can be displayed in converted or raw form by clicking the Converted or Raw radio buttons respectively.
      - By clicking the Study Number in Table 2 you will be linked back to the Risk Rankings Results tab for that study.
      - By clicking the Site ID number in Table 2 you will be linked back to the Site Level Details tab for that CI in that study.

2. UPDATE RISK RANKINGS RESULTS Tab
    1. The Multiple column on the Risk Ranking Results tab was enhanced to display the number of studies within the application that are associated with the Clinical Investigator listed.
    2. By clicking on the number of studies for a given CI listed in the Multiple column you will be linked to the new CI Cross Ref tab.
3. COUNTRY CODES
   The country codes used throughout the GCP Tool now use the three-character ISO codes.
4. FORMS
   The Consult and Assignment forms were updated with the latest management information and other standard information used on all forms.

Additional information on the new features in the GCP Tool is located in the User Guide Section 3.3.5

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
08/07/2013