CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208079Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208079 SUPPL # HFD # 540

Trade Name Sernivo

Generic Name (betamethasone dipropionate) Spray, 0.05%

Applicant Name Promius Pharma, LLC

Approval Date, If Known February 5, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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 ☒ NO ☐

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

N/A

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

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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

NDA#	019555	Diprolene (augmented betamethasone dipropionate) Cream, 0.05%
NDA#	019137	Diprolene (betamethasone dipropionate) Cream, 0.05%
NDA#	019716	Diprolene (betamethasone dipropionate) Lotion, 0.05%
NDA#	018741	Diprolene (augmented betamethasone dipropionate) Ointment, 0.05%
NDA#	019141	Betamethasone dipropionate Ointment, 0.05%
NDA#	207589	Enstilar (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%
NDA#	021852	Taclonex (calcipotriene and betamethasone dipropionate) Ointment, 0.005%/0.064%
NDA#	022185	Taclonex (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064%
NDA#	018827	Lotrisone (clotrimazole and betamethasone dipropionate) Cream, 0.05%/1%
NDA#	020010	Lotrisone (clotrimazole and betamethasone dipropionate) Lotion, 0.05%/1%

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to

disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Vasoconstriction assay studies- BDS1103; BDS1204; DFD01-CD-009
Dermal Safety Studies- DFD01-CD-008; DFD01-CD-010; DFD01-CD-011; DFD01-CD-012
HPA axis suppression study- BDS1307
Safety/Efficacy/Bridging Studies- BDS1205; BDS1206

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 BDS1205 YES ☐ NO ☒

Investigation #2 BDS1205 YES ☐ NO ☒

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

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

Investigation #1 BDS1205 YES ☐ NO ☒

Investigation #2 BDS1206 YES ☐ NO ☒

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

N/A

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"):

1. BDS1205
2. BDS1206

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 # 104853 YES ☒ ! NO ☐
! Explain:

Investigation #2		!
		!
IND # 104853	YES ☒	! NO ☐
		! Explain:

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

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Dawn Williams
Title: RPM
Date: January 12, 2016

Name of Division Director signing form: Kendall A. Marcus, MD
Title: Director

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

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

/s/

DAWN WILLIAMS
02/05/2016

KENDALL A MARCUS
02/05/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208079 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Sernivo Established/Proper Name: betamethasone dipropionate Dosage Form: Spray, 0.05%		Applicant: Promius Pharma, LLC Agent for Applicant (if applicable):
RPM: Dawn Williams		Division: Division of Dermatology and Dental Products

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

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

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

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

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: January 20, 2016

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

❖ Actions	
• Proposed action • User Fee Goal Date is 2/5/2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ 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 _____	☐ 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): Type 3- New Dosage Form
(confirm chemical classification at time of approval)

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

(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 required 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

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

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

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

Comments:

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	❖ Action(s) and date(s) February 5, 2016 Approval
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ *Included*
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	9/9/2015 Proprietary Name Conditionally Acceptable 9/3/2015 Proprietary Name Memorandum
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 1/20/2016 DMEPA: ☐ None 12/2/2015 DMPP/PLT (DRISK): ☐ None 11/24/2015 OPDP: ☐ None 11/27/2015 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) 2/1/2016
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 12/9/2016 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)*	10/1/2015 Information Request 9/4/2015 OPQ Information Request 7/29/2015 Information Request 6/16/2015 No Filing Issues Identified
❖ 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	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg January 12, 2015
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 1/6/2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 1/4/2016
PMR/PMC Development Templates *(indicate total number)*	☐ None 1
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	12/29/2015 Clinical Review 5/21/2015 Filing Review
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 12 of 12/29/2015 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 12/9/2015 Biostatistics Review 5/22/2015 Filing Checklist
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/8/2015 Clinical Pharmacology Review 5/14/2015 Filing Form
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/7/2015 Pharm Tox Review 5/27/2015 Filing Checklist
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 1/22/2016 Memorandum-Final Approval Recommendation 12/18/2015 Integrated Quality Assessment 6/1/2015 Filing Review
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 72 of January 22, 2016 Product Quality Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable Re-evaluation date: ☐ Withhold recommendation ☒ Not applicable

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

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

/s/

DAWN WILLIAMS
02/05/2016

PeRC Meeting Minutes
December 9, 2015

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Linda Lewis (Chaired the review of NON-RESPONSIV) (products not reviewed after NON-RESPONSIV
Lily Mulugeta
Thomas Smith
Daiva Shetty
Gettie Audain
Meshaun Payne
George Greeley
Gregory Reaman (Sernivo NON-RESPONSIVE were not reviewed)
Dianne Murphy
Andrew Mulberg
Barbara Buch
Adrienne Hornatko-Munoz
Michelle Roth-Kline
Rosemary Addy
Dionna Greene
Ikram Elayan NON- was not review)
Freda Cooner NON-RESPONSIVE were reviewed)

Agenda

8:30	NON-RESPONSIVE				
8:50					
9:10					
9:30					
9:40					
9:50					
10:00					
10:10					
10:20					
10:30					
10:50	NDA 208059	Sernivo (betamethasone dipropionate) Partial Waiver/Deferral/Plan (with Agreed iPSP)	DDDP	Dawn Williams	Treatment of mild to moderate plaque psoriasis in patients 18 years of age or older
11:00	NON-RESPONSIVE				
11:10					
11:20					
11:40					
11:50					

6 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

Sernivo (betamethasone dipropionate) Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Proposed Indication: Treatment of mild to moderate plaque psoriasis in patients 18 years of age or older
- The application triggers PREA for new indication(s), and dosage form
- PDUFA goal date: February 6, 2016
- The Division noted that a pediatric protocol has already been submitted and pediatric studies have already been initiated as described in the Agreed iPSP.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division that a partial waiver for ages from birth to less than 12 years old is appropriate because 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.
  - The PeRC agrees with the deferral for ages 12 to less than 17 years of age since the product is ready for approval in adults and pediatric studies are ongoing. The PeRC also recommends amending the timelines in the PREA PMR to reflect that the protocol has already been submitted and studies have been initiated.

NON-RESPONSIVE

4 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

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/s/

GETTIE AUDAIN
01/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208079

INFORMATION REQUEST

Promius Pharma, LLC
Attention: Hari Nagaradona, PhD
Vice President and Head of Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagaradona:

Please refer to your New Drug Application (NDA) dated and received April 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sernivo™ (betamethasone dipropionate) Spray, 0.05%.

We are reviewing the clinical pharmacology and clinical studies sections of your submission and have the following comments and information requests. We request a prompt written response by October 16, 2015, in order to continue our evaluation of your NDA.

1. In trial BDS1307, there were 7 pairs of plasma cortisol samples that were analyzed outside of the 3 days demonstrated stability period. Several sample pairs were analyzed more than 5 days beyond what were required in the protocol. Provide detailed information as to why these significant protocol deviations occurred and what corrective action you have taken to prevent future occurrence.

2. Submit the statistical analysis programs for the analyses using multiple imputation (dataset generation and analysis) for the primary and key secondary analyses in Studies BDS1205 and BDS1206. Include the randomization seed(s) used for Study BDS1206, as this is not specified in the Statistical Analysis Plan.

If you have any questions, please contact Dawn Williams, Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Hon Sum Ko, MD
Cross Discipline Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HON SUM KO
10/01/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208079

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Promius Pharma, LLC
107 College Road East
Princeton, NJ 08540

ATTENTION: Hari Nagaradona, PhD
Senior Director, Head of Regulatory Affairs

Dear Dr. Nagaradona:

Please refer to your New Drug Application (NDA) dated and received April 6, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Betamethasone Dipropionate Topical Spray, 0.05%.

We also refer to your correspondence, dated and received June 30, 2015, requesting review of your proposed proprietary name, Sernivo.

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

If any of the proposed product characteristics as stated in your June 30, 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 Dawn Williams, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5376.

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/

DAVIS MATHEW
09/09/2015

TODD D BRIDGES
09/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208079

INFORMATION REQUEST

Promius Pharma, LLC
c/o Dr. Reddy's Laboratories, Inc.
Attention: Hari Nagarodona, PhD
Senior Director/Head of Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagarodona:

Please refer to your New Drug Application (NDA) dated and received April 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sernivo™ (betamethasone dipropionate) spray, 0.05%.

We are reviewing the prescribing information contained in 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.

(b) (4)

Regarding control strategy for *Burkholderia cepacia*.

- A description of the BCC risk assessment and its outcome is necessary for review. Please provide this information.

- If the outcome of the risk assessment results in the addition of a BCC specification for raw materials or finished product, this information should be submitted for review. This information should include a description of validation studies performed to ensure the appropriateness of the selected test method.

- Please note that the "[redacted] (b) (4)" is not adequate to demonstrate the effectiveness of the use of this this test method with the drug product or raw materials, as the sampling method described demonstrates recovery of BCC from water. Please refer to the original information request (Dated 16 June 2015) regarding the Agency's expectations and suggestions for validation study parameters.

If you have questions, call Melinda Bauerlien, Senior Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Office of New Drug Products
Office of Pharmaceutical Quality
CDER/FDA

Yichun Sun -S

Digitally signed by Yichun Sun -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yichun Sun -S, 0.9.2342.19200300.100.1.1=13 00393310
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208079

INFORMATION REQUEST

Promius Pharma, LLC
c/o Dr. Reddy's Laboratories, Inc.
Attention: Hari Nagarodona, PhD
Senior Director/Head of Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagarodona:

Please refer to your New Drug Application (NDA) dated and received April 6, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sernivo™ (betamethasone dipropionate) spray, 0.05%.

We are reviewing the prescribing information contained in 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 went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review, we note that you did not provide a review and summary of the available literature on both human and nonclinical data to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled.

However, because the application was submitted prior to the PLLR effective date of June 30, 2015, you have the option to fully comply with PLLR requirements during this review cycle or fully comply before June 30, 2019. If you choose to voluntarily comply with PLLR in full during this review cycle, we request that you submit the following information on betamethasone dipropionate use in pregnant and lactating women by August 14, 2015:

- a review and summary of the available published literature,
- a review and summary from your pharmacovigilance database,
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

In addition, you should submit any data on a drug's negative impact on fertility, if applicable.

If you choose to wait until June 30, 2019, the format and content of labeling must revert to the original non-PLLR format. No partial PLLR conversions may be made.

Refer to the 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).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by the dates listed above. 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 Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Hon Sum Ko, MD
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/

HON SUM KO
07/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208079

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Promius Pharma, LLC
c/o Dr. Reddy's Laboratories, Inc.
Attention: Hari Nagaradona, PhD
Senior Director/Head of Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagaradona:

Please refer to your New Drug Application (NDA) dated and received April 6, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Sernivo™ (betamethasone dipropionate) spray, 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 February 6, 2016.

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 January 16, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. We recommend that you develop an *in vitro* release test (IVRT) methodology and propose an *in vitro* release acceptance criterion (range) for your drug product to be used systemically at

release and during stability as a quality control parameter. Your proposed acceptance criterion should be based on generated data for the final to-be-marketed batches. Submit all the generated data in electronic format.

2. 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 is not 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

3. The IVRT method validation report should contain (but is not 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

4. The IVRT method's sensitivity, specificity, selectivity and robustness need to be performed 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 reference.

5. Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of the Food and Drug Administration's perspective on BCC, see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

    In order to control for the presence of BCC in the proposed drug product, consider the following:

    A. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process

controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

B. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. The test methods should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (eg, temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or the drug products without preservatives to demonstrate that the proposed method is capable of detecting small numbers of BCC. The submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, refer to Envir Microbiol 2011; 13(1): 1-12 and J. Appl Microbiol 1997; 83(3): 322-6.

6. The drug substance is insoluble in water, and you have proposed to use it in an emulsified, aqueous, topical spray formulation. Include a multi-point particle size distribution test in the drug substance specification.

7. Provide a comparison regarding the composition and manufacturing process between the commercial and the pivotal batches of the drug product.

8. Provide a table to summarize drug product lots and their uses during development.

9. The drug product specification needs to be updated to include all the tests proposed for commercial batches. Future and ongoing stability studies should be performed according to the updated drug product specification.

10. The dermal carcinogenicity study waiver for your drug product was granted under IND 104853 on April 22, 2015. Resubmit draft package insert for your drug product to incorporate the results from the 13-week rat dermal toxicity study (study #13-2355) on which the waiver was based into Section 13.1.

11. For the analysis of plasma cortisol in trial BDS1307, provide the duration and conditions of sample storage from collection to time of sample analysis. Provide storage stability data to support the duration and storage temperature of all samples in this trial.

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. 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
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We reference the partial waiver granted on December 4, 2014, for the pediatric study requirement for this application for pediatric patients under the age of 12 years.

We reference the partial deferral granted on December 4, 2014, for the hypothalamic-pituitary-adrenal (HPA) axis suppression pediatric study requirement with pharmacokinetic sampling in psoriasis patients 12 to 16.9 years of age.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

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
06/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104853

MEETING MINUTES

Promius Pharma, LLC
Attention: Hari Nagaradona, PhD
Senior Director/Head of Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagaradona:

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

We also refer to the meeting between representatives of your firm and the FDA on January 12, 2015. The purpose of the meeting was to discuss the content and format of your planned NDA submission.

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 Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
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
Meeting Date and Time:	January 12, 2015
Meeting Location:	Room 1313, Building 22, White Oak Campus
Application Number:	IND 104853
Product Name:	betamethasone dipropionate spray, 0.05%
Proposed Indication:	Topical treatment of moderate plaque psoriasis
Sponsor Name:	Promius Pharma
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Dawn Williams, BSN

FDA ATTENDEES
Kendall Marcus, MD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Roxolana Harbowyj, MD, Clinical Reviewer, DDDP
Jasmine Gatti, MD, Clinical Reviewer, DDDP
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP III
Shulin Ding, PhD, Quality Assessment Lead, Brach V, DNDP II
Yichun Sun, PhD, Acting Quality Assessment Lead, Branch V, DNDP II
Roy Blay, PhD, Good Clinical Practice Assessment Branch, OSI

SPONSOR ATTENDEES
Hari Nagaradona, PhD, Senior Director, Regulatory Affairs, Dr. Reddy's Laboratories, Ltd
Robert D'Urso, MBA, Senior Director, Marketing and Sales, Promius Pharma, LLC
Joanne Fraser, PhD, Senior Director, Clinical Development, Promius Pharma, LLC
Kent Allenby, MD, Vice President, Drug Development, Dr. Reddy's Laboratories, Ltd
Franklin Okumu, PhD, Vice President, Parenteral and Topical Drug Delivery, Dr. Reddy's Laboratories, Ltd
Raghav Chari, PhD, Executive Vice President, Dr. Reddy's Laboratories, Ltd

Rajeev Raghuvansi, PhD, Vice President- Differentiated Formulations R&D, Dr. Reddy's Laboratories, Ltd
D. Mallikarjuna Rao, PhD, Director, Regulatory Affairs, Dr. Reddy's Laboratories, Ltd
Mary Hilgart, MS, Director, Project Management, Dr. Reddy's Laboratories, Ltd
R. Isil Pakunlu, PhD, Senior Manager, R&D, Promius Pharma, LLC
Balaji MR, MVSc, Director, Safety and Toxicology, Dr. Reddy's Laboratories, Ltd

MEETING OBJECTIVES:
To discuss the content and format of Promius Pharma's proposed NDA submission for betamethasone dipropionate spray, 0.05%.

Regulatory Correspondence History

We have had the following teleconferences with you:
- March 16, 2011 Guidance
- June 17, 2009 Pre-IND

We have sent the following correspondences:
- December 4, 2014 Agreed Upon iPSP
- October 20, 2014 Advice
- October 2, 2014 Advice
- September 8, 2014 iPSP Written Response
- March 3, 2014 Advice/Information Request
- August 1, 2013 Advice
- January 15, 2013 Advice
- April 28, 2011 Advice
- November 17, 2010 Advice
- July 22, 2010 Advice

Regulatory:

Question 1:
As communicated by the Agency following the Pre-IND meeting (PIND 104853 Meeting Minutes dated July 1, 2009), Betamethasone Dipropionate Spray, 0.05% will be labeled as a spray in the package insert. Does the Agency concur?

Response:
We will need to examine a representative sample packaged in the to-be-marketed container/closure system before making a preliminary assessment for the proposed product regarding dosage form. The ultimate decision on dosage form is made in the NDA review.

Meeting Discussion:
The sponsor agreed to submit samples for each fill size at the time of NDA submission.

Chemistry, Manufacturing and Controls (CMC)

Question 2:
Are the release and stability specifications for betamethasone dipropionate spray, 0.05% described in the document acceptable?

Response:
No, the specifications are inadequate.

Add the following tests to drug product release specification: microscopic appearance, pump functionality (number of prime, amount dispensed per actuation, and total deliverable), and package integrity (e.g. interaction with formulation, leakage, etc.).

Add the following tests to drug product stability specification: microscopic appearance, content uniformity, viscosity, pump functionality (number of prime, amount per actuation, and total deliverable), and package integrity (e.g. interaction with formulation, leakage, etc.).

Meeting Discussion:
The sponsor acknowledged that some the recommended tests are not currently implemented in their release and stability program. However, they agreed to implement all of the recommended tests and provide an update of stability information within 3 months of the NDA submission.

The sponsor should address whether the viscosity of the formulation inside the bottle changes over time and impacts pump functionality.

Question 3:
(b) (4)

(b) (4) . Would 3 months of stability data in the new bottle be adequate to bridge to the 12 months stability data in the old bottle?

Response:
Yes, provided that adequate CMC information (including test results of USP<661> and the study results of extractables/leachables) will be provided in the initial submission of the proposed NDA for the to-be-marketed container/closure system.

Meeting Discussion:
The sponsor stated they intend to submit USP 661 in the original NDA submission. Updated extractable/leachable studies will be submitted within 3 months after NDA submission (see discussion under question 6).

Question 4:
An unknown degradation product was observed over the identification threshold after anlaysis of stability samples stored at accelerated conditions (40ºC 75% RH) for 3 months. The degradation product was identified as the (b) (4) of betamethasone dipropionate. Analysis of a single lot of Diprolene Lotion (NDC 0085-0962-02), an FDA approved and commercially available topical formulation containing betamethasone dipropionate, has confirmed the presence of (b) (4) of betamethasone dipropionate after storage at accelerated conditions (40ºC 75% RH). It is note anticipated that the degradation product will exceed the qualification threshold after storage at 25ºC/60% RH for 24 months. In the event the degradation product exceeds the qualification threshold during long term storage at 25ºC/60% RH, the sponsor would proceed to qualify the degradation product and submit the data to the FDA when it becomes available. Would it be acceptable to the Agency for the sponsor to submit qualification of the (b) (4) degradation product to the FDA after filing the NDA should the levels exceed the qualification threshold?

Response:
Yes, provided that you would propose a limit that is at or below the ICH qualification threshold for this (b) (4) degradant in the initial submission of the NDA.

Question 5:
(b) (4)

(b) (4). Would this approach be acceptable if the new bottle and drug product sizes are not accepted with the NDA (refer to question 13)?

Response:
This approach is also reasonable.

Question 6:
The sponsor plans to submit extractable and migration data in the NDA. (b) (4) Full leachable reports will be maintained and submitted to the FDA by the sponsor (b) (4) Does the Agency concur?

Response:
You should include the leachables data generated from the accelerated temperature stability studies in the initial submission of the NDA. If the data from the accelerated temperature stability studies indicate the possible presence of leachables in the long term stability samples, you should address the leachables issue in the initial submission of the NDA according to ICH

guidance on impurities. For example, you may set the limit at or below the identification threshold for the most prominent leachables if you have not identified them.

Meeting Discussion:
The sponsor agreed to submit available extractable/leachable data generated to date in the initial NDA submission. The sponsor agreed to repeat the leachable study using IPA aqueous solution in the pump configuration, but collecting just the initial actuation volume. This data will be included in the initial NDA submission. The leachable data from the actual formulation will be submitted within 3 months of the NDA submission.

Additional Comments

1. You will need to include the results of in-use stability studies from three drug product batches (packaged in the to-be-marketed container/closure system) in the initial submission of the NDA to support the proposed in-use period. The in-use stability studies should examine all critical product attributes including viscosity, package integrity, weight loss, pump functionality, and leachables. The analytical samples of the in-use stability studies should be the pumped-out formulation. Each drug product batch should be packaged with a different pump lot.

Meeting Discussion:
The sponsor agreed to submit in-use stability data to support the proposed in-use period for the (b) (4). The sponsor agreed to perform in-use stability study from 3 product lots using 2 pump lots. The certificates of analysis for the pump lots and manufacturing dates will be included in the NDA submission. The Agency agreed that the sponsor can submit the in-use stability data within 3 months of NDA submission.

2. Extractables/leachables from the spray pump should also be investigated, and the results should be included in the initial submission of the NDA.

3. We recommend that you include microscopic appearance, viscosity and droplet size as three tests in the in-process control over the drug product manufacturing process.

   Clarify whether the spray pump used in the Phase 3 clinical studies is identical to the to-be-marketed spray pump. If they are not identical, provide in-use stability data for both Phase 3 and to-be-marketed container/closure systems.

Meeting Discussion:
The sponsor clarified that the spray pump used in the Phase 3 clinical trials is identical to the to-be-marketed spray pump.

Pharmacology/Toxicology

Question 7:
Promius has completed all required nonclinical studies to support development of Betamethasone Dipropionate Spray, 0.05%. In one recent communication (October 2, 2014, Appendix 4) the Agency has concurred with the adequacy of Promius' nonclinical program. The

nonclinical studies will be submitted in relevant sections of the eCTD. Does the Agency concur with the proposed approach?

Response:
Yes, the nonclinical studies should be submitted in the relevant sections of the eCTD.

Question 8:
As communicated in the advice letter from the Agency (October 2, 2014), Promius will not be performing a carcinogenicity study in rats. We are planning to submit a request for a dermal carcinogenicity waiver to the IND. [redacted (b) (4)]. Does the Agency agree?

Response:
[redacted (b) (4)] the carcinogenicity waiver should be submitted to the IND prior to NDA submission.

Clinical/Clinical Pharmacology/Biostatistics

Question 9:
[redacted (b) (4)]. Does the Agency concur?

Response:
Literature references that provide pivotal data required for approval should be included with the IND submission. It is not necessary to submit copies of literature references that do not provide pivotal data required for approval.

Question 10:
Promius plans to submit CDISC compliant SDTM and AdaM data sets for the Phase 2 and 3 studies and SDTM compliant data sets for the Phase 2 dermal safety studies. For the Phase 1 clinical pharmacology studies of steroid potency ranking (vasoconstrictor studies), SAS data sets in transport file format that are not SDS complaint will be submitted. Is this plan acceptable?

Response:
It is acceptable you submit Phase 1 clinical pharmacology studies not in CDISC format, but it should still follow the guideline of Study Data Technical Conformance Guide v2.0 which replaces Study Data Specification 2.0.

Submit the datasets for the clinical trials in SAS transport form (.xpt). The analysis datasets for the Phase 3 studies 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.

Include dataset documentation (define.xml and define.pdf) for tabulation and analysis datasets. The analysis dataset documentation (define.pdf file) should include sufficient detail, such as

definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

Include statistical programs for any non-standard or complex analyses. For the multiple imputation programs, include supporting information such as the randomization seed.

Question 11:
Promius plans to pool data from the two Phase 3 studies (BDS1205 and BDS1206) for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE). We will be presenting all the other Phase 1 and Phase 2 studies individually. Does the Agency concur with this approach?

Response:
Yes, your plan is acceptable. However, in addition to pooled results, the ISE should include comprehensive in-depth analysis of the individual study results in addition to pooled efficacy results, and should discuss the extent to which the results of the relevant studies reinforce or do not reinforce each other. This may require additional discussion beyond individual study summaries and a pooled analysis. For additional information on the content of the ISE refer to Guidance for Industry: Integrated Summary of Effectiveness (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf)

Question 12:
The statistical analysis plans for ISS and ISE are included in Appendix 1 and Appendix 2 respectively. Are the proposed ISS and ISE plans acceptable to the Agency?

Response:
We have no further comments on the pooled analyses proposed in the ISE and ISS SAPs. See also the response to Question 11.

Question 13:
Does the Agency require that CDISC compliant data sets of the pooled Phase 3 studies be submitted in the NDA?

Response:
While not currently required, we prefer you submit pooled study data in CDISC format as this will facilitate validation and review by the Agency.

Question 14:
Does the Agency agree that the two Phase 3 efficacy studies (BDS1205 and BDS1206) and Phase 2 safety study, HPA axis suppression study (BDS1307), could support approval of Betamethasone Dipropionate Spray, 0.05% for the treatment for up to 4 weeks of moderate plaque psoriasis in patients 18 years of age and older and that no additional studies are required?

Response:
We agree that your application as described is acceptable for filing and review of an NDA.

Question 15:
Promius has completed three Phase 1 clinical pharmacology studies to assess topical corticosteroid potency and one Phase 2 HPA axis suppression study that included PK sampling (BDS1307). Does the Agency agree that no additional clinical pharmacology studies are required?

Response:
The proposed clinical pharmacology program appears reasonable. The final determination will be made during NDA review. We have the following comments for your NDA submission:

- Provide a table outlining the formulation(s) used for all clinical trials, including the VCA trials.
- Submit bioanalytical and validation reports for the cortisol assay. The reports should include in-house validation and quality control results during the same timeframe of study sample analysis if a commercial kit was used.

Question 16:
Promius plans to include Case Report Forms (CRFs) (b) (4) oes the Agency concur with this strategy?

Response:
Provide case report forms (CRFs) for all deaths, serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason. Case Report Forms should be referenced under the appropriate study's Study Tagging Files (STF) to which they belong, organized by site as per the specifications and tagged as "case report form".

You should provide patient narratives for deaths, serious adverse events, and discontinuation due to adverse events.

eSubmission Comments

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

1. For archival purposes, also submit a pdf file of the labeling document submitted in word. When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
2. Please use leaf titles that are clear and indicative of the content (e.g. study report 12345.pdf, protocol 12345, or something similar)
3. Do not include placeholder stating "N/A", for sections without documents (e.g. 5m.1). Only provide eCTD sections that have documents.
4. The study STF.xml file should be referenced in the index.xml file but should not be submitted as a file

5. The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5

Cross referencing (m1.4.4)

Sponsors options of cross referencing information submitted to another application (if any), 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. The applications need to include the appropriate prefix in the href links (e.g. nda, ind). 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 nda XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

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

   To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf

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. 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.

4. 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 Division of Pediatric and Maternal Health 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.				

505(b)(2) REGULATORY PATHWAY

The Division recommends 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 draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. 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 that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, 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.

If you intend to rely, in part, 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 or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the 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 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. 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.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to 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 published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
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)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX "TRADENAME"	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYY "TRADENAME"	Previous finding of safety for Carcinogenicity, labeling section XXX
4.	

Office of Scientific Investigations (OSI) Requests

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).

Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
Site number
Principal investigator
Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
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.

Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
Number of subjects screened at each site
Number of subjects randomized at each site
Number of subjects treated who prematurely discontinued for each site by site

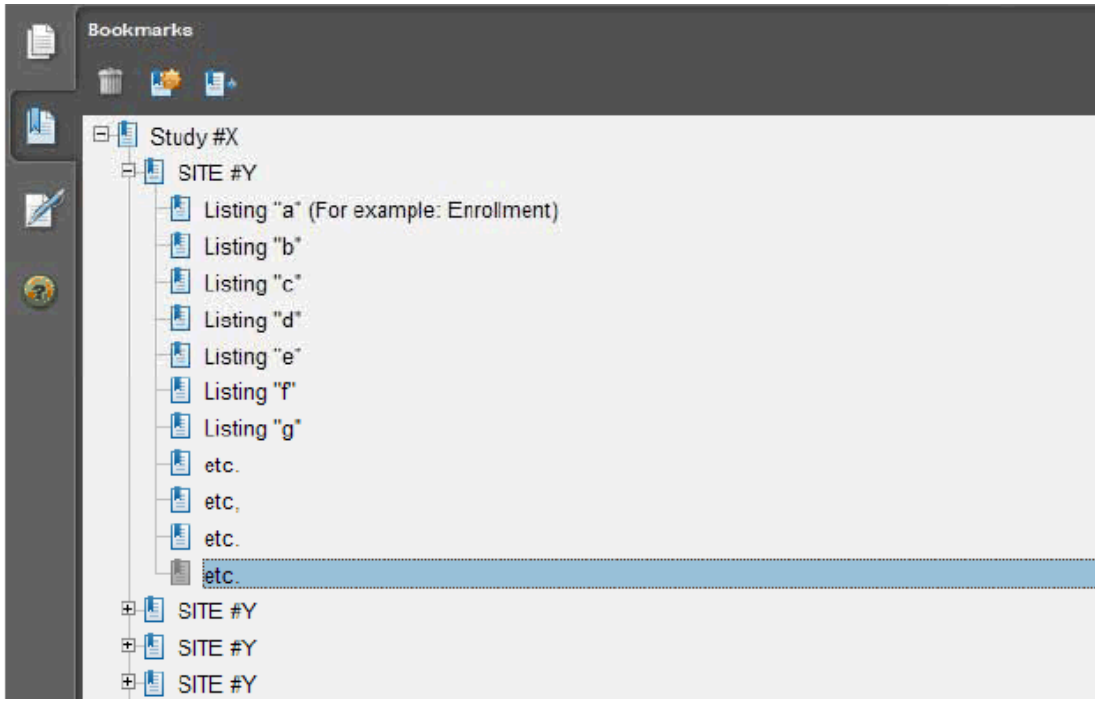
Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety 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
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.
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.

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).
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

For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
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
Subject listing for treatment assignment (randomization)
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
Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
By subject listing, of AEs, SAEs, deaths and dates
By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
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.
By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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:

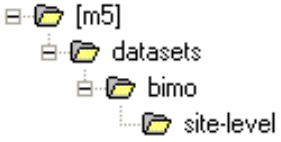
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide 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 Item1	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:



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

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.

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/

DAVID L KETTL
01/16/2015