

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208183Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208183

SUPPL #

HFD # 540

Trade Name Ultravate Lotion

Generic Name halobetasol propionate lotion, 0.05%

Applicant Name Ferndale Laboratories, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES x NO

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

505(b)(1)

b) 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 x 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:

c) Did the applicant request exclusivity?

YES x NO

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

three years from the date of approval

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

YES NO x

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

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

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

YES NO x

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 x NO

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

NDA# 19967 Halobetasol cream
NDA# 19968 Halobetasol ointment
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 x

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:

000-0551-304: A Multicenter, Randomized, Double-Blind, Parallel Group Comparison of Halobetasol Propionate Lotion, 0.05% versus Vehicle Lotion in Subjects with Plaque Psoriasis

000-0551-305: A Multicenter, Randomized, Double-Blind, Parallel Group Comparison of Halobetasol Propionate Lotion, 0.05% versus Vehicle Lotion in Subjects with Plaque Psoriasis

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 x

Investigation #2 YES NO x

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 x

Investigation #2 YES NO x

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"):

000-0551-304: A Multicenter, Randomized, Double-Blind, Parallel Group Comparison of Halobetasol Propionate Lotion, 0.05% versus Vehicle Lotion in Subjects with Plaque Psoriasis

000-0551-305: A Multicenter, Randomized, Double-Blind, Parallel Group Comparison of Halobetasol Propionate Lotion, 0.05% versus Vehicle Lotion in Subjects with Plaque Psoriasis

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 # (b) (4) YES NO x

! Explain: At the pre-NDA meeting (October 27, 2014), (b) (4) informed the Agency of plans to transfer sponsorship of IND (b) (4) to Ferndale Laboratories, Inc., and Ferndale assumed all responsibilities and commitments and filed the NDA. Investigation #1 was initiated on May 14, 2013 and was completed on December 12, 2013.

Investigation #2

IND # (b) (4)

YES

!
!
! NO x

! Explain: At the pre-NDA meeting (October 27, 2014), (b) (4) informed the Agency of plans to transfer sponsorship of IND (b) (4) to Ferndale Laboratories, Inc., and Ferndale assumed all responsibilities and commitments and filed the NDA. Investigation #2 was initiated on June 26, 2013 and was completed on February 27, 2014.

(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

Explain:
certification.

!
!
! NO x
! Explain: The reviewer did not find any such

Investigation #2

YES

Explain:
certification.

!
!
! NO x
! Explain: The reviewer did not find any such

(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: Brenda Carr
Title: Medical Officer
Date: September 28, 2015

Name of Office/Division Director signing form:
Title:

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/

CRISTINA Petruccelli Attinello
11/04/2015

JILL A LINDSTROM
11/06/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208183 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Ultravate Established/Proper Name: halobetasol propionate Dosage Form: lotion, 0.05%		Applicant: Ferndale Laboratories Inc. Agent for Applicant (if applicable):
RPM: Cristina Attinello		Division: DDDP
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) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>11-6-15</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 checked="" type="checkbox"/> None
❖ 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 _____		<input type="checkbox"/> Received
❖ 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, 505(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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): corticosteroid
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <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 |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 <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>)	AP, 11-6-15
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	n/a
• Original applicant-proposed labeling	n/a
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	7-30-15
• Review(s) (<i>indicate date(s)</i>)	7-21-15
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 3-9-15 DMEPA: 8-26-15 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 9-8-15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> 11-3-15 Other: PLLR 9-16-15
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	3-9-15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<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
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>7-15-15</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	6-8-15, 3-18-15, 1-13-15, 1-5-15
❖ 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)	n/a
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	10-27-14
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	7-25-12
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	n/a
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
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>)	11-6-15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	11-6-15
PMR/PMC Development Templates (<i>indicate total number</i>)	1
Clinical	
❖ Clinical Reviews	

<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	10-29-15
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ 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>)	pg. 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</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>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	9-28-15, 8-28-15, 7-27-15
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	9-3-15, 2-20-15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	9-8-15, 3-4-15
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	10-14-15, 8-19-15, 2-23-15, 8-8-14, 10-2-13, 11-7-12, 11-1-12, 8-26-10, 4-9-09, 2-17-09, 12-3-08, 11-25-08
❖ 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
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	11-3-15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	10-20-15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	Quality Micro 6-25-15
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	n/a
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/

CRISTINA Petruccelli Attinello
11/06/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208183

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Ferndale Laboratories, Inc.
780 W. 8 Mile Road
Ferndale, MI 48220

ATTENTION: Sarah Van Hoof
Director, Regulatory Affairs and Compliance

Dear Ms. Van Hoof:

Please refer to your New Drug Application (NDA), dated December 23, 2014, and received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Halobetasol Propionate Lotion, 0.05%.

We also refer to your correspondence, dated and received May 8, 2015, requesting review of your proposed proprietary name, Ultravate.

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

If any of the proposed product characteristics as stated in your May 8, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Cristina Attinello, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
07/30/2015

**PeRC Meeting Minutes
July 15, 2015**

PeRC Members Attending:

Lynne Yao
Wiley Chambers
Gettie Audain
Rosemary Addy
Hari Cheryl Sachs
Robert "Skip" Nelson
Lily Mulugeta
Gilbert Burckart
Linda Lewis
Andrew Mulberg
Freda Cooner
Kevin Krudys
Thomas Smith
Belinda Hayes
Gregory Reaman
Julia Pinto
Ikram Elayan
Dionna Green

Agenda

Non-Responsive

10:20	NDA	208183	Ultravate Lotion (halobetasol propionate, 0.05%) Partial Waiver/Deferral/Plan w/Agreed iPSP	Plaque Psoriasis
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Non-Responsive

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Non-Responsive

Ultravate Lotion (halobetasol propionate, 0.05%) Partial Waiver/Deferral/Plan w/Agreed iPSP

- Proposed Indications: Tropical treatment of plaque psoriasis
- The division clarified that the pediatric plan is based on an Agreed iPSP. Additionally, the division clarified that waivers are being granted for this product in psoriasis patients less than 12 years of age because other halobetasol formulations of the same strength (0.05%) are only approved down to 12 years of age. If this product was to be studied and labeling was included for patients less than 12 years of age then there could be confusion between these products. Such confusion could present a safety concern because of the known variability in the HPA axis suppression in corticosteroid products based on the formulation/presentation (e.g., foam vs. ointment vs. cream).
- *PeRC Recommendations:*
 - The PeRC agreed with the plan.
 - The division noted that the protocol for the pediatric study has already been submitted and that the study plans to initiate enrollment in September 2015.
 - The PeRC recommended that in the future, the division eliminate statements that tie the timeline for the initiation of studies to an NDA approval (e.g., comments made on page 10 of the Agreed iPSP).

Non-Responsive

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/s/

GETTIE AUDAIN
07/28/2015

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: **208183**

PRODUCT PROPRIETARY NAME: **Ultravate lotion** ESTABLISHED/GENERIC NAME: **halobetasol propionate lotion, 0.05%**

APPLICANT/SPONSOR:

PREVIOUSLY APPROVED INDICATION/S:

- (1) none
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

- (1) topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.
- (2) _____
- (3) _____
- (4) _____

BLA/NDA STAMP DATE:

PDUFA GOAL DATE:

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

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

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

Did the sponsor submit an Agreed iPSP? Yes ***No***

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ***No***

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ***No***

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ***No***

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ***No***

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

- Pediatric age group(s) to be waived. < 12 years
- Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)
 - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (*This reason is for Partial Waivers Only*)

3. Provide justification for Waiver:

Many topical corticosteroid products of varying potency are available for treating pediatric patients with psoriasis.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Safety and effectiveness of TRADE NAME Lotion in patients younger than 18 years of age have not been established; (b) (4)

(b) (4)

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with (b) (4) use of topical corticosteroids in infants and children. [See *Warnings and Precautions (5.1)*].

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema [See *Warnings and Precautions (5.1)*].

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

 basal cell and squamous cell skin cancer

 bladder

 breast

 cervical

 colorectal

 endometrial

 esophageal

cancer (continued):

 follicular lymphoma

 gastric

 hairy cell leukemia

 hepatocellular

 indolent non-Hodgkin lymphoma

 lung (small & non-small cell)

 multiple myeloma

 oropharynx (squamous cell)

 ovarian (non-germ cell)

 pancreatic

 prostate

 refractory advanced melanoma

 renal cell

 uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request: 12- 17 years
2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
Waiver has been requested for the pediatric population < 12 years.
3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*
 - a. Adult studies are completed and ready for approval **x**
 - b. Additional safety or effectiveness data needed (**describe**)
 - c. Other (**specify**)
4. Provide projected date for the submission of the pediatric assessment (deferral date):
Estimated Final Report Date: September 2017
5. Did applicant provide certification of grounds for deferring assessments? Yes No
6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? **x** Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? **x** Yes No
2. Does the division agree with the sponsor's plan? **x** Yes No

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? Yes No
- a. Protocol Submission: September 2014
 - b. Study Completion: estimated initiation: September 2015
 - c. Study Submission: estimated final report date: September 2017
4. Has a Written Request been issued? Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. Has a PPSR been submitted? Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design: PK/HPA study

Nonclinical Studies: none

Clinical Studies: (b) (4) study with HBP Lotion, 0.05% to determine the pharmacokinetic properties and adrenal suppression potential of HBP Lotion, 0.05% in pediatric subjects from 12 to 17 years of age with plaque psoriasis (b) (4)

Age group and population (indication) in which study will be performed: 12 to 17 years with plaque psoriasis

This section should list the age group and population exactly as it is in the plan.

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

(b) (4)

Example:

Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

(b) (4)

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients must have a negative pregnancy test if female..

Clinical endpoints:

Proposed endpoints for the PK/HPA study:

[Redacted content] (b) (4)

Example:

Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments: Not found in the iPSP

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):

(b) (4)

Example:

Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

<p>Division comments on product safety: <i>Are there any safety concerns currently being assessed?</i> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><i>Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies?</i> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><i>Will a DSMB be required?</i> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><i>Other comments:</i></p>
<p>Division comments on product efficacy:</p> <p>The applicant has established efficacy of their product for treatment of topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.</p>
<p>Division comments on sponsor proposal to satisfy PREA: The applicant's proposal is acceptable.</p>

<p>PeRC ASSESSMENT TEMPLATE</p> <p><i>Please attach:</i></p> <ul style="list-style-type: none"> <input type="checkbox"/> <i>Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.</i> <input type="checkbox"/> <i>Pediatric Record</i> <p>Date of PREA PMR:</p>

Description of PREA PMR: (*Description from the PMC database is acceptable*)

Was Plan Reviewed by PeRC? Yes No If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols*.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:

Example:

Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):

This section should list the statistical tests conducted.

Example:

Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.

Timing of assessments:

Example:

Baseline, week 2, week, 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

CRISTINA Petruccelli Attinello
07/01/2015



NDA 208183

INFORMATION REQUEST

Ferndale Laboratories, Inc.
Attention: Sarah Van Hoof
Director, Regulatory Affairs & Compliance
780 W. 8 Mile Road
Ferndale, MI 48220

Dear Ms. Van Hoof:

Please refer to your New Drug Application (NDA) dated December 23, 2014, received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for halobetasol propionate lotion, 0.05%.

We also refer to your April 13, 2015 submission, containing an updated proposed drug label.

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.

On December 4, 2014, the Food and Drug Administration published the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the format and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation.

The PLLR implementation date is June 30, 2015; however, we encourage you to comply with PLLR with your current submission. See guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

PLLR requires the Risk Summary statements for 8.1 Pregnancy and 8.2 Lactation be based on available human and nonclinical data. We request that you review the medical literature for available published epidemiologic studies on the safety of topical

halobetasol in pregnancy and published lactation studies, and submit labeling recommendations based on your review, if applicable.

We request that you address the above issues and resubmit labeling (in Microsoft Word format) by June 29, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, please contact Cristina Attinello, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JILL A LINDSTROM
06/08/2015



NDA 208183

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Ferndale Laboratories, Inc.
Attention: Sarah Van Hoof
Senior Manager, Regulatory Affairs
780 W. 8 Mile Road
Ferndale, MI 48220

Dear Ms. Van Hoof:

Please refer to your New Drug Application (NDA) dated December 23, 2014, received January 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for halobetasol propionate lotion, 0.05%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 8, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 23, 2015.

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

Clinical Pharmacology

1. The bioanalytical report for the analysis of halobetasol propionate in human plasma for trial 000-0551-202 states that sample storage stability has been demonstrated for at least 532 days at -20 °C. However, the validation report submitted only support stability up to 167 days.

Provide data to support storage stability of 532 days or a duration sufficient to support the storage duration of samples from trial 000-0551-202.

2. Provide a bioanalytical report for the analysis of serum cortisol concentration for samples from trial 000-0551-202. Include specific details of sample storage (e.g., temperature and duration) for all samples. It appears that some samples were stored for extended periods (up to 2.5 months) prior to analysis at [REDACTED] (b) (4). Provide in tabular format and electronic dataset all individual samples' measured cortisol level and duration of sample storage. Provide storage stability data to support the duration and storage temperature of all samples in this trial.

Microbiology Quality

3. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the *Burkholderia cepacia* complex (Bcc). We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for these species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of Bcc and cells that are acclimated to the product and the environments (e.g., warm or cold water) that may be tested.
4. Provide study results verifying the suitability of the following microbiological test methods for the halobetasol propionate, 0.05% drug product:
 - a. SOP QM-105: Total Aerobic Microbial Count Method and Total Yeasts and Molds Count Method
 - b. SOP QM-110: Method for Verifying the Absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in Products, and for Screening for Gram Negative Bacilli and Beta-Hemolytic *Streptococcus* spp.

Drug Product Quality

5. Provide results of leachables study on the container closure system of the drug product.
6. Provide batch information for the registration stability batches of the drug product. Additionally, indicate orientation of the stability samples of the drug product during the registration stability study.
7. Provide a comparison of the drug product manufacturing process among pivotal clinical batches, registration stability batches and production batches.

Drug Substance Quality

8. The supplier's System Suitability criterion for the Residual Solvents method (as found in the NDA) is inadequate; and information cannot be located in the NDA submission demonstrating that this method has been verified at the drug product facility. Submit your

verification of this method, including System Suitability studies, along with other parameters, to include RSD for peak areas as well as resolution between appropriate peaks (or number of Theoretical Plates).

9. We agree that the drug substance manufacturing process is not likely to produce the USP impurities, Diflorasone 21-Chloro, Diflorasone 11-Propionate, 21-Chloro, Halobetasol Propionate 9-Chloro and Halobetasol Propionate 6-Chloro, and that they are not likely to form via degradations of the drug substance. However, the original impurity profile of the drug substance, as provided in the NDA for analyzing batch #00012, actually reflects the impurities generated by the drug substance manufacturing process. Thus, we recommend that you amend the drug substance specification to include both the USP impurity tests and the original DMF impurity tests reported for batches produced prior to 2010.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We also request that you submit the following information:

Clinical

1. Address the long-term safety of halobetasol propionate lotion, 0.05%.
2. Provide a description of the steps taken to minimize potential bias of clinical study results by Stacy Smith, MD.

Nonclinical

3. We recommend that your proposed prescribing information conform to the FDA published *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the “Pregnancy and Lactation Labeling Rule” (PLLR or final rule).

Biopharmaceutics Quality

4. We recommend that you develop an *in vitro* release test (IVRT) methodology and propose *in vitro* release acceptance criteria (range) for your drug product to be used systemically at release and during stability as a quality control parameter. Your proposed acceptance criteria should be based on generated data for the final to-be-marketed batches. Submit all the generated data to support your proposed acceptance criteria.
5. Also, along with the proposed *in vitro* release specification, include the IVRT method development and validation report. The IVRT method development report should contain

(but not be limited to) justification for the selection of the following methodology components:

- a. Diffusion apparatus
 - b. Receptor medium selection
 - c. Membrane selection
 - d. Sampling time points
 - e. Temperature
6. The IVRT method validation report should contain (but not be limited to) the following validation components:
- a. Linearity and Range
 - b. Accuracy/Precision and Reproducibility
 - c. Mass Balance
 - d. Sensitivity and Specificity
 - e. Selectivity
 - f. Robustness
 - g. Membrane Inertness
 - h. Receptor Solution Solubility/Stability
7. The IVRT method's sensitivity, specificity, selectivity and robustness need to be evaluated with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling comments and questions:

1. The length of Highlights (HL) must be one-half page or less unless a waiver has been granted in a previous submission. Revise HL to be one-half page or less in length.
2. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the Full Prescribing Information (FPI). Elongate the horizontal

line that separates HL from the TOC. Add a horizontal line to separate the TOC from the FPI.

3. The bolded HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters. Revise the HL Limitation Statement to comply with this PLR guideline.
4. The verbatim bolded statement must be present toward the end of HL: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”. Revise this statement in the draft proposed label to include the manufacturer’s name and phone number.
5. The Patient Counseling Information statement must include the bolded verbatim statement: “**See 17 for PATIENT COUNSELING INFORMATION**”. Revise the Patient Counseling Information statement to appear as written above.
6. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement should precede the presentation of adverse reactions: “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 practice.” Revise the statement to reflect the above.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 13, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

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

professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KENDALL A MARCUS
03/18/2015



NDA 208183

**NDA ACKNOWLEDGEMENT
USER FEES RECEIVED**

Ferndale Laboratories, Inc.
Attention: Sarah Van Hoof
Senior Manager, Regulatory Affairs
780 W. 8 Mile Road
Ferndale, MI 48220

Dear Ms. Van Hoof:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for halobetasol propionate lotion, 0.05%.

You were notified in our letter dated January 5, 2015, that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received or waived all required fees and your application has been accepted as of January 8, 2015.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 9, 2015 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 cited above should be included 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 Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact Cristina Attinello, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Cristina Attinello, MPH
Senior Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

CRISTINA Petruccelli Attinello
01/13/2015



NDA 208183

UNACCEPTABLE FOR FILING

Ferndale Laboratories, Inc.
Attention: Sarah Van Hoof
Senior Manager, Regulatory Affairs
780 W. 8 Mile Road
Ferndale, MI 48220

Dear Ms. Van Hoof:

Please refer to your New Drug Application (NDA) dated December 23, 2014, received December 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for halobetasol propionate lotion, 0.05%.

We note that you are in arrears for payment of fees for products, or establishments, or previously submitted applications. Because an application is considered incomplete and cannot be accepted for filing until all fees owed have been paid, review of the application referenced above may not begin at this time. Upon receipt of the outstanding fees, we will start the user fee clock and commence review of your application. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox (b)(4)
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the appropriate user fee coversheet (Form 3397 or 3792) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box (b)(4)) should be included on any check you submit.

Please cite the NDA Number listed above at the top of the first page of all submissions to this application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

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

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 wish to send payment by wire transfer, or if you have any other user fee questions, please call the Prescription Drug User Fee staff at 301-796-7900.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Cristina Attinello, MPH
Senior Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

CRISTINA Petruccelli Attinello
01/05/2015



IND (b) (4)

MEETING MINUTES

(b) (4)

Dear (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for halobetasol propionate lotion, 0.05%.

We also refer to the meeting between representatives of your firm and the FDA on October 27, 2014. The purpose of the meeting was to discuss the planned NDA submission for halobetasol propionate lotion, 0.05%.

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 Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental 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: October 27, 2014, 1:30 PM
Meeting Location: WO22, Rm 1311

Application Number: IND (b) (4)
Product Name: halobetasol propionate lotion, 0.05%
Proposed Indication: treatment of plaque psoriasis in patients 18 years of age and older
Sponsor Name: (b) (4)

Meeting Chair: Tatiana Oussova, MD, MPH
Meeting Recorder: Cristina Attinello

FDA ATTENDEES

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Jill Lindstrom, MD, Clinical Team Lead, DDDP
Jane Liedtka, MD, MPH, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DPA II, Branch III
Hitesh Shroff, PhD, Product Quality Reviewer, DPA II, Branch III
Mohamed Alosch, PhD, Biostatistics Team Lead, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
Barbara Gould, MBAHCM, Chief Project Management Staff, DDDP
Cristina Attinello, MPH, Senior Regulatory Project Manager, DDDP
Roy Blay, PhD, Reviewer, OSI
Lisa Lin, Senior Regulatory Analyst, OBI
Nyedra Booker, DRISK Reviewer, OSE
Carolyn McCloskey, PharmD, Medical Officer, OSE
Carlos Mena-Grillasca, RPh, Safety Evaluator, OSE/DMEPA

SPONSOR ATTENDEES

(b) (4)

Richard Hamer, VP Regulatory/Clinical Affairs and Compliance, Ferndale Laboratories, Inc.
Sarah Van Hoof, Sr. Manager, Regulatory Affairs, Ferndale Laboratories, Inc.
Leon Dupuis, PhD, VP Quality Control/Validation, Ferndale Laboratories, Inc.

Purpose of the Meeting:

To discuss the planned NDA submission for halobetasol propionate lotion, 0.05%

Regulatory Correspondence History

We have had the following meeting with you:

- July 25, 2012: End of Phase 2 Meeting

We have sent the following correspondences:

- August 13, 2014: Advice/Information Request Letter
- May 15, 2014: Agreed PSP Letter
- February 6, 2014: PSP Advice Letter
- August 2, 2013: Advice/Information Request Letter
- December 5, 2012: SPA Agreement Letter
- October 11, 2011: Advice/Information Request Letter
- October 13, 2010: Advice/Information Request Letter
- August 6, 2010: Advice/Information Request Letter
- July 20, 2010: Advice/Information Request Letter
- April 30, 2009: Advice/Information Request Letter
- December 19, 2008: Advice/Information Request Letter

Regulatory

Question 16:

Since a right-of-reference to the Ultravate NDAs (19-967 [cream] and 19-968 [ointment]) has been secured, the Sponsor will rely on information in the approved Ultravate labeling to cover subjects not specifically investigated with HBP Lotion, 0.05%. Such sections and text will be noted by reference to the Ultravate labeling in the HBP Lotion, 0.05% annotated labeling to be provided in the NDA.

The package insert will be prepared in accordance with the Physician Labeling Rule (21 CFR 201.56 and 201.57) and will rely on approved labeling text from the Ultravate label to cover subjects not specifically investigated with HBP Lotion, 0.05%. Does the Agency agree with this approach?

Response:

Your approach seems reasonable at this time. However, the acceptability of the content of labeling will be determined during NDA review.

Question 17:

Does the Agency agree that the proposed proprietary name and trade dress can be submitted during the NDA review, without impacting the PDUFA goal date?

Response:

The proposed proprietary name request for review has a separate PDUFA goal date of 90 days, which is independent from the application (NDA) PDUFA goal date. You can submit your proposed proprietary name for review with the initial NDA submission or any time during the NDA review cycle. However, we encourage you to submit your proposed proprietary name for review as early in the review cycle as possible. Refer to guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*.¹

You should submit a draft trade dress (i.e. container labels and carton labeling) with your initial NDA submission. You can either include your proposed proprietary name or use a placeholder instead throughout.

Question 18:

Due to the extensive marketing experience and well established safety profile of topical drug products containing halobetasol propionate, 0.05% (Ultravate Cream and Ointment, and numerous generics), as well as 591 subject exposures during the clinical development of HBP Lotion, we do not believe there is a benefit to developing additional risk management plans beyond the safety information contained in the product labeling.

We propose that all of the risks associated with HBP can be addressed through adequate labeling instructions in the Package Insert and that no medication guide or formal REMS program exceeding normal pharmacovigilance practices are required. Does the Agency concur?

Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Chemistry, Manufacturing and Controls (CMC)

Question 1:

The compendial drug substance, halobetasol propionate, is manufactured and supplied by (b) (4) in conformance with the USP monograph as described in their Type II Drug Master File (DMF) # (b) (4). We intend to submit only limited information from the open portion of the DMF on the drug substance.

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

Does the Agency agree that the drug substance specifications, test parameters and acceptance criteria are appropriate and adequate to support filing of an NDA?

Response:

The specifications with test parameters and acceptance criteria are adequate for filing. The internal method for residual solvents by GC (b) (4) must be validated per ICH Q2(R1) guidance at the time of NDA submission.

You will need to provide establishment information in the NDA for manufacturing/testing facilities. A statement of readiness for inspection needs to be provided for each facility.

Question 2:

The commercial production of HBP Lotion 0.05%, including bulk manufacturing, packaging, labeling, testing, and product release, will be performed by Ferndale Laboratories, Inc. To date, Ferndale has manufactured a total of four (4) (b) (4) batches of drug products. In anticipation of commercial launch, Ferndale is preparing to scale-up the current process to (b) (4) and (b) (4) batch sizes. Process validation of three (3) commercial batches of each size will be performed prior to commercialization.

Does the Agency agree that the drug product specifications, test parameters and acceptance criteria are appropriate and adequate to support filing of an NDA?

Response:

Your proposed drug product specification has “report results” as the acceptance criteria for multiple tests. It is unacceptable in the NDA phase to have “report results” in drug product specification for batch release and stability studies. Replace “report results” with meaningful numeric acceptance criteria in the initial submission of the proposed NDA. Provide justification for each proposed acceptance criterion.

Add package integrity to drug product release specification.

Additionally, analytical methods must be validated per the ICH Q2(R1) guidance at the time of NDA filing.

Meeting Discussion:

The sponsor clarified that their manufacturing experience is very limited. However; they desire to submit their NDA this year. The Agency suggested that the Phase 3 batch(es) be used as the benchmark and the physicochemical properties of the batch(es) should be the targeted properties of future commercial batches. The sponsor was advised to propose acceptance criteria for the tests included in the drug product specification.

Question 3:

Does the Agency agree with the Sponsor’s proposal to defer establishment of acceptance limits for certain test parameters (impurities, degradation products, pH, viscosity, droplet size and microscopic appearance) until results on the (b) (4) production batches are available?

Response:

No, we do not agree. Propose acceptance criterion for each test present in drug product specification with justification at time of NDA submission.

Additional Comments

1.  (b) (4)
- 2.
- 3.

Pharmacology/Toxicology

Question 4:

Based on previous FDA feedback, the recommended nonclinical toxicology studies were completed with the to-be-marketed formulation (HBP Lotion, 0.05%). These include dermal and ocular irritation studies in rabbits, a 4-week dermal toxicity study in minipigs, and a 13-week repeat-dose dermal toxicity study in rats. A waiver for the dermal carcinogenicity study on HBP Lotion, 0.05% was granted by the CAC on 13 August 2014.

Does the Agency agree that (b) (4) has fulfilled the necessary studies, as recommended by FDA, to demonstrate the safety of HBP Lotion, 0.05% and that no additional nonclinical studies on HBP Lotion are needed?

Response:

Yes, we agree that (b) (4) has completed the necessary studies to demonstrate the safety of HBP Lotion, 0.05% and that no additional nonclinical studies on HBP Lotion are needed.

Question 5:

A right-of-reference to both Ultravate[®] (halobetasol propionate), 0.05% NDAs (19-967 [cream] and 19-968 [ointment]) has been secured and we propose to include the full study reports for the following toxicity studies that supported the Ultravate NDA approvals: 3-month repeat dose oral toxicity in rats and dogs; genetic toxicity (Ames, *in vitro* cytogenetics, *in vivo* micronucleus, nuclear anomaly, chromosomal aberration, sister chromatid exchange); fertility and early embryonic development in rats; and embryofetal development in rats and rabbits. Please see Section 10.3.4.2 for brief summaries of the legacy reports we intend to include in Module 4 of the pending NDA submission. A preliminary Index listing the NDA submission contents, including Module 4, is provided in Section 11, Appendix C.

Does the Agency agree that the inclusion of the above-listed nonclinical toxicology studies on HBP from the Ultravate Ointment NDA is adequate to support filing of an NDA for HBP Lotion, 0.05% submitted under Section 505(b)(1) and that no additional nonclinical studies are needed?

Response:

Yes, the inclusion of the above-listed nonclinical toxicology studies on HBP from the Ultravate Ointment (NDA 19968) is adequate to support filing of a 505(b)(1) NDA for HBP Lotion, 0.05%. No other nonclinical studies are needed.

Question 6:

Because the nonclinical pharmacology and pharmacokinetics (excluding toxicokinetics) for HBP is well established, the Sponsor plans to include only brief written summaries of the information from the Ultravate NDAs and will not be preparing tabulated summaries to cover CTD sections 2.6.3 and 2.6.5 in the NDA submission. Does FDA agree with the omission of these CTD sections?

Response:

Yes, it is acceptable to omit tabulated summaries for CTD sections 2.6.3 and 2.6.5 in the NDA submission.

Clinical Pharmacology

Question 7:

Clinical pharmacology studies conducted with HBP Lotion included two studies in 298 healthy subjects (36 subjects in a single point vasoconstriction (VCA) study and 262 subjects in a repeat insult patch test (RIPT) study). One comparative pharmacokinetic/hypothalamic-pituitary axis (PK/HPA) suppression study using Ultravate Cream as the reference drug was conducted in 43 adult subjects with plaque psoriasis under maximal use conditions. A subset of 24 subjects (12 in each treatment group) participated in the PK part of the protocol. Please see Sections 10.4.3.1 and 10.4.4 for further information.

Does the Agency agree that the completed clinical pharmacology studies conducted with HBP Lotion, in combination with the information from the approved Ultravate NDAs, are adequate to support the clinical pharmacology section of the labeling?

Response:

Your clinical pharmacology development program appears adequate to support filing of the NDA. Whether the data are adequate to support labeling will be considered during NDA review.

Additional Comments

Submit to the NDA method validation reports and bioanalytical reports for the assessment of cortisol and halobetasol. If a commercial system was used, the validation report should include results of in-house validation (i.e., at the site of sample analysis) and results of quality control assessment from similar time frame as study samples analysis.

Submit raw and calculated PK parameters values in SAS transport format (.xpt).

Meeting Discussion:

The sponsor clarified that they will submit validation data for the cortisol assay. The sponsor also inquired whether the PK data files need to be in SDTM format. The Agency clarified that the PK data files do not need to be in SDTM format.

Clinical/Biostatistics

Question 8:

In total, 591 subjects have been exposed to HBP Lotion and almost half (277/591; 46.9%) of those subjects were treated for the indicated dermatologic condition: plaque psoriasis. HBP Lotion has demonstrated a safety profile similar to Ultravate halobetasol propionate formulations and no unanticipated drug-related safety events were identified in multiple clinical trials. Please see Section 10.4 for further information.

Does the Agency agree that the safety data from the completed HBP Lotion studies, in combination with the known safety information for other 0.05% halobetasol propionate dosage forms, are adequate to support the extent of patient exposure and the safety requirement for the HBP Lotion 0.05% NDA?

Response:

From the information provided, the extent of your safety database appears acceptable. Clarify to what other “known safety information for other 0.05% halobetasol propionate dosage forms” you refer.

Question 9:

In accordance with §314.50(f)(2), we intend to only include CRFs for patients who died during a clinical study or who discontinued the study due to an adverse event. Does the Agency agree?

Response:

Provide the following:

- Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the trials conducted with halobetasol propionate lotion, 0.05%.
- Case report forms (CRFs)
 - for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:
 - Electronic links for:
 - a. all serious AEs
 - b. all severe AEs
 - c. all patients discontinued regardless of reason
 - d. all deaths
 - CRFs should be referenced under the study in which it belongs and tagged as “case report-forms” in that study’s stf.xml file.
 - CRFs that are not submitted should be readily available upon request.

Question 10:

Based on the recent precedents disclosed in FDA approval packages of other topical steroid products, the clinical experience to date with the drug product, and the lack of potential for QT prolongation concerns with decades of use of topical corticosteroids as a drug class, TI does not see any need for any additional clinical evaluations regarding the potential for QT/QTc interval prolongation with this drug product. Does the FDA concur? If not please explain.

Response:

Per ICH E14, TQT studies are typically needed for novel agents and for new formulations of older agents which result in significantly higher exposure. In your application, provide your scientific rationale for why your product does not present a risk for prolongation of cardiac repolarization.

Question 11:

In addition to the HPA/PK and the Phase 2 pilot efficacy studies, two Phase 3 pivotal studies to determine the safety and effectiveness of HBP Lotion in patients with plaque psoriasis have been completed as per the SPA Agreement Letters received from the Agency. Both Phase 3 studies met the primary efficacy endpoint with significantly more subjects achieving “treatment success” in the HBP Lotion group (45%) versus the VEH Lotion group (7%) at Day 15 ($p < 0.001$). Please see Section 10.4.2 for further information.

Since both Phase 3 studies have met the conditions specified in the SPA Agreement and the pre-specified primary endpoint, we believe that these studies are adequate to file the NDA. Does the Agency agree?

Response:

Your Phase 2 and Phase 3 trials appear to be acceptable for the filing of your NDA.

Question 12:

(b) (4) plans to provide raw datasets (Case Report Tabulations) and analysis datasets, including define.xml documentation, for the pivotal Phase 3 clinical studies (000-0551-304, and 000-0551-305), supportive Phase 2 studies (000-0551-202 and 000-0551-207), and integrated analyses of safety and efficacy. The raw datasets will be modeled in accordance with the CDISC Study Data Tabulation Model (SDTM) Implementation Guide: Human Clinical Trials which comprises Version 3.1.3 of the Submission Data Standards. The analysis data sets will be modeled in accordance with the CDISC Analysis Data Model (ADaM), Version 2.1. All SDTM and ADaM datasets will be submitted in SAS transport form (.xpt). Does the Agency Agree with this plan?

Response:

Your plan is acceptable, assuming that the raw datasets are pulling directly from the CRFs and serve as the basis for analyses presented in the ADaM-formatted analysis datasets. If not, also submit any intermediary files to ensure reviewers can trace data back from datasets to CRFs.

The primary method for handling missing efficacy data in your trials is the Multiple Imputation (MI) approach, which involves generating multiple datasets. Instead of submitting the multiple

imputed datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze these datasets.

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subject was enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Question 13:

(b) (4) plans to provide raw datasets in transport form (.xpt) for the Phase 1 VCA (000-0551-101) and RIPT (000-0551-103) studies. These datasets will not be in SDTM format. Does the Agency Agree with this plan?

Response:

Your plan is acceptable. We prefer that you submit datasets based on [Study Data Specifications](#).

Question 14:

As the objective of the TEWL study (000-0551-108) was to evaluate the occlusivity and moisturization potential of the HBP Lotion formulation, datasets were neither generated for this study nor does (b) (4) plan to prepare datasets for this study in the NDA. We do not believe the inclusion of datasets for this study would provide pivotal information for FDA's review of safety and efficacy of HBP Lotion, 0.05%. Does the Agency Agree?

Response:

This seems reasonable at this time.

Question 15:

The Integrated Summary of Safety (ISS) will present the relevant safety summaries for each of the seven clinical studies, as well as, a pooled analysis of the four Phase 2 and Phase 3 studies. The safety summaries for the Phase 1 studies (Studies # 000-0551-101, # 000-0551-108, and # 000-0551-103) which enrolled healthy subjects with limited exposure to HBP Lotion (b) (4) will be presented for the individual studies. The safety results of the Phase 2 and 3 studies (Studies #

000-0551-202, # 000-0551-207, # 000-0551-304, and # 000-0551-305) which enrolled adults with plaque psoriasis and exposed to HBP Lotion for two weeks (approximately 50g/week) will be presented individually and pooled as described in the draft SAP provided in Section 10.5.2.

The Integrated Summary of Efficacy (ISE) will include individual and integrated summaries of the supportive efficacy study (Study # 000-0551-207) and the two pivotal Phase 3 studies (Studies # 000-0551-304 and # 000-0551-305). The two Phase 3 studies were conducted using identical protocols. The supportive efficacy study (Study # 000-0551-207) was similar to the Phase 3 studies with regards to baseline disease characteristics, identical dosing regimens, identical study methodology, and efficacy endpoints that were measured using essentially the same severity disease scale.

A draft statistical analysis plan, which summarizes the statistical methods and analyses to be performed for the integrating studies described above, is provided in Section 10.5.2.

Does the Agency agree with the Sponsor's proposal for the pooling of studies to be included in the ISS and ISE and the statistical analyses to be conducted?

Response:

Your proposal appears acceptable at this time.

Question 19:

As confirmed in the Agreed Initial Pediatric Study Plan (Agreed iPSP dated 15 May 2014), the Sponsor will conduct a hypothalamic-pituitary-adrenal (HPA) axis suppression and pharmacokinetic (PK) study in adolescents 12-17 years of age with plaque psoriasis (b) (4)

information. please see Section 10.6 for further information.

Does the Agency agree that the Agreed iPSP is sufficient to satisfy the PREA requirements for the NDA?

Response:

Your approach appears reasonable at this time. However, the determination as to satisfaction of PREA requirements will be determined during review of the NDA.

Question 20:

In order to ensure all administrative aspects of the pending NDA submission are covered and no gaps are identified post-submission, we would like to discuss the following administrative components of the submission:

(b) (4) plans to transfer sponsorship of IND (b) (4) to Ferndale Laboratories, Inc. who will assume all responsibilities and commitments and file the NDA. The NDA will be prepared in compliance with FDA's eCTD specifications. The NDA will be prepared in compliance with FDA's eCTD specifications. Appendix C provides a preliminary Index of the planned NDA components, granularity, and structure.

Does the Agency agree with the proposed eCTD index and location of the required data elements?

Response:

From a technical standpoint (not related to content) yes, the proposed format for the planned NDA is acceptable. However, see additional comments/recommendations below:

- FDA Form 356h, should reside under m1.1.2 (not m1.1.1.) eCTD structure.
- FDA Form 3674 should reside under m1.2 cover letter section (not m1.1.3), with a clear leaf title.
- Do not create additional nodes (e.g. m1.1.3, m1.2.1, etc..) in the eCTD structure, beyond what is in the specifications.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.

Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non-eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc..) of the referenced document along with a hypertext link to the location of the information, when possible.
2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. In this case, both applications will be on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind,). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work. In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being cross referenced.

Prior to using cross application linking in an application, it is recommended that the sponsor submit an "eCTD cross application links" sample, to ensure successful use of cross application links.

- To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team: esub@fda.hhs.gov. For more information on an eCTD sample, refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).
3. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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>.

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 labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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.				

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

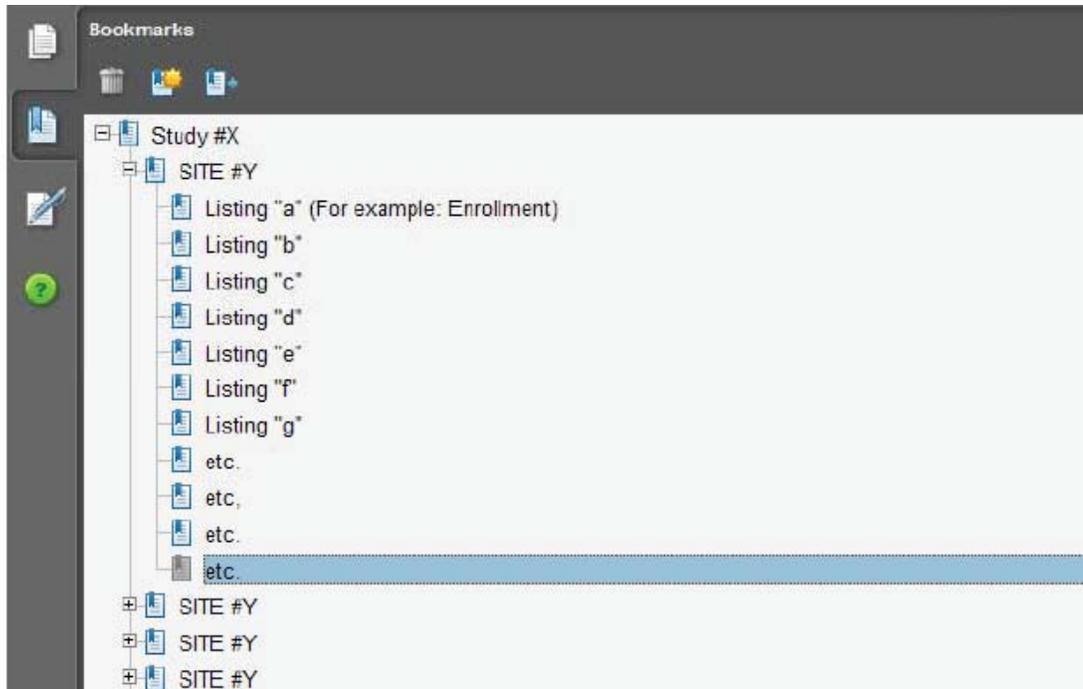
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

TATIANA OUSSOVA
11/10/2014



IND (b) (4)

MEETING MINUTES

(b) (4)

Dear (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (halobetasol propionate) Lotion, 0.05%.

We also refer to the meeting between representatives of your firm and the FDA on July 25, 2012. The purpose of the meeting was to discuss the clinical development plan for IND (b) (4).

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 Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: July 25, 2012, 9AM
Meeting Location: WO22, Rm 1315

Application Number: IND (b) (4)
Product Name: (halobetasol propionate) Lotion, 0.05%
Proposed Indication: For treatment of plaque psoriasis in patients 18 years of age and older

Sponsor Name: (b) (4)

Meeting Chair: Susan Walker, MD
Meeting Recorder: Cristina Attinello, MPH

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Victoria Kusiak, MD, Deputy Director, ODE III
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
Susan Walker, MD, FAAD, Division Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Jill Lindstrom, MD, Clinical Team Lead, DDDP
Jane Liedtka, MD, M.P.H., Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Cristina Attinello, MPH, Regulatory Project Manager, DDDP
Strother D. Dixon, Regulatory Health Project Manager, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DPA II, Branch III
Hitesh Shroff, PhD, Product Quality Reviewer, DPA II, Branch III
Mohamed Alosch, PhD, Biostatistics Team Lead, DB III
Yuqing Tang, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Roy Blay, Reviewer, OSI

SPONSOR ATTENDEES

(b) (4)

Richard Hamer, Chemistry, Manufacturing and Controls/OA – Ferndale Lab
(b) (4)

(b) (4), MS, Regulatory Affairs

Purpose of the Meeting:

The purpose of this meeting is to discuss the clinical development plan for IND (b) (4).

Regulatory Correspondence History

We have sent the following correspondences:

- October 11, 2011: Advice/Information Request Letter
- October 13, 2010: Advice/Information Request Letter
- August 6, 2010: Advice/Information Request Letter
- July 20, 2010: Advice/Information Request Letter
- April 30, 2009: Advice/Information Request Letter
- December 19, 2008: Advice/Information Request Letter

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does the Agency agree that the drug substance specifications, test parameters and acceptance criteria are appropriate and adequate to support the Phase 3 program?

Response:

Yes. The proposed drug substance specification is reasonable to support the Phase 3 program.

Question 2:

Does the Agency agree that the drug product specifications and the analytical methods are appropriate and adequate to support the Phase 3 program?

Response:

No. Add the following tests to the drug product specification:

- Droplet size
- Microscopic appearance

Meeting Discussion:

The sponsor inquired about the intent of these two tests and about analytical methods. The Agency replied that the proposed formulation is an (b) (4); by monitoring droplet size (b) (4), the stability of the (b) (4) can be evaluated. Droplet size can be measured by multiple analytical technologies (e.g., laser defraction, optical microscopy, etc.). The sponsor can choose a method that is most suitable for them. The test on microscopic appearance is to examine the appearance of the (b) (4) under the microscope and to look for potential precipitation of the active ingredient, which is dissolved (b) (4).

Question 3:

Does the Agency agree that the manufacturing plan and stability program are adequate to support the Phase 3 program?

Response:

The proposed manufacturing plan and stability program for Phase 3 are reasonable, provided that you will monitor droplet size and microscopic appearance in the drug product stability studies.

Pharmacology/Toxicology

Question 4:

Per the advice received from the Agency dated 13 October 2010, the Sponsor intends to complete a 13-week range-finding study in rats on HBP Lotion 0.05%. With this study and the completed nonclinical studies, does the Agency agree that no additional nonclinical studies are required to support an NDA filing?

Response:

No additional nonclinical studies are required to support an NDA submission. However, if the 13-week range finding study indicates a 2-year dermal carcinogenicity study is feasible, then a carcinogenicity protocol will be required to be submitted to the IND. Also, a proposed timeline for conduct of the carcinogenicity study as a PMR should be included in the NDA submission.

Question 5:

Assuming a clinical bridge is established between HBP Lotion and the RLD, Ultravate Cream, does the Agency agree that adequate information will be available so that the Sponsor can rely on the Agency's previous findings of safety and that no additional nonclinical studies are required?

Response:

Yes, the Agency agrees that if an adequate clinical bridge is established between HBP Lotion and Ultravate[®] Cream the sponsor can rely on the Agency's previous findings of safety.

Question 6:

Does the Agency agree that the outline provided for the 13-week dermal range-finding study in rats is adequate (including the dosing frequency and proposed doses, which range from the clinical concentration to the maximum feasible concentration)?

Response:

The protocol outline (Section 5.5) stipulates six groups, including two controls (untreated control and vehicle control) and four different HBP concentrations, to be treated with daily dermal dosing for 13 weeks. However, Table 2 (Future Studies R9860) suggests only two HBP concentrations. An acceptable dermal range-finding study should include at least three concentrations with the high concentration being the maximum feasible concentration, in addition to an untreated control and a vehicle control. The 13 week rat dermal range-finding study protocol outlined in Section 5.5 of the briefing document appears acceptable.

Meeting Discussion:

The sponsor proposed using the maximum feasible concentration (0.1%) and the clinical dose (0.05%) without using a third dose level in the 13-week dermal rat study. The Agency responded that this was acceptable.

The sponsor informed the Agency that their design would be to both prevent oral ingestion and to maximize body surface area (BSA). This may result in less than 10% BSA exposure. The Agency responded that this was acceptable, but stressed the importance of maintaining a high BSA exposure.

Question 7:

Does the Agency agree that a decision about the feasibility of conducting the 2-year dermal carcinogenicity study will be made following completion of the 13-week dermal range-finding study in rats and evaluation of the results by the Agency and the Sponsor?

Response:

Yes. You should submit the study report from the 13-week dermal range finding study with either a proposed protocol for the 2-year dermal carcinogenicity study as a Special Protocol Assessment (see Guidance for Industry, May 2002) or, if the data suggest that the conduct of a carcinogenicity study is not possible, a waiver request. The Agency will review and respond to a Special Protocol Assessment within 45 days.

Clinical/Biostatistics/Clinical Pharmacology

Question 8:

Does the Agency agree that the data from the three completed Phase 1 and 2 studies and the data from the proposed Phase 1 RIPT study and the Phase 3 study with an RLD arm are sufficient to establish a clinical bridge to the RLD, assuming the Phase 3 study results are favorable?

Response:

The adequacy of the clinical bridge will be an NDA review issue.

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf> . In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>) .

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is

scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. For a topical product, this is accomplished through conduct of well-controlled trials with clinical endpoints and for a topical corticosteroid, also includes assessment of the effect of the products on the HPA axis. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

In your submission of a 505(b)(2) application, you should clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any of the published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, you should include a copy of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, your marketing application should summarize the information that supports the application in a table similar to the one below.

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA 012345</i> <i>“DRUGNAME”</i>	<i>Previous finding of safety for nonclinical toxicology</i>

Meeting Discussion:

The Agency added that the sponsor’s proposed elements seem acceptable.

Question 9:

For the Phase 3 program, does the Agency agree that the following are appropriate and adequate to support the NDA and the indication of the drug product?

- a) Overall protocol design
- b) Targeted study population
- c) Primary and secondary efficacy endpoints
- d) Sample size
- e) Overall plan for data analysis
- f) Safety parameters and monitoring plan

Response:

We recommend that you conduct two adequate and well-controlled Phase 3 trials as this provides independent substantiation of the efficacy result. You are referred to *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

As an alternative, you could conduct a single study and establish the superiority of your product to vehicle and the non-inferiority of your product to the RLD. However, in this case you would need to provide an appropriate non-inferiority margin based on data from efficacy studies performed using Ultravate Cream.

With regard to overall protocol design, the multicenter, randomized, double-blind, four-arm parallel group comparison of (halobetasol propionate) Lotion, 0.05% versus vehicle lotion and an evaluator-blinded parallel group comparison of (halobetasol propionate) Lotion, 0.05% and Ultravate® (halobetasol propionate) Cream, 0.05% in subjects with plaque psoriasis appears acceptable.

With regard to target population, subjects with a clinical diagnosis of stable plaque psoriasis involving a minimum of 2% affected body surface area (BSA) (excluding the face, scalp, groin, axillae and other intertriginous areas) and an overall disease severity (ODS) on an agreed upon scale of at least 3 (moderate) appears acceptable.

Primary Endpoint

You have proposed a primary efficacy endpoint that involves treatment of a “designated treatment area” and propose that no lesions outside the treatment area will be treated during the duration of the study. This could introduce bias based on the attributes (e.g., location, severity) of the lesion selected. In addition, we understand most patients to seek treatment of all affected areas, and therefore it would be desirable to provide information in labeling on the response rate for treatment of all relevant affected areas. We recommend that you include all relevant involved areas (except for face, scalp and fold areas which may not be appropriate for treatment with your product) in the treatment and assessment area in your Phase 3 trials. This will eliminate the bias that could be introduced by selection of a designated treatment area, and will provide for more clinically meaningful labeling because the trial parameters will more closely reflect anticipated “real world use.” You may limit the BSA involvement that can be enrolled in order to adhere to the limitation of 50 grams maximum per week for your product.

For the primary efficacy assessment, you should use an acceptable static Physician’s Global Assessment Scale (PGA scale) dichotomized to success vs. failure a priori in the protocol. Success should be defined as a PGA score of 0 or 1 (representing “Cleared” or “Almost Clear”) with at least 2 grades reduction from the base line.

The scale you have proposed for your primary efficacy endpoint, the Overall Disease Severity Scale (ODS), is presented below:

Clear (0)	
Scaling	No evidence of scaling.
Erythema	No erythema (hyperpigmentation may be present).
Plaque elevation	No evidence of plaque elevation above normal skin level.

Almost Clear (1)	
Scaling	Limited amount of very fine scales partially covers some of the plaques.
Erythema	Faint red coloration.
Plaque elevation	Very slight elevation above normal skin level, easier felt than seen.

Mild (2)	
Scaling	Mainly fine scales; some plaques are partially covered.
Erythema	Light red coloration.

Plaque elevation	Slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques.
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Moderate (3)	
Scaling	Somewhat coarser scales predominate; most plaques are partially covered.
Erythema	Moderate red coloration.
Plaque elevation	Moderate elevation with rounded or sloped edges on most of the plaques.

Severe/Very Severe (4)	
Scaling	Coarse, thick tenacious scales predominate; virtually all or all plaques are covered; rough surface.
Erythema	Dusky to deep red coloration.
Plaque elevation	Marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques.

The ODS presented above assumes that psoriasis plaques will exhibit scaling, erythema and plaque elevation proportional to each other. This will not always be the case. We recommend qualifying the descriptors with a phrase such as “No more than” to allow for instances where one parameter improves more than others. The choice of category would then be driven by the worst score amongst the scores for scaling, erythema and plaque elevation.

For example, the “Almost Clear” category would read:

- No more than a limited amount of very fine scales partially covering some of the plaques.
- No more than faint red coloration.
- No more than a very slight elevation above normal skin level, easier felt than seen.

You proposed Cochran-Mantel-Haenszel (CMH) test stratified by center to analyze the primary endpoint of success in Overall Disease Severity (ODS), however, no details about the randomization are provided in your protocol. It should be noted that the method of analysis should follow the method of randomization and the randomization should be stratified by center. Furthermore, your protocol should plan to test for treatment-by-center interaction to ensure that efficacy results are not driven by extreme centers.

For handling missing data, you proposed to use last observation carried forward (LOCF) to impute the missing values. As there is no universally appropriate approach for handling missing data, all efforts should be made to follow each subject to reduce the occurrence of missing data. As the scientific rationale for LOCF is weak, you should propose a more scientifically sound methodology (i.e. modeling approach) as the primary imputation method. Sensitivity analysis should be planned in your protocol to ensure that the efficacy results are not driven by the method of imputation.

Secondary Endpoints

You propose numerous secondary endpoints, yet no methodology is specified for multiplicity adjustment. Secondary efficacy endpoints intended for labeling should be limited in number and clinically relevant and adjusted for multiplicity to control the type I error rate.

The assessment of pruritus you propose as a secondary endpoint involves a patient reported outcome. You have proposed the Itch Evaluation Scoring Scale to measure this secondary endpoint. Categories for an acceptable scale should be non-comparative (i.e. no category should be based on other categories within the scale). We refer you to *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* for more detailed recommendations regarding scale development.

You state that the total number of subjects with psoriasis treated with (haleboetsol propionate) Lotion, 0.05% in your development program is anticipated to be 177. Your clinical program should be designed to detect local or unanticipated adverse events which occur at the frequency of 1% for this new high potency product.

Meeting Discussion:

The sponsor stated that they plan to conduct two Phase 3 studies, one of which will include the listed drug.

The sponsor agreed to revise the Phase 3 protocol so that the efficacy evaluation will be based on the ODS (modified as recommended above) assessed after treatment of the total area of psoriasis involvement (not on a designated treatment area) excluding face, scalp and fold areas.

The sponsor stated that randomization will be stratified by center. The Agency stated that the study should plan to enroll a minimum number of subjects per treatment arm, per center (e.g., 8 subjects). This will allow a reasonable estimate of the treatment effect per center and enable an assessment of investigating center to center variability. The protocol should also include an algorithm to pool small sites to meet such a requirement in case the actual enrollment does not meet the above criteria.

The sponsor inquired whether the Agency recommends a certain method for handling missing data. In response, the Agency noted that it would be difficult to recommend a specific method without knowing the pattern of missing data. The sponsor may propose any scientifically sound method for the primary analysis of missing data and may use another approach for handling missing data in the sensitivity analysis. The Agency referred the sponsor to a report about handling missing data, titled "*The prevention and treatment of missing data in clinical trials,*" by The National Academies Press (2010) at www.nap.edu/catalog/12955.html.

The sponsor stated that they would consider the Agency comment concerning secondary endpoints, including addressing the multiplicity issue.

Question 10:

The Phase 3 study includes a placebo cream treatment group for blinding purposes only. To the extent reasonably possible, this placebo cream will be similar in appearance to the reference listed drug. The packaging, however, will not be identical, but the placebo tubes will be over labeled and boxed. The Sponsor does not have access to a matched placebo cream for Ultravate. Is this placebo cream acceptable to the Agency?

Response:

Maintenance of blinding is imperative to ensure the robustness of study results. Clarify the physical appearance of all test articles in the final studies and provide photographs to the Agency. You should make every effort to ensure maintenance of blinding.

Meeting Discussion:

The sponsor agreed to submit samples of all test articles.

Question 11:

In light of the UV/VIS scan data included in the Initial IND and the lack of absorbance in any of the scans, does the Agency agree that the requirement to conduct clinical phototoxicity and photocontact allergy studies on HBP Lotion, 0.05 % can be waived?

Response:

Yes, this seems reasonable.

Question 12:

Given the minimal irritation observed with HBP Lotion, 0.05% in the completed nonclinical and clinical studies, the extensive safety database of HBP and excipients in the drug product, and the proposed human RIPT study with the HBP Lotion in approximately 200 healthy volunteers, the Sponsor is planning to request a waiver for conducting a 21-day cumulative irritation study in humans. Does the Agency agree with this approach?

Response:

You will need to provide sufficient information in your NDA application to support labeling with reference to local adverse events, such as irritation.

Question 13:

HBP Lotion, 0.05% is anticipated to be super-potent, Class 1, topical corticosteroid indicated for the treatment of plaque psoriasis, a condition that is rarely found in the pediatric population. The Sponsor believes such a product would not be suitable for the pediatric population and the Sponsor plans to request a waiver from conducting pediatric studies in children with plaque psoriasis. Does the Agency agree with this approach?

Response:

If you base your waiver request on a determination of low disease prevalence in the pediatric population, you would need to provide evidence to support your rationale, such as prevalence

data. However, there may be safety concerns, related to the degree of HPA axis suppression that may provide a basis for a waiver request.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a Pediatric Study Plan, and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes.
7. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

8. Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

9. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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/s/

SUSAN J WALKER
08/07/2012

Memorandum

To: IND (b) (4)

From: Jill C Merrill

Re:

Amendment date: 08-06-10

Supporting Doc. No.: 13

Amendment type: information amendment

Drug: Halobetasol propionate lotion, 0.05%

Sponsor: (b) (4)

Indication: moderate to severe plaque psoriasis

Information to sponsor: yes

Review date: 08-17-10

Background:

The sponsor has submitted an IND for a potential 505(b)2 approval of a novel topical formulation containing 0.05% halobetasol propionate for the treatment of moderate to severe plaque psoriasis. The active ingredient is well characterized and the concentration is known to be safe and effective as an anti-inflammatory and antipruritic agent in different topical dosage formulations approved by the FDA. The sponsor was informed (12-19-2008) that given the long history of safe use of multiple halobetasol propionate formulations and assuming an adequate clinical bridge could be established to a previously approved topical halobetasol propionate formulation (i.e., Ultravate® Cream) it was acceptable to use the Agency's findings of safety to support the systemic safety of their topical formulation and use the 505(b)2 regulatory pathway. In the same communication, they were specifically advised "...to conduct a dermal carcinogenicity study and also assess the photocarcinogenic potential of the to-be-marketed formulation." These recommendations were to support an NDA submission.

Information contained in submission:

The stated purpose of the current submission is to "...review the historical perspective regarding the requirement of dermal carcinogenicity study for topical corticosteroid NDA approval." The sponsor notes that during the 1990's dermal carcinogenicity studies were not requested by FDA as either pre or post-approval requirements for topical corticosteroids. Furthermore, they note "More recently, dermal carcinogenicity has become a post-approval requirement." The sponsor then notes the recently revised labeling for Vanos® Cream (NDA 21-758; approved February 2005; label revised 3-8-2010) which states:

- Long-term animal studies have not been performed to evaluate the carcinogenic potential of Vanos Cream because of the severe immunosuppression induced in a 13-week dermal study.

They note this finding is a consequence of the adrenal suppression known to be caused by systemic corticosteroid absorption, but propose to submit a protocol for a 13-week dose ranging study in rats. A complete protocol for the requested 2-year dermal carcinogenicity study would be submitted to the FDA for review as part of the pre-NDA meeting submission. Upon completion of the dose ranging study, either at or before the pre-NDA meeting, they will provide a complete study report and seek further guidance from the Agency to determine if they should move forward with the 2-year dermal carcinogenicity study as proposed, or re-assess the feasibility and appropriateness of conducting such a study. If after this review the Agency deems the 2-year study is still required, the Sponsor will provide proof of study initiation within 10 business days after receipt of FDA's notification that the NDA has been accepted for review.

Pharmacology/Toxicology discussion:

The sponsor's proposal for handling the recommendation for a dermal carcinogenicity study is reasonable and consistent with current advice to sponsors with similar drug products. They will be advised that these plans are acceptable to the Division. However, it would not be acceptable to submit the 2 year dermal carcinogenicity study protocol in a Pre-NDA briefing package. The 2 year dermal carcinogenicity study protocol should be submitted in a separate IND submission to allow for evaluation by the Exec CAC.

The sponsor has not mentioned the photocarcinogenicity recommendation that was also part of the same communication (dated 12-19-2008). However, in January 2010 a revised ICH M3 document was published which no longer recommends photocarcinogenicity testing. The sponsor will be advised of this change and granted a waiver for the previous recommendation.

Comments to be relayed to the sponsor:

1. Your plans to submit a protocol for a 13-week range finding study to the IND to determine appropriate levels for a subsequent 2-year dermal carcinogenicity study which would be conducted as a Postmarketing study to be initiated during the NDA review cycle is acceptable. However, your proposal to submit the protocol for a 2 year dermal carcinogenicity study with a pre-NDA meeting package is not acceptable. Your protocol for a 2 year dermal carcinogenicity study should be submitted in a separate IND submission. Refer to the following guidance documents for additional information.
 - Guidance for Industry – Carcinogenicity Study Protocol Submissions (May 2002)
 - Guidance for Industry – Special Protocol Assessment (May 2002)
2. As per the January 2010 ICH M3(R2) Tripartite Guideline “Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals”, conduct of a nonclinical

photocarcinogenicity study is no longer considered appropriate. Therefore, you are granted a waiver for this requirement.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND- (b) (4)

ORIG-1

(b) (4)

HALOBETASOLE PROPIONATE
LOTION, 0.05%

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/s/

JILL C MERRILL
08/26/2010

BARBARA A HILL
08/26/2010
I concur

Memorandum

To: IND (b) (4)

Re:

Amendment date: 03-03-09
Supporting Doc. No.: 04
Amendment type: information amendment
Drug: Halobetasol propionate lotion, 0.05%
Sponsor: (b) (4)
Indication: moderate to severe plaque psoriasis

Information to sponsor: yes

Review date: 04-09-09

Background:

The sponsor has submitted an IND for a potential 505(b)2 approval of a novel topical formulation containing 0.05% halobetasol propionate for the treatment of moderate to severe plaque psoriasis. The active ingredient is well characterized and the concentration is known to be safe and effective as an anti-inflammatory and antipruritic agent in different topical dosage formulations approved by the FDA. At the time of the original IND submission (10-22-08), the sponsor intended to conduct a 28-day repeat-dose dermal toxicity study in minipigs with the final formulation selected from results of their VCA study and then subsequently initiate an HPA-axis study. The planned repeat-dose dermal study would include the clinical concentration (0.05%) and an enhanced concentration (0.1%) and would also include toxicokinetic evaluation.

Information contained in submission:

Based on the preliminary results from the VCA study, the sponsor has selected Formula (b) (4) for further development. However, they now seek Agency approval on postponing their 28-day repeat dose minipig study until the start of phase 3 and modifying it to exclude both the enhanced formulation and the toxicokinetic evaluation.

Reviewer's comment: Although dermal toxicity studies typically have 3 dose levels, given the extensive information already available for the active, it was previously agreed that the 28-day repeat dose dermal minipig study could be conducted with the clinical concentration and an enhanced concentration. Therefore dropping the enhanced concentration, as the sponsor is now proposing, reduces this study to a single halobetasol propionate concentration.

Questions posed by the sponsor in the current submission:

Does the Agency agree that the Phase 2 HPA/PK study may be conducted prior to the 28-day repeat-dose minipig study?

Does the Agency agree that the 28-day repeat-dose dermal toxicity study in the minipig need not include a toxicokinetic evaluation?

Does the Agency agree that the 28-day repeat-dose dermal toxicity study in the minipig need not include an 'enhanced' formulation (i.e., potency > 0.05%) arm assuming, subject to Agency review, the HPA/PK study findings support analogous potency between the lotion and the RLD? If a higher dose group is requested, does the Agency agree that this can be more easily achieved with use of more frequent dosing (twice vs once a day) of the selected 0.05% formulation?

Pharmacology/Toxicology discussion:

The sponsor is being asked to conduct a 28-day repeat dose dermal toxicity study in minipigs to evaluate the effect of application of the active ingredient in the topical formulation prior to phase 3 clinical testing. Although the active ingredient has been well studied and is being used at levels that have previously been approved (0.05% halobetasol propionate), vehicle composition is known to significantly effect the extent of dermal absorption of drugs. The extent of dermal absorption has a direct effect on the extent of systemic exposure and is therefore of concern prior to extended clinical use. In view of the minimal nonclinical data that would otherwise be available for this specific formulation prior to the initiation of phase 3 testing (i.e, dermal irritation study in rabbits, sensitization study in guinea pigs), it seems appropriate to request that the sponsor proceed with the nonclinical development plan, as previously agreed.

Comments to be relayed to the sponsor:

Sponsor's question #1:

Does the Agency agree that the Phase 2 HPA/PK study may be conducted prior to the 28-day repeat-dose minipig study?

Pharmacology/toxicology response:

No. The purpose of the proposed minipig dermal toxicity study is to provide nonclinical data to support repeat clinical use of your specific topical halobetasol propionate formulation. Therefore it is necessary to conduct this pivotal nonclinical study prior to phase 3 testing.

Sponsor's question #2:

Does the Agency agree that the 28-day repeat-dose dermal toxicity study in the minipig need not include a toxicokinetic evaluation?

Pharmacology/toxicology response:

No. The systemic exposure is dependent on the extent of dermal absorption of topical ingredients which is known to be significantly altered by the composition of the formulation. Thus the Agency is specifically interested in the toxicokinetic data after repeat dose dermal administration of the proposed clinical formulation.

Sponsor's question #3:

Does the Agency agree that the 28-day repeat-dose dermal toxicity study in the minipig need not include an 'enhanced' formulation (i.e., potency > 0.05%) arm assuming, subject to Agency review, the HPA/PK study findings support analogous potency between the lotion and the RLD? If a higher dose group is requested, does the Agency agree that this can be more easily achieved with use of more frequent dosing (twice vs once a day) of the selected 0.05% formulation?

Pharmacology/toxicology response:

No. Repeat dose dermal toxicity studies typically employ three dose levels and as such a study design with two dose levels, (0.05% and 0.1%) is minimally acceptable to the Agency, given the existing information available for the active ingredient. Thus an enhanced dose arm is required. Additionally, the enhanced formulation is to be achieved by increasing the concentration of halobetasol propionate in the formulation with use of the same volume of administration. Alternative methods are to be considered only when it is not feasible to enhance the clinical formulation.

Therefore you should conduct a 28-day repeat-dose dermal toxicity study in minipigs prior to phase 3 testing. This pivotal study should include measurements of hematology and clinical chemistry parameters, complete histopathological analysis for all dose groups and toxicokinetic analysis. An untreated control, vehicle control, clinical concentration (0.05%), and enhanced concentration (0.1%) should be incorporated into the study. At least 4 animals/sex/group should be used in this study.

Linked Applications

Sponsor Name

Drug Name / Subject

(b) (4)

(b) (4)

HALOBETASOLE PROPIONATE LOTION,
0.05%

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/s/

JILL C MERRILL
04/09/2009

BARBARA A HILL
04/09/2009

Memorandum

To: IND (b) (4)

From: Jill C Merrill

Re:

Amendment date: 01-28-09

Supporting Doc. No.: 03

Amendment type: information amendment

Drug: Halobetasol propionate lotion, 0.05%

Sponsor: (b) (4)

Indication: moderate to severe plaque psoriasis

Information to sponsor: no

Review date: 02-17-09

The sponsor has submitted a final report entitled: Primary dermal irritation study in rabbits (0420LT28.010). A draft version of this study was submitted with the original IND and reviewed by Dr. Jill Merrill (11-24-08). The supporting data and conclusions remain the same in the final version and will not be reviewed further.

Comments to be relayed to the sponsor:

None at this time.

Linked Applications

Sponsor Name

Drug Name / Subject

[REDACTED] (b) (4)

[REDACTED] (b) (4)

HALOBETASOLE PROPIONATE LOTION,
0.05%

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JILL C MERRILL
02/17/2009

BARBARA A HILL
02/17/2009

Memorandum

To: IND (b) (4)
From: Jill C Merrill
Re:

SD Date: 10-22-08
SDN: 2
SD Type: original submission
Drug: Halobetasol Propionate Lotion, 0.05%
Sponsor: (b) (4)
Indication: Treatment of moderate to severe plaque psoriasis in adults

Information to sponsor: yes

Review date: 12-03-08

Background:

The sponsor submitted the following pharmacology/toxicology questions in the original submission and they were inadvertently not included in the review:

Based on a review of the available information on halobetasol propionate, it was concluded that the systemic toxicity of this material has been well characterized. In a dermal irritation study, two Halobetasol Propionate 0.05% Lotion formulations were tested. Neither one was shown to be irritating. From these data, it was determined that there are no safety concerns with the initial Phase 1 VCA clinical trial that the sponsor is proposing to perform.

The nonclinical questions and corresponding responses to be relayed to the sponsor are provided below.

Nonclinical Questions and Responses (to be relayed to the sponsor):

Question 1: Given the long history of safe use of halobetasol propionate in topical formulations and the well characterized inactive ingredients that are being considered for possible development, does the Agency concur that the rabbit dermal irritation study audited draft report (on two of the formulations) and results of the 290-700 nm wavelength scan of the five halobetasol propionate lotions included in the initial IND are adequate to support the first clinical study, a single dose VCA study in healthy volunteers?

Response: Given the long history of safe use of halobetasol propionate in topical formulations and the well characterized inactive ingredients, it is acceptable to begin the single dose VCA study in healthy volunteers based on the rabbit dermal irritation study

and the results of the 290-700 nm wavelength scan of the five halobetasol propionate lotions.

Question 2: Given the long history of safe use of multiple formulations of halobetasol propionate and its well characterized safety profile and assuming a clinical bridge is demonstrated, does the Agency concur that there is adequate safety information from this widespread use and the data to be referenced under the 505(b)(2) regulatory path to support the systemic safety of halobetasol propionate, and that no additional nonclinical systemic toxicology studies need to be conducted?

Response: Assuming an adequate clinical bridge is established to a previously approved topical halobetasol propionate formulation (i.e., Ultravate® Cream), it is acceptable to use the Agency's findings of safety to support the systemic safety of your topical formulation and use the 505(b)(2) regulatory pathway. However, it is necessary to conduct a dermal carcinogenicity study and also assess the photocarcinogenic potential of the to-be-marketed formulation.

Question 3: Given that each of the inactive ingredients used in the proposed formulations appears in the FDA's Inactive Ingredient Database for approved products and that each is well characterized with respect to safety, does the Agency concur that there are no safety concerns with any of the excipients in the drug products and that no additional toxicology studies (other than those already proposed) are needed?

Response: Other than the already proposed nonclinical studies the Agency does not anticipate any further concerns over the inactive ingredients in the halobetasol propionate lotion formulation.

Question 4: Based on the findings from the VCA study, the sponsor will select a single formulation to develop. Using this formulation, we propose to conduct a delayed contact sensitization study in guinea pigs and a 28-day repeat-dose dermal toxicity study in minipigs. Does the Agency concur that these GLP studies will address the topical safety of the formulated product and support a clinical study of up to 14 days in duration?

Response: No. In addition to the nonclinical tests mentioned, it will be necessary to also assess the potential ocular irritation of the drug product before phase 3 clinical testing.

Question 5: Given the long history of safe use of halobetasol propionate in topical formulations and the well characterized inactive ingredients that are being used in the proposed formulations, we propose to initiate the Phase 2 study after providing the Agency with a draft report from the 28-day minipig study. Does the Agency agree with this plan?

Response: Yes, it is acceptable to initiate the phase 2 HPA axis/PK study after the Agency has reviewed the draft report of the 28-day minipig study.

Question 6: As specified by the ICH M3 guidelines and consistent with the recently released draft FDA guidelines for reformulated drug products, a single species (minipig), 28-day repeat-dose study is being proposed to be conducted in conjunction with the 14-day Phase 3 program for the new Halobetasol Propionate Lotion. Does the Agency concur that this study will be adequate to support an NDA submission?

Response: No. To support an NDA submission, it will also be necessary to conduct a dermal carcinogenicity study and to assess the photocarcinogenic potential of the drug product.

Linked Applications

Sponsor Name

Drug Name

[REDACTED] (b) (4)

[REDACTED] (b) (4)

HALOBETASOLE PROPIONATE LOTION,
0.05%

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/s/

JILL C MERRILL
12/03/2008

BARBARA A HILL
12/03/2008