CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209483Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209483	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Impoyz Established/Proper Name: clobetasol propionate Dosage Form: cream		Applicant: Promius Pharma, LLC Agent for Applicant (if applicable): NA
RPM: Angela Brown		Division: 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:

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 11/30/2017	☒ 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):
(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)*	Approval- 11/28/17
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)*	Letters: **10/19/17- Granted** **8/17/17- Withdrawn** **7/26/17- Granted** **5/10/17-Granted** **4/20/17- Denied** **Proprietary Name Reviews:** **10/16/17** **7/26/17** **4/12/17**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 2/17/17 DMEPA: ☒ 10/18/17; **9/29/17;** 4/12/17 DMPP/PLT (DRISK): ☒ 9/25/17 OPDP: ☒ 9/25/17; Memorandum (9/21/17) SEALD: ☒ None CSS: ☒ None Product Quality ☒ 09/27/17 DPMH: ☒ 08/23/17
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	4/12/17- RPM Filing review Meeting ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP 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 08/16/17 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	N/A
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	N/A
• 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)*	N/A
❖ 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 Master File letters; do not include previous action letters, as these are located elsewhere in package)*	(1)- Filing Letter (1)- Acknowledgement
❖ 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)*	☒ 10/12/16
• 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)*	Guidance Meeting 7/27/15

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

❖ 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
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 10/19/17
PMR/PMC Development Templates *(indicate total number)*	☒ 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)*	10/19/17
• 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)*	10/19/17, see Clinical Review page 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ 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)*	☒ Letters: 10/10/17 10/10/17 Review: 10/02/17

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

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)*	☒ 09/29/17
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)*	☐ 09/27/17
❖ 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)*	☐ 06/16/15- IND 110799
❖ 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	☒ 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[6]	
• 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)*	☒ Drug Substance- 08/04/17 Drug Product 09/11/17 Product Labeling 09/11/17 Drug Produce Manuf. Process- 09/18/17 Biopharmaceutics- 09/19/17 Microbiology-07/19/17 Facilities- 09/18/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ 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)*	09/11/17- See Drug Product Review: page 35, Categorical Exclusion: Adequate
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ 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	11/28/17
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	**11/30/17**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209483

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Hari Nagaradona, Ph.D.
Vice President and Global Head of Regulatory Affairs

Dear Dr. Nagaradona:

Please refer to your New Drug Application (NDA) dated and received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clobetasol Propionate Cream, 0.025%.

We also refer to your correspondence, dated and received August 4, 2017, requesting review of your proposed proprietary name, Impoyz.

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

If any of the proposed product characteristics as stated in your August 4, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Tri M. Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Angela Brown, Regulatory Project Manager in the Office of New Drugs, at (240) 402-0095.

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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
10/19/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209483

PROPRIETARY NAME REQUEST ACKNOWLEDGEMENT/WITHDRAWAL

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

ATTENTION: Hari Nagaradona, Ph.D.
Vice President and Global Head of Regulatory Affairs

Dear Dr. Nagaradona:

Please refer to your New Drug Application (NDA) dated and received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clobetasol Propionate Cream, 0.025%.

We also refer to your correspondence, dated and received on August 4, 2017, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4) Therefore, (b) (4) is considered withdrawn as of August 4, 2017.

Finally, we refer to your correspondence, dated and received August 4, 2017, requesting review of your proposed proprietary name, Impoyz. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

Therefore, the user fee goal date is November 2, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Tri M. Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Angela Brown, Regulatory Project Manager, in the Office of New Drugs at (240) 402-0095.

Sincerely,

{See appended electronic signature page}

Tri M. Bui Nguyen, Ph.D., MS
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TRI M BUI NGUYEN
08/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209483

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Hari Nagaradona, Ph.D.
Vice President and Global Head of Regulatory Affairs

Please refer to your New Drug Application (NDA) dated and received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clobetasol Propionate Cream, 0.025%.

We also refer to your correspondence, dated and received May 4, 2017, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your May 4, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Tri M. Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Angela Brown, Regulatory Project Manager, in the Office of New Drugs at (240) 402-0095.

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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
07/26/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209483

PROPRIETARY NAME ACKNOWLEDGEMENT

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

ATTENTION: Hari Nagaradona, Ph.D.
Vice President and Global Head of Regulatory Affairs

Dear Dr. Nagaradona:

Please refer to your New Drug Application (NDA) dated and received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clobetasol Propionate Cream, 0.025%.

We acknowledge receipt of your correspondence, dated and received May 4, 2017, requesting a review of your proposed proprietary name, (b) (4)

The user fee goal date is August 2, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Tri M. Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Angela Brown, Regulatory Project Manager, in the Office of New Drugs at (240) 402-0095.

Sincerely,

{See appended electronic signature page}

Tri Bui Nguyen, Ph.D., MS.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TRI M BUI NGUYEN
05/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209483

PROPRIETARY NAME REQUEST
UNACCEPTABLE

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

ATTENTION: Hari Nagaradona, Ph.D.
Vice President and Global Head of Regulatory Affairs

Dear Dr. Nagaradona:

Please refer to your New Drug Application (NDA) dated and received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clobetasol Propionate Cream, 0.025%.

We also refer to your correspondence, dated and received January 30, 2017, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, (b) (4) may be confused with another approved product, (b) (4) due to orthographic similarity,and overlapping product characteristics.

(b) (4)

The similarity of this name pair is further supported by FDA's Phonetic and Orthographic Computer Analysis (POCA)[1] system, which calculates a combined orthographic and phonetic score of 71% (orthographic only score of 79%) for this name pair. This further suggests that the names (b) (4) and (b) (4) have high orthographic similarity and pose a risk for confusion.

In addition to the orthographic similarity of this name pair, the products share overlapping product characteristics, which increase the potential for error. (b) (4) and (b) (4) are (b) (4)

[1] POCA search conducted on (February 8, 2017), POCA tool updated to incorporate a revised orthographic algorithm

(b) (4)

(b) (4)

We acknowledge that our conclusion differs from that of the (b) (4) external study submitted in support of the proposed proprietary name. This external study did identify (b) (4) as a potential look-alike and sound-alike name, but found the name acceptable due to differences with respect to indication and multiple strengths. However, considering our post marketing experience as noted above, we determined that the name pair, (b) (4) and (b) (4) may be at risk for name confusion.

Therefore, based on orthographic similarities, overlapping product characteristics, and postmarketing evidence, the proposed product, (b) (4) and (b) (4) are vulnerable to medication errors due to name confusion.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

[2] "Use As Directed" Can Cause Confusion For Both Patients and Practitioners. ISMP Medication Safety Alert. August 25, 2016. https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=1146

[3] "Institute for Safe Medication Practices. Safety briefs: Misspelling leads to mix-up. ISMP Med Saf Alert Acute Care. 2005;4(12): December, 2005. http://www.ismp.org/Newsletters/ambulatory/Issues/community200512.pdf

[4] Tu, CM, Taylor, K, and Chai, G. Use of Proprietary Names by Prescribers for Discontinued Brand Drug Products with Existing Generic Equivalents. Drug Information Journal, published online August 21, 2012, available at: http://dij.sagepub.com/content/early/2012/08/21/0092861512456282 full.pdf+html

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)
- 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 Tri Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Angela M. Brown, Regulatory Project Manager in the Office of New Drugs, at (240) 402-0095.

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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
04/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209483

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

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

Dear Dr. Nagarandona:

Please refer to your New Drug Application (NDA) dated and received January 30, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for clobetasol propionate cream, 0.025%.

We also refer to your amendments dated March 10 and 20, 2017.

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 30, 2017.

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 October 21, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. 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.

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* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- 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 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.

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

1. In the Highlights section of the label, add the word "contact" before the manufacturer name in your Adverse Reactions statement.

2. In the Clinical Trial Experience sub-section, replace the word (b) (4) with "Because" at the beginning of the paragraph.

3. Replace the first paragraph of the Postmarketing Experience subsection with the following verbatim statement:

   "The following adverse reactions have been identified during post-approval use (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

4. Include the following verbatim FDA-approved patient labeling statement:
   "Advise the patient to read the FDA-approved patient labeling (Patient Information)."

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 28, 2017. 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. The checklist is available at the following link:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

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 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) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Dermatology and Dental Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

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 Angela Brown, Regulatory Project Manager, at (240) 402-0095.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Acting Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JILL A LINDSTROM
04/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209483

NDA ACKNOWLEDGMENT

Promius Pharama, LLC
Attention: Hari Nagaradona, Ph.D.
Vice President and Global Head of Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Dr. Nagaradona:

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

Name of Drug Product: (clobetasol propionate) cream, 0.025%

Date of Application: January 30, 2017

Date of Receipt: January 30, 2017

Our Reference Number: NDA 209483

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of 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 have any questions, call me at (240) 240-0095.

Sincerely,

{See appended electronic signature page}

Angela Brown, MPH
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

STROTHER D DIXON
02/10/2017
Signed on behalf of Angela Brown, MPH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110799

MEETING MINUTES

Promius Pharma, LLC
Attention: Hari Nagaradona, PhD
Vice President and Head- 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 clobetasol propionate cream, 0.025%.

We also refer to the meeting between representatives of your firm and the FDA on October 12, 2016. The purpose of the meeting was to discuss the development program for clobetasol propionate cream, 0.025% and submission of a New Drug Application (NDA) for the treatment of moderate to severe plaque psoriasis.

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 Belainesh Robnett, Regulatory Health Project Manager at (240) 402-4236.

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

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 12, 2016; 10:00 AM (ET)
Meeting Location:	White Oak Campus
Application Number:	IND 110799
Product Name:	clobetasol propionate cream, 0.025%
Proposed Indication:	Treatment of moderate to severe plaque psoriasis
Sponsor Name:	Promius Pharma, LLC
Meeting Chair:	Kendall A, Marcus, MD
Meeting Recorder:	Belainesh Robnett

FDA ATTENDEES
Julie Beitz, MD, Director, Office of Drug Evaluation III (ODE III)
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Kendall A, Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Duan Renqin, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biopharmaceutics III (DB III)
Carin Kim, PhD, Biostatistics Reviewer, DB III
Jie Wang, PhD, Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
Yichun Sun, PhD, Acting Quality Assessment Lead, DNDP II, NDPB V
Stephen Langille, PhD, Branch Chief, Division of Microbiology Assessment Branch III
Marla Stevens-Riley, PhD, Senior Microbiologist, Division of Microbiology Assessment
Roy Blay, PhD, Good Clinical Practice Assessment Branch, Office of Scientific Investigations (OSI)
J. Paul Phillips, MS, Lead Regulatory Health Project Manager, DDDP
Belainesh Robnett, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Hari Nagaradona, PhD, Vice president & Global Head of Regulatory Affairs, Dr. Reddy's Laboratories, Inc.

Raghav Chari, PhD, President, Promius Pharma, LLC
Anil Namboodiripad, PhD, Sr. Vice President, Drug Development, Dr. Reddy's Laboratories, Inc.
Kent Allenby, MD, Vice President, Clinical Development, Dr. Reddy's Laboratories, Inc.
Srinivas Sidgiddi, MD, Director, Dermatology, Clinical Development, Dr. Reddy's Laboratories, Inc.
Kevin Carey, Associate Director, Project Management, Dr. Reddy's Laboratories, Inc.
Reena Zade, Associate Director, Regulatory Affairs, Dr. Reddy's Laboratories, Inc.
Tarun Deshmukh, Associate Director, Regulatory Affairs, Dr. Reddy's Laboratories, Inc.
(b) (4)
Jeffrey Stein, Senior Director, Clinical Statistics, Accenture
Praveen Raju, Director, CMC, Dr. Reddy's Laboratories, Inc.
Robert Hanes, Director, Late Stage CMC, Dr. Reddy's Laboratories, Inc.
Balaji, MR, MVSc, Director, Toxicology, Dr. Reddy's laboratories, Ltd.
Rajeev Raghuvanshi, PhD, Sr. Vice President, Global CMC, Dr. Reddy's Laboratories Ltd
D. Mallikarjuna Rao, PhD, Sr. Director, Regulatory Affairs, Dr. Reddy's Laboratories Ltd

1.0 BACKGROUND

The purpose of the meeting is to discuss the development program for clobetasol propionate cream, 0.025% and submission of a New Drug Application (NDA) for the treatment of moderate to severe plaque psoriasis.

Recent Regulatory Correspondence History

We have had the following teleconference with you:

- 07/27/2015 Guidance

We have sent the following correspondences:

- 09/12/2016 Advice
- 03/17/2016 Advice
- 11/03/2015 Pediatric Study Plan-initial Agreement
- 10/16/2015 Special Protocol No-Agreement

2.0 DISCUSSION

2.1. Regulatory

Question 1:
Promius has obtained the right of reference from Fougera Pharmaceuticals, Inc., for all forms of Temovate products (clobetasol propionate, 0.05%) included in NDAs 019322, 019323, 019966, 020337 and 020340. Hence, Promius intends to file the NDA for DFD-06 according to 505(b) (1) regulatory pathway. Does the Agency concur that the proposed regulatory path is appropriate for DFD-06?

FDA Response:

You should clearly identify the information on which you plan to rely to support your future marketing application (NDA). If you have obtained a right of reference for information you do not own, but on which you plan to rely and which is necessary for approval of your application, then your application would be reviewed under the 505(b)(1) regulatory pathway.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 2:
Promius has included the proposed to-be-marketed product specifications for release and stability testing which include additional parameters than those that were provided in the briefing document for the Type C meeting (July 27, 2015). Does the Agency concur with the proposed specifications with the additional test parameters for the to-be-marketed product?

FDA Response:
Besides the tests listed in the drug product specification, the test of globule size of the cream is recommended to be added to the drug product specification.

Regarding microbial limit tests of the drug product, we recommend that in the application the methods for microbial enumeration and absence of specific microorganisms be described. It is acceptable to refer to the tests described in the current USP. (b) (4) (b) (4) (b) (4) The test methods and acceptance criteria of the drug product specification will be evaluated during NDA review.

Additional CMC Comment
The results of extractable and leachable studies on the aluminum tubes should be included in your NDA submission.

Meeting Discussion:
The sponsor inquired about the stage of the drug product manufacturing steps in which the specification should include the recommended test. The sponsor also requested the Agency to clarify if the test method of the recommended test can be submitted after the NDA submission. Additionally the sponsor asked if it is acceptable to implement the test on the validation and commercial batches of the drug product.

The Agency stated that the recommended test should be implemented for the finished drug product at release and during stability studies. The Agency also stated that the test method

should be submitted with the NDA. The Agency also confirmed that the proposal of implementing the recommended test on the validation and commercial batches of the drug product is acceptable.

2.3. Pharmacology/Toxicology

Question 3:
Promius believes that all the required nonclinical studies (listed above) as per relevant guidelines have been completed to support nonclinical safety of DFD-06 (Clobetasol Propionate Cream, 0.025%). Further, the nonclinical safety established for Temovate products and published literature information on safety of clobetasol propionate will support the NDA and therefore no additional studies are planned. The reports of nonclinical studies conducted with DFD-06 will be submitted in relevant sections of the eCTD. The right of reference to Temovate NDA's and copies of published literature will also be provided in the NDA. Does the Agency agree that the nonclinical program for Clobetasol Propionate Cream, 0.025% is adequate to support NDA submission?

FDA Response:
We agree that the nonclinical program for clobetasol propionate cream, 0.025% is adequate to support your NDA submission.

Question 4:
Promius has submitted a request to waive testing for carcinogenicity of DFD-06 on August 1, 2016 (Sequence # 0033) after completing the 13-week dose ranging toxicity study as recommended by the agency. In the event, a final decision is not reached by the agency prior to submitting the NDA, Promius intends to proceed with the submission of NDA and will submit the outcome of the waiver request during NDA review. Does the agency concur with the proposed approach?

FDA Response:
You have been granted a waiver for conduct of a dermal carcinogenicity study with clobetasol propionate cream, 0.025% based on the extent of immune suppression noted at very low concentrations of clobetasol propionate cream in the 13 week repeat dose dermal toxicity study in rats. This decision and related comments and recommendations were relayed to you on September 12, 2016.

2.4. Clinical/Clinical Pharmacology/Biostatistics

Question 5:
Promius does not plan to provide copies of the published literature articles as part of the NDA submission for clinical references but will provide them upon request. Does the Agency concur?

FDA Response:
Yes.

Question 6:
Temovate Cream, 0.05% (NDA 019322) was a marketed reference product when product development was initiated by Promius and Temovate Cream was used as the comparator in the HPA axis suppression study, DFD-06-CD-007, to establish a bridge between DFD-06 and Temovate as RLD. However, since then Temovate has since been withdrawn from the market for reasons other than product safety as published in Federal Register. Since the HPA axis suppression study (DFD-06-CD-007) was initiated prior to the discontinuation of the listed product and Promius has the right of reference to the Temovate NDAs, does the Agency concur that Temovate Cream (NDA 019322) used in the study can still serve as the reference drug?

FDA Response:
Yes.

Question 7:
Promius plans to pool data from the two Phase 3 studies (DFD-06-CD-004 and DFD-06-CD-005) for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE). All the other Phase 1 and Phase 2 studies will be presented individually. Does the Agency concur with the approach?

FDA Response:
For the ISE, refer to the guidance for industry *Integrated Summary of Effectiveness* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf) for recommendations on what to include. In particular, note that while pooled analyses of the Phase 3 studies can be a component of the ISE, the ISE should include discussions regarding the strength of evidence across all studies, including discussion of any difference in outcomes across studies.

We recommend that you consider including data from DFD-06-treated subjects in the HPA axis suppression study, DFD-06-CD-007 in the pooled safety database. Also, you did not present your proposal for the 120-Day Safety Update.

Meeting Discussion:
The sponsor proposed to submit a literature based safety update 120 days after submission of the NDA. The Agency agreed this would be acceptable.

Question 8:
The draft statistical analysis plans (SAPs) and mock up tables, listings and figures (TLFs) for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) are included in Appendix 1 and Appendix 2, respectively, of the briefing package. Does the Agency concur that the SAPs for the analysis and mock up TLFs of the pooled datasets from the two Phase 3 studies are appropriate?

FDA Response:
See response to Question 7. For your ISE, you might conduct pooled efficacy analyses as exploratory analyses.

We recommend that you report the incidence of common treatment emergent adverse events at an incidence of ≥ 1% (you propose incidence > 2%).

Question 9:
The Agency had commented on the Phase 3 statistical analysis plans submitted to the IND on Nov 13, 2015 and Dec 14, 2015, however, both Phase 3 studies were almost fully enrolled by the time Agency comments were received. In response to the Agency's feedback, prior to unblinding, Promius modified the statistical analysis plan for both the Phase 3 studies which are identical, to address the concern of stratified randomization at the study level and not at the site level. The SAP for one of the studies (DFD-06-CD-005) is included in Appendix 3. Does the Agency concur with the adequacy of these measures to address the issue of site to site variability?

FDA Response:
In this submission, you stated that the Agency's feedback (advice letter dated: 3/17/2016) regarding the randomization stratified by study (stamp dates: 11/13/2015, 12/14/2015) was received when subject enrollment for both Phase 3 trials were almost fully enrolled. Then in your amended Phase 3 SAP for Trial 005 (Appendix 3 in this submission), you included a pooling algorithm and modified your primary analysis method for the primary efficacy endpoint.

As your protocol for Trial 004 specified that "stratification will be by study, not by site" and that your protocols specified that "a randomization schedule will be produced for each site independently for use in randomization by way of the interactive web response system (IWRS)", clarify whether the same investigators enrolled subjects across the two trials. It should be noted that such randomization stratified by study may impact the assessment of the site-to-site variability in efficacy and may also impact the chance of having replication of study findings.

At this stage, as you have already completed your trials, it would be difficult to provide comments on the implication of your randomization approach (i.e., stratification by study) in interpreting the study findings.

Meeting Discussion:
In response to the Agency concerns about randomization, the sponsor acknowledged the issues and stated that the misstatement in the protocols was due to inaccuracies in the description of the randomization stratified by study. Additionally, the sponsor stated that they did not delete previous statements about randomization within a study by site. The sponsor agreed to provide details about the randomization including the programs for carrying out the randomization as requested by the Agency.

Post-meeting Addendum:
The sponsor inquired about the location within the NDA to include the randomization program. For each Phase 3 trial, full details relevant to the randomization may be included

under 5.3.5.1 Study Reports of Controlled Clinical Studies as a separate folder named "Randomization Scheme".

Question 10:

Does the Agency concur that the two Phase 3 efficacy studies (DFD-06-CD-004 and DFD-06-CD-005) and the Phase 2 HPA axis suppression study (DFD-06-CD-007) would be adequate to support the approval of DFD-06 (Clobetasol Propionate Cream, 0.025%) for the treatment of moderate to severe plaque psoriasis?

FDA Response:

Based on the information provided in the briefing package, the referenced studies would appear to be adequate to support submission of a marketing application; "approvability" is a review issue.

Question 11:

Promius has completed two Phase 1 clinical pharmacology studies (CDS0801 (b) (4) to assess topical corticosteroid potency/pharmacodynamics and one Phase 2 study that included PK sampling (DFD-06-CD-007). Does the Agency agree that no additional clinical pharmacology studies are required?

FDA Response:

(b) (4)

The Clinical Pharmacology studies conducted to-date appears reasonable to support your NDA submission. We have the following comments:

1. Clarify if the to-be-marketed formulation was used in Phase 2 HPA axis suppression/ Systemic absorption pharmacokinetic (PK) study (DFD-06-CD-007) and Phase 1 vasoconstrictor potency study (DFD-06-DC-003a).

2. In Phase 2 HPA axis suppression/ Systemic absorption PK study (DFD-06-CD-007) study, in your NDA submission provide information on the % body surface area involved (% BSA) that was treated and also provide information on the amount of formulation that was used per subject. We remind you to submit the bioanalytical method validation as well as bioanalysis reports for plasma clobetasol propionate and plasma cortisol measurements. Submit the PK data sets in XPT format.

3. In the NDA, you should address the potential for drug interactions. For further information, you are referred to draft guidance for industry, *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*.

Meeting Discussion:

(b) (4)

Question 12:

Promius plans to include Case Report Forms (CRFs) for all deaths and serious AEs, and other CRFs will be available upon request. Does the Agency concur with this strategy?

FDA Response:
Also submit case report forms for subjects who discontinued from the studies. 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 electronic links to the submitted CRFs.

Question 13:
Promius plans to submit CDISC compliant SDTM and AdaM datasets for the Phase 2 and 3 studies and SDTM compliant data sets for the Phase 1 dermal safety studies. For the Phase 1 clinical study to determine steroid potency ranking (DFD-06-CD-003a), legacy data sets (non-STDM) will be submitted in .xpt file format. Is the proposed plan acceptable to the agency?

FDA Response:
Your proposal to submit SDTM and ADaM formatted datasets for the NDA submission is acceptable. The primary method for handling missing efficacy data in your trial is multiple imputation (MI). Submit the SAS code used to implement the MI as well as the SAS code used to analyze the imputed datasets. For the analysis datasets, we have the following general comments:

- Each analysis dataset should include treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables, including the center variables (i.e., original and analysis), 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 subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies. Further, assign a unique ID to the original site (center) to permit analysis across the Phase 3 trials.

- 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).

To enable review of your Phase 3 data, submit full details regarding the randomization procedure that used the IWRS**:**

- For your Phase 3 trials, submit the program that was used to generate the randomization codes. The program should clearly describe the randomization process

based on a subject's baseline IGA score and the sequential process for assigning treatment. In addition, submit the randomization dataset which should include the unique site ID variable, study variable, subject ID, randomization date, randomization number, randomized sequence, treatment assignment as well as treatment date.

Additional Comments

1. Provide subject narratives for all deaths, all other serious adverse events, all discontinuations due to adverse events. Include a list of the subjects for whom narratives are provided, and each subject's ID number should be in the form of a hyperlink to his/her narrative.

2. Provide a table containing the following information for each of the Phase 3 trials:

    a) Site number
    b) Principle investigator
    c) Location: City State, Country
    d) Number of subjects screened
    e) Number of subjects randomized
    f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)
    g) Number of protocol violations (major, minor, including definition)

3. For each of the Phase 3 trials, provide a table which presents treatment success outcomes by study site.

4. Discuss study-to-study differences in efficacy results and any efficacy issues that may need further exploration. Provide your statement as to why the data presented represents a demonstration of substantial evidence of effectiveness for the proposed indication.

5. Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. See *Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators*.

6. Include the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped.

7. Include reference ranges for all laboratory values in the data listings where those laboratory values are presented.

8. In the presentation of laboratory data, "flag" all laboratory values that are outside of the reference ranges.

9. Include tables that would allow the reviewer to make the association between the investigator's verbatim terminology used to describe an adverse event and the preferred term used for coding the adverse event in the submission's adverse event tables.

3.0 ADMINISTRATIVE INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was not held.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (iPSP) 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft 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).

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.				

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).

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

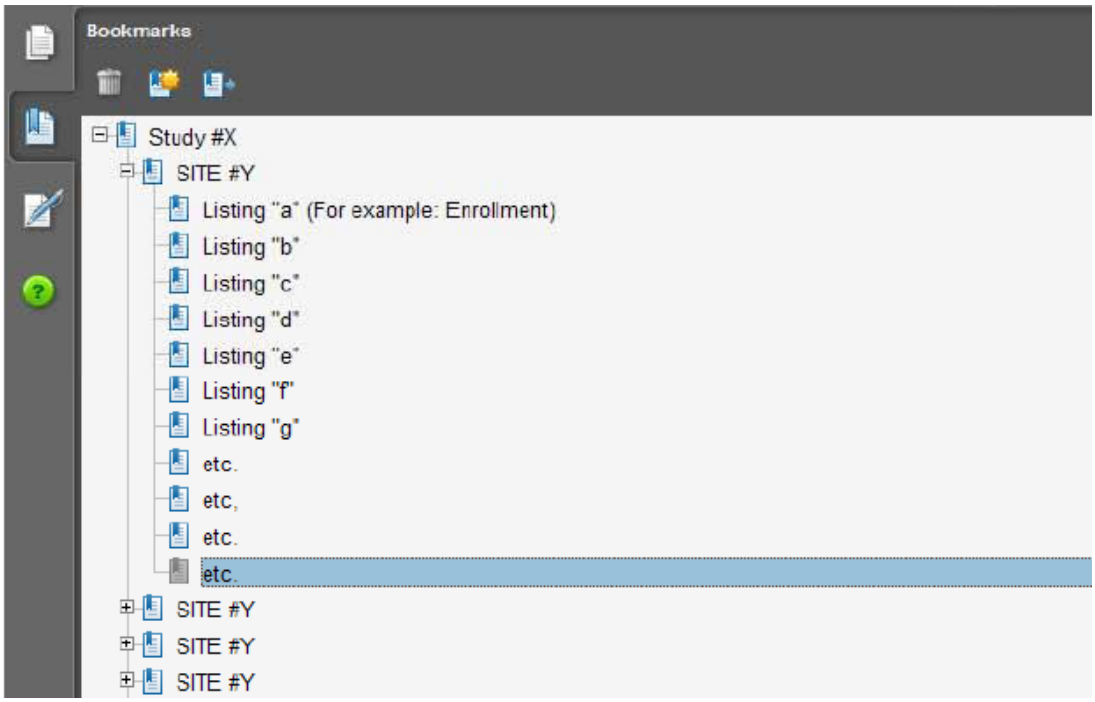
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

(b) (4) 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/

KENDALL A MARCUS
10/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110799

MEETING MINUTES

Promius Pharma, LLC
Attention: Hari Nagaradona, PhD
Senior Director, 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 clobetasol propionate cream, 0.025%.

We also refer to the teleconference between representatives of your firm and the FDA on July 27, 2015. The purpose of the meeting was to discuss the development plan for clobetasol propionate cream, 0.025%.

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

If you have any questions, call Belainesh Robnett, Regulatory Project Manager, at (204) 402-4236.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Acting Deputy Director
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 (C)
Meeting Category: Guidance

Meeting Date and Time: July 27, 2015; 9:00 a.m. (EST)
Meeting Format: Teleconference

Application Number: 110799
Product Name: clobetasol propionate cream, 0.025%.
Proposed Indication: Treatment of moderate plaque psoriasis
Sponsor Name: Promius Pharma, LLC

Meeting Chair: Jill A. Lindstrom, MD
Meeting Recorder: Barbara J. Gould, MBAHCM

FDA ATTENDEES
Jill A. Lindstrom, MD, Acting Deputy Director, Division of Dermatology and Dental Products (DDDP)
Hon Sum Ko, MD, Acting Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Renqin Duan, PhD, Pharmacology Reviewer, DDDP
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III
Yichun Sun, PhD, Acting Quality Assessment Lead, Branch V, Division of New Drug Quality Assessment II (DNDQA II)
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES
Hari Nagaradona, PhD, Vice president & Head of Regulatory Affairs, Promius Pharma, LLC
Robert D'urso, MBA Senior Director, Head of Marketing and Sales, Promius Pharma, LLC
Joanne Fraser, PhD, Senior Director, Clinical Development, Promius Pharma, LLC
Kent Allenby, MD, Vice President, Drug Development, Promius Pharma, LLC
Franklin Okuma, PhD, Vice President, Parenteral and Topical Drug Delivery, Promius Pharma, LLC
Raghav Chari, PhD, President, Promius Pharma, LLC
Rajeev Raghuvanshi, PhD, Vice President, Differentiated Formulations R&D, Promius Pharma, LLC
Sally Wixson, VMP, MS, RAC, Associate Director, Regulatory Affairs, Promius Pharma, LLC
Kevin Carey, Associate Director, Project Management, Promius Pharma, LLC

Sateesh Kandavilli, PhD, Senior Manager, Differentiated Formulations R&D, Promius Pharma, LLC

Purpose of the Teleconference:
To discuss the development program for clobetasol propionate cream, 0.025%

Regulatory Correspondence History

We have sent the following correspondences to you:

- July 9, 2015 PSP Written Response
- June 18, 2015 Advice
- April 24, 2015 Advice
- October 18, 2013 Advice
- August 8, 2013 Information Request
- April 19, 2011 Information Request
- April 15, 2011 Information Request
- April 8, 2011 Advice/Information Request

Introductory Comment

We do not believe that you are at the end of Phase 2 of your development program. We refer you to our responses below.

Regulatory

Question 1:
Promius is in the process of obtaining right of reference to NDAs 019322, 19323, 01966, 020337 and 020340 for all forms of Temovate products (0.05% clobetasol propionate). Hence, Promius plans to submit the NDA for DFD-06 as a 505(b) (1) application. Does the agency concur that the regulatory path chosen is appropriate for DFD-06?

Response:
It is your decision whether to file the application via the 505(b)(1) or 505(b)(2) regulatory route. We provide regulatory advice based on a sponsor's chosen route of NDA filing.

Chemistry, Manufacturing and Controls (CMC)

Question 8:
Are the proposed release and stability specifications DFD-06 acceptable for the Phase 3 clinical supplies and marketing application?

Response:
The tests listed in the drug product release and stability specifications are reasonable to support the Phase 3 clinical studies and marketing application. The acceptability of the test methods and acceptance criteria of the specifications will be determined during NDA review.

Question 9:

(b) (4)

Response:

(b) (4)

is not adequate for determination of expiration dating period of the drug product. (b) (4)

Question 10:

The product will be packaged in (b) (4) aluminum tubes. The sponsor does not plan to conduct photostability of DFD-06 as the aluminum tubes (container closure system) are completely impermeable to light. Does the agency concur?

Response:

Although your proposal for not conducting photostability on DFD-06 packaged in (b) (4) aluminum tubes is reasonable, photostability testing on DFD-06 (without packaging) is still recommended.

Pharmacology/Toxicology

Question 2:

Does the Agency agree that the proposed non-clinical development program for DFD-06 is adequate to support the proposed Phase 3 study and NDA submission?

Response:

No, we do not agree that your proposed nonclinical development plan is adequate to support an NDA submission. (b) (4)

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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 (iPSP) 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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.

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.	

Please 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 a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to 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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and 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 clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm).

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

/s/

JILL A LINDSTROM
08/13/2015