CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207071Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207071 SUPPL # NA HFD # 540

Trade Name Finacea®

Generic Name azelaic acid

Applicant Name Bayer HealthCare Pharmaceuticals Inc.

Approval Date, If Known July 30, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

NA

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

NA

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

NA

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA #(s).

NDA# 021470 Finacea® (azelaic acid) gel, 15%

NDA# 020428 Azelex® (azelaic acid) cream, 20%

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 021470 Finacea® (azelaic acid) gel, 15%

NDA# 020428 Azelex® (azelaic acid) cream, 20%

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted

or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

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

Study 1401846 - A randomized, double-blind, vehicle-controlled, multicenter, parallel-group clinical trial to assess the safety and efficacy of azelaic acid foam 15%, topically applied twice daily for 12 weeks in patients with papulopustular rosacea.

Study 1403120 - A randomized double-blind, vehicle-controlled, multicenter, parallel-group study to investigate the safety and efficacy of azelaic acid foam, 15% applied twice daily for 12 weeks in subjects with papulopustular rosacea.

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

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

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

Investigation #1 Study 1401846 YES ☐ NO ☒

Investigation #3 Study 1403120 YES ☐ NO ☒

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

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

Investigation #1 Study 1401846 YES ☐ NO ☒

Investigation #3 Study 1403120 YES ☐ NO ☒

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

NA

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

Study 1401846 - A randomized, double-blind, vehicle-controlled, multicenter, parallel-group clinical trial to assess the safety and efficacy of azelaic acid foam 15%, topically applied twice daily for 12 weeks in patients with papulopustular rosacea.

Study 1403120 - A randomized double-blind, vehicle-controlled, multicenter, parallel-group study to investigate the safety and efficacy of azelaic acid foam, 15% applied twice daily for 12 weeks in subjects with papulopustular rosacea.

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

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

Investigation #1 Study 1401846 !

!

IND 077516 YES ☒ ! NO ☐

! Explain:

Investigation #3 Study 1403120 !

!

IND 077516 YES ☒ ! NO ☐

! Explain:

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

Investigation #1 !

!

YES ☐ ! NO ☐

Explain: ! Explain:

Investigation #2 !

!

YES ☐ ! NO ☐

Explain: ! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Omolara Laiyemo
Title: Regulatory Health Project Manager
Date: June 30, 2015

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

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

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

/s/

OMOLARA R LAIYEMO
07/29/2015

KENDALL A MARCUS
07/29/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207071 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Finacea® Established/Proper Name: azelaic acid Dosage Form: foam		Applicant: Bayer Healthcare Pharmaceuticals Inc. Agent for Applicant (if applicable):
RPM: Omolara Laiyemo		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 07/30/2015	☒ 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.

For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 3 – New dosage form
(confirm chemical classification at time of approval)

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

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

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

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

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

Comments:

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 7/29/15
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)*	Accepted 12/18/2014 12/12/2014
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 12/01/2014 DMEPA: ☐ None 2/26/2015, 5/29/2015 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None 05/28/2015 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None 05/29/2015 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	12/01/2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☒ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC April 15, 2015 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	07/15/2015 Email – Labeling discussion 07/15/2015 Email- Labeling discussion 06/26/2015 Email - Labeling discussion 06/16/2015 Email - Labeling discussion 06/16/2015 Email - Labeling discussion 05/05/2015 Information Request 02/17/2015 Information Request 12/02/2014 74-day letter – no filing review issues identified 11/07/2014 Information Request 11/04/2015 Email 10/09/2015 Acknowledgement Letter 08/27/2012 Advice 03/30/2012 Special Protocol Assessment
❖ 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)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 07/09/2014
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 11/09/2011
• 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)*	
❖ 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 7/27/15
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 06/18/2015
PMR/PMC Development Templates *(indicate total number)*	☐ None 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)*	06/15/2015
• 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)*	Located in the clinical review / 06/15/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 05/28/2015

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 05/21/2015
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 05/06/2015 Non clinical review 06/11/2009 IND (077516) Non-clinical review 05/22/2008 IND (077516) Non-clinical review 04/03/2008 IND (077516) Non-clinical review 12/13/2007 IND (077516) Non-clinical review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☐ None 03/10/2015 Included in P/T review, page 47 (appendix 1)
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review *(indicate date for each review)*	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 07/23/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None 04/06/2015 – Product Quality Microbiology assessment
❖ 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)*	07/23/2015. Page 68 of CMC Final review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

➢ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)* NA
• Finalize 505(b)(2) assessment	☐ Done NA
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)* NA
❖ 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 NA
❖ 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 NA
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

OMOLARA R LAIYEMO
07/30/2015

From: Laiyemo, Omolara
To: "Karen Costa"
Cc: Williams, Dawn
Subject: RE: NDA 207071: Agency Proposed Labeling
Date: Thursday, July 09, 2015 4:44:00 PM
Attachments: NDA 207071 Finacea Foam Agency Proposed 09 Jul 2015.docx

---

Dr. Costa,

After further discussion, see the attached Agency's latest proposed label for NDA 207071 Finacea foam, 15%. Please submit your concurrence with or counter-proposal to the Agency proposed label by noon on Friday, July 10th, 2015.

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

From: Laiyemo, Omolara
Sent: Thursday, July 09, 2015 1:10 PM
To: 'Karen Costa'
Cc: Williams, Dawn
Subject: RE: NDA 207071: Agency Proposed Labeling

Dr. Costa,

We can extend the response time till noon on Friday July 10, 2015 to allow us enough time to respond to your email.

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

From: Karen Costa [mailto:karen.costa@bayer.com]
Sent: Thursday, July 09, 2015 12:12 PM
To: Laiyemo, Omolara
Cc: Williams, Dawn
Subject: RE: NDA 207071: Agency Proposed Labeling

Dear Dr. Laiyemo,

Bayer thanks the Agency for this proposal. Before Bayer can provide a final response to the Agency's proposed changes, we respectfully request the Agency's rationale for deleting the phrase [redacted] (b) (4) Bayer considers the phrase [redacted] (b) (4) as an important specification to support correct use of the product which is supported by the clinical data. Bayer is willing to have a t-con with the Agency to discuss this further.

Thank you,

Karen Costa

Kind regards, Mit freundlichen Grüssen, Meilleures salutations,

Karen A. Costa, M.S., Ph.D.
Bayer HealthCare Pharmaceuticals Inc.
Global Regulatory Affairs
Specialty Medicine: Dermatology & Ophthalmology

Science For A Better Life

100 Bayer Boulevard
Bldg 200; 2A3203
Whippany, NJ 07981-0915
Telephone: 1 (862) 404-3306
Email: Karen.Costa@bayer.com

From: Karen Costa
Sent: Thursday, July 09, 2015 10:24 AM
To: 'Laiyemo, Omolara'
Cc: Williams, Dawn
Subject: RE: NDA 207071: Agency Proposed Labeling

Dear Dr. Laiyemo,
Bayer is in receipt of this proposed USPI. Before we respond, can we kindly request a rationale for the Agency's removal of the phrase [redacted] (b) (4) ?
Thank you,
Karen Costa

Kind regards, Mit freundlichen Grüssen, Meilleures salutations,

Karen A. Costa, M.S., Ph.D.
Bayer HealthCare Pharmaceuticals Inc.
Global Regulatory Affairs
Specialty Medicine: Dermatology & Ophthalmology

Bayer HealthCare
Science For A Better Life

100 Bayer Boulevard
Bldg 200; 2A3203
Whippany, NJ 07981-0915
Telephone: 1 (862) 404-3306
Email: Karen.Costa@bayer.com

From: Laiyemo, Omolara [mailto:Omolara.Laiyemo@fda.hhs.gov]
Sent: Wednesday, July 08, 2015 5:38 PM
To: Karen Costa
Cc: Williams, Dawn
Subject: NDA 207071: Agency Proposed Labeling

Dr. Costa,

Please see the attached Agency proposed label for NDA 207071 Finacea foam, 15%. Please submit your concurrence with or counter-proposal to the Agency proposed label by noon on Thursday, July

9th, 2015.

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

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/s/

OMOLARA R LAIYEMO
07/15/2015

From:	Laiyemo, Omolara
To:	karen.costa@bayer.com
Cc:	Williams, Dawn
Subject:	NDA 207071: Agency Proposed Labeling
Date:	Monday, July 06, 2015 11:52:00 AM
Attachments:	NDA 207071 Finacea Foam Agency Proposed 06Jul 2015.docx

Dr. Costa,

Please see the attached Agency proposed label for NDA 207071 Finacea foam, 15%. Please submit your concurrence with or counter-proposal to the Agency proposed label by noon on Tuesday, July 7th, 2015.

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

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/s/

OMOLARA R LAIYEMO
07/15/2015

From:	Laiyemo, Omolara
To:	"Karen Costa"
Cc:	Dixon, Strother; Williams, Dawn
Subject:	NDA 207071: Agency Proposed Labeling
Date:	Friday, June 26, 2015 9:50:00 AM
Attachments:	Agency Proposed 26Jun2015_draft-uspi.docx

Dr. Costa,

Please see the attached Agency proposed label for NDA 207071 Finacea foam, 15%. Please submit your concurrence with or counter-proposal to the Agency proposed label by Monday, June 29th, 2015.

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

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/s/

OMOLARA R LAIYEMO
06/26/2015

From: Laiyemo, Omolara
To: "Karen Costa"
Cc: Williams, Dawn
Subject: RE: NDA 207071: Agency Proposed Label
Date: Tuesday, June 16, 2015 2:27:00 PM

Dr. Costa,

Below is the response to your email requesting rationale for some of the Agency's proposed changes to the labeling

- Inclusion under Section 5.1 of a statement pertaining to hypopigmentation and listing it as the first statement in Section 5

  Division Rationale: According to the guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format*, clinically significant adverse reactions that are anticipated to occur should be included in Section 5 (the Warnings and Precautions section).

  We believe that hypopigmentation is an anticipated clinically significant adverse reaction that can occur following the use of the active moiety azelaic acid in Finacea Foam, 15%. Hypopigmentation has been reported in patients with dark complexions following azelaic acid use. Indeed, published medical literature indicates that azelaic acid interferes with melanogenesis and has been used as a hypopigmenting drug (Kabir Sardana and Sneha Ghunawat, 2015). Moreover, hypopigmentation is included in Section 5.1 of the labeling for Finacea (azelaic acid) Gel, 15%. Thus, even though hypopigmentation has not been reported in your clinical trial experience with Finacea (azelaic acid) Foam 15% that studied limited number of subjects with dark complexions, we believe hypopigmentation should be included in the Warnings and Precautions section.

(b) (4)

[redacted]

(b) (4)

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

From: Karen Costa [mailto:karen.costa@bayer.com]
Sent: Monday, June 15, 2015 4:47 PM
To: Laiyemo, Omolara
Cc: Williams, Dawn
Subject: RE: NDA 207071: Agency Proposed Label

Dear Dr. Omolara,

Bayer is in receipt of the Agency's proposed labeling. We are in the process of compiling our response. It would be greatly appreciated if the Agency's rationale could be provided for the following proposed labeling changes:

- Inclusion under Section 5.1 of a statement pertaining to hypopigmentation and listing it as the first statement in Section 5

(b) (4)

Thank you for any information you can provide.

Kind regards,
Karen

Kind regards, Mit freundlichen Grüssen, Meilleures salutations,

Karen A. Costa, M.S., Ph.D.
Bayer HealthCare Pharmaceuticals Inc.
Global Regulatory Affairs
Specialty Medicine: Dermatology & Ophthalmology

Bayer HealthCare

Science For A Better Life

100 Bayer Boulevard
Bldg 200; 2A3203
Whippany, NJ 07981-0915
Telephone: 1 (862) 404-3306
Email: Karen.Costa@bayer.com

From: Laiyemo, Omolara [mailto:Omolara.Laiyemo@fda.hhs.gov]
Sent: Thursday, June 11, 2015 3:25 PM
To: Karen Costa
Cc: Williams, Dawn
Subject: NDA 207071: Agency Proposed Label

Dr. Costa,

Please see the attached Agency proposed label for NDA 207071 Finacea foam, 15%. Please submit your concurrence with or counter-proposal to the Agency proposed label by Thursday, June 18th, 2015. Attached also is the list of recommendations for carton and container labels for your consideration. We request that you respond by Thursday, June 18, 2015.

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

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/s/

OMOLARA R LAIYEMO
06/16/2015

From:	Laiyemo, Omolara
To:	karen.costa@bayer.com
Cc:	Williams, Dawn
Subject:	NDA 207071: Agency Proposed Label
Date:	Thursday, June 11, 2015 3:24:00 PM
Attachments:	NDA 207071_SCPI_5_14_15.docx NDA 207071 Carton and Container Recommendations.docx

---

Dr. Costa,

Please see the attached Agency proposed label for NDA 207071 Finacea foam, 15%. Please submit your concurrence with or counter-proposal to the Agency proposed label by Thursday, June 18th, 2015. Attached also is the list of recommendations for carton and container labels for your consideration. We request that you respond by Thursday, June 18, 2015.

Thank you,

Omolara Laiyemo, PharmD
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Omolara.laiyemo@fda.hhs.gov
240-402-3842

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

A. General Comments (all container labels and carton labeling)

1. The product name appears as Finacea (b) (4) (azelaic acid) Foam, 15%. The product name should be revised to Finacea (azelaic acid) Foam, 15%.

2. Ensure the lot number and expiration date are present on the container labels and carton labeling. The images provided do not indicate where this information will be presented.

3. Delete or reduce the size of the (b) (4) rainbow-like graphic from the principal display panel. As currently presented the use of multiple graphics on the principal display panel crowds the labels and detracts from the presentation of the relevant product information (i.e. proprietary name, established name, dosage form, and strength).

4. Revise the "Directions" statement to separate the 'directions' from the 'dosage statement' to read:

   Shake well before using.
   Dosage: Apply a thin layer…

5. Relocate the route of administration statement to the principal display panel where the (b) (4) rainbow-like graphic is currently located and increase its prominence to read:

   For Topical Use Only
   Not for ophthalmic, oral or intravaginal use

6. Provide bar code (21CFR 201.25) on the immediate drug product container label.

B. Container Label (30 g)

1. Decrease the prominence of the "Rx Only" statement so that it does not compete in prominence with the established name, dosage form, and strength statement. Alternatively, you may relocate the "Rx Only" statement to the lower portion of the principal display panel.

C. Container Label (50 g)

1. Include the statement "Discard product 8 weeks after opening" in bold font below the dosage statement.

D. Carton Labeling (30 g, 50 g)

1. Include the statements "Discard product 8 weeks after opening.

   Date Opened: _____" in bold font under the storage statement.

2. To implement comment D.1., we recommend you relocate the manufacturer information to a side panel.

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/s/

OMOLARA R LAIYEMO
06/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207071

INFORMATION REQUEST

Bayer HealthCare Pharmaceuticals Inc.
Attention: Karen A. Costa, MS, PhD
Global Regulatory Affairs, Specialty Medicine (Dermatology)
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981

Dear Dr. Costa:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finacea (azelaic acid) foam, 15%.

We also refer to your September 30, 2014 submission, containing your original NDA for Finacea (azelaic acid) foam, 15% for the treatment of the inflammatory papules and pustules of mild to moderate rosacea.

We are reviewing your submitted draft labeling and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

> Table 1 in Section 6 of the proposed Finacea foam prescribing information splits events into two System Organ Class sections, "Application site conditions" and (b) (4) . Similar events should be categorized together in the table. For example, pool similar adverse reactions together, such as Preferred Terms application site pruritus and pruritus.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 8, 2015. The resubmitted labeling will be used for further labeling discussions. Use the Selected Requirements of Prescribing Information (SRPI) checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The SRPI checklist is available at:
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.

If you have any questions, please contact Omolara Laiyemo, Regulatory Project Manager, at (240) 402 3842.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Acting Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
05/05/2015

PeRC Meeting Minutes
April 15, 2015

PeRC Members Attending:
Lynne Yao
Robert "Skip" Nelson
Wiley Chambers
Rosemary Addy
George Greeley
Ruthanna Davi NON-RESPONSIVE
Tom Smith
Karen Davis-Bruno
Daiva Shetty
Andrew Mulberg NON-RESPONSIVE
Greg Reaman NON-RESPONSIVE
Adrienne Hornatko-Munoz
Andrew Mosholder
Hari Cheryl Sachs
Julia Pinto NON-RESPONSIVE
Lily Mulugeta
Kevin Krudys
Rachel Witten
Dianne Murphy
Maura O'Leary
Olivia Ziolkowski

Agenda

NON-RESPONSIVE

	NDA	*207071*	*Azelaic Acid (Full Waiver)*	*Topical treatment of inflammatory papules and pustules of mild to moderate rosacea*

NON-RESPONSIVE

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NON-RESPONSIVE

Azelaic Acid iPSP

- Proposed Indication: Topical treatment of inflammatory papules and pustules of mild to moderate rosacea
- PeRC Recommendations:
  - The PeRC agreed with the plan for full waiver

NON-RESPONSIVE

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/s/

GEORGE E GREELEY
04/29/2015

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2015

To: Karen A. Costa, Ph.D.	**From:** Adele Seifried
Company: Bayer HeathCare Pharmaceuticals	OND IO
Fax number: (862) 404-3175	**Fax number**: 301-796-9855
Phone number: (862) 404-3306	**Phone number:** 301-796-0535

Subject: Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report – NDA 207-071

Total no. of pages including cover: 4

email to Karen.costa@bayer.com

Document to be mailed: ☐ YES ☑ NO

Executive CAC
Date of Meeting: March 10, 2015

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Timothy McGovern, Ph.D., OND IO, Member
Albert Defelice, Ph.D., DCRP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogenicity bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Standardized Study Data (December 2014) and the latest Study Data Technical Conformance Guide.

NDA #: 207071
Drug Name: FINACEA (azelaic acid) Foam, 15%
Sponsor: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ

Background:

The sponsor submitted NDA 207071 on 09/30/2014 to pursue marketing approval of FINACEA (azelaic acid) Foam, 15% for the treatment of rosacea. A 2-year dermal mouse carcinogenicity study protocol and a dose range-finding study were included in the initial NDA submission. The 2-year dermal mouse carcinogenicity study will be conducted as a post-marketing commitment (PMC).

Two-year dermal mouse carcinogenicity study protocol:

Species/strain:	CD-1 mouse
Number/sex/dose:	(b) (4)
Duration:	104 weeks
Route:	Topical
Dose volume:	(b) (4)
Body surface area (BSA) treated:	
Doses proposed:	

Vehicle:

(b) (4)

Dosing procedure:

Justification for Dose Selection:

(b) (4)

Executive CAC Recommendations and Conclusions:

(b) (4)

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, DDDP
/B. Hill, Supervisor, DDDP
/J. Wang, P/T reviewer, DDDP
/O. Laiyemo, Project Manager, DDDP
/A. Seifried, OND IO

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/s/

ADELE S SEIFRIED
03/11/2015

ABIGAIL C JACOBS
03/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207071

INFORMATION REQUEST

Bayer HealthCare Pharmaceuticals Inc.
Attention: Karen A. Costa, MS, PhD
Global Regulatory Affairs, Specialty Medicine
Dermatology & Ophthalmology
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981

Dear Dr. Costa:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finacea (azelaic acid) foam, 15%.

We are reviewing your NDA and have the following information request. We ask that you respond to the below request by February 19, 2015.

> For trial 1401843, entitled "Investigator-Blinded, Randomized, Cross-Over, Multiple Dose, Phase 1 Study on Safety and Pharmacokinetics of Topically Applied Azelaic Acid Foam, 15% Compared to Azelaic Acid Gel, 15% in Subjects with Papulopustular Rosacea", provide a statistical summary in a tabular format containing information about the total amount of azelaic acid foam and gel formulations used. Provide the average amount of formulation used per dose.

If you have any questions, please contact Omolara Laiyemo, Regulatory Project Manager, at (240) 402-3842.

Sincerely,

{See appended electronic signature page}

Denise Cook, MD
Acting Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DENISE COOK
02/17/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207071

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bayer HealthCare Pharmaceuticals Inc.
100 Bayer Boulevard
PO Box 915
Whippany, NJ 07981-0915

ATTENTION: Karen A. Costa, M.S., Ph.D.
Global Regulatory Affairs, Specialty Medicine (Dermatology)

Dear Dr. Costa:

Please refer to your New Drug Application (NDA) dated and received September 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelaic Acid Foam, 15%.

We also refer to your correspondence, dated and received October 24, 2014, requesting review of your proposed proprietary name, Finacea Foam.

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

If any of the proposed product characteristics as stated in your October 24, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Omolara Laiyemo, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3842.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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/

JANET L ANDERSON
12/18/2014

TODD D BRIDGES
12/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207071

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Bayer HealthCare Pharmaceuticals Inc.
Attention: Karen A. Costa, MS, PhD
Global Regulatory Affairs, Specialty Medicine (Dermatology)
100 Bayer Boulevard
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Costa:

Please refer to your New Drug Application (NDA) dated September 30, 2014, received September 30, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Finacea (azelaic acid) Foam, 15%.

We also refer to your amendments dated October 24 and 31, November 10, 13 and 14, 2014.

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 July 30, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 19, 2015.

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

We request that you submit the following information:

1. Provide a representative sample (2 units) for each of the proposed to-be-marketed trade size and the physician sample.

2. Provide stability update for all registration stability batches.
3. Assign the functions of propylene glycol and dimethyl isosorbide in the proposed formulation based on physicochemical properties. (b) (4)

PRESCRIBING INFORMATION

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

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

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

1. Pharmacological class need to be stated in "Indications and Usage in Highlights"

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by December 19, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Omolara Laiyemo, Regulatory Project Manager, at (240) 402-3842.

Sincerely,

{See appended electronic signature page}

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

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/s/

KENDALL A MARCUS
12/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207071

INFORMATION REQUEST

Bayer HealthCare Pharmaceuticals Inc.
Attention: Karen A. Costa, MS, PhD
Global Regulatory Affairs, Specialty Medicine (Dermatology)
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981

Dear Dr. Costa:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Finacea (azelaic acid) foam, 15%.

We also refer to your September 30, 2014 submission, containing your original NDA for Finacea (azelaic acid) foam, 15% for the treatment of the inflammatory papules and pustules of mild to moderate rosacea.

We are reviewing your NDA and have the following information request. We ask that you respond to the below request by November 13, 2014.

- Submit the raw plasma azelaic acid and pimelic acid concentrations as well as the calculated PK parameter data sets from the maximal use PK trial (1401843) in SAS transport format.

If you have any questions, please contact Omolara Laiyemo, Regulatory Project Manager, at (240) 402-3842.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
11/07/2014

From: Simakova, Olga (CDER)
To: "Karen Costa"
Subject: RE: NDA 207071 finacea foam: IR
Date: Tuesday, November 04, 2014 9:21:00 AM

Dear Dr. Costa,

Please see our reasons for the inquiry:

- Drug substance facility information is completely missing in Module 2 and Module 3. Drug product facility information is provided in Modules 2 and 3 but incomplete (specifically, missing contact information, and the statement of readiness for inspection for each facility).
  The absence of drug substance establishment information in Modules 2 and 3 prevents the Agency from verifying the information provided in Form 356h for drug substance. Furthermore, inconsistency has been noted between the limited establishment information provided in Modules 2 and 3, and that provided in form 356h.
- Although Bayer listed DMFs in Form 356h under Section 30 Cross References, they are not listed under Section 29 Establishment Information. You should provide the relevant Type II DMF number for a drug substance facility in Section 29 of Form 356h in addition to Section 30. The DMF number that we are asking for is not Type I facility DMF.

  [redacted] (b) (4)
  on drug substance is considered by the Agency as a drug substance manufacturing facility. Furthermore, Module 2 references only to DMF 9289 (Bayer Pharma at Berlin) for drug substance information without referencing to DMF [redacted] (b) (4)
  Does this mean that [redacted] (b) (4) is not considered to be a drug substance manufacturer for this NDA but Bayer Pharma at Berlin is (according to Module 2)? Please clarify. The correct establishment information needs to be present in Modules 2 and 3 in addition to Form 356h.

Best regards,

Olga

Olga Simakova, PhD
Regulatory Health Project Manager
Office of New Drug Quality Assessment
FDA/CDER/OPS
10903 New Hampshire Ave.
WO21, Rm. 2667
Silver Spring, MD 20993
Olga.simakova@fda.hhs.gov
(240) 402-3814

From: Karen Costa [mailto:karen.costa@bayer.com]
Sent: Monday, November 03, 2014 10:01 AM
To: Simakova, Olga (CDER)
Subject: RE: NDA 207071 finacea foam: IR

Dear Dr. Simakova. Bayer is in receipt of this Information Request but we require some further clarity on the Agency's request before we can respond properly. Below we have broken out what we need additional clarity on.

Can you kindly provide further guidance to us on this Information Request so that we can respond properly? I am not in the office today, but if you prefer, I can phone you at your convenience. Please let me know if you prefer a call.

Finally, can you also kindly confirm receipt of this email response?

1. Amend Modules 2 & 3 to Name and address, FEI number, DUNS number, functions, contact information, and statement of readiness for inspection.
   Bayer notes that the Name, address, FEI number and function is already included in Modules 2 and 3. The DUNS number, contact information and statement of readiness for inspection is provided via 356h. Please clarify if this explanation is acceptable. If not, then what would need to be rectified as we do not understand.
2. (1) DMF references for the following two facilities: Bayer Pharma AG located at Berlin, Germany, and [redacted] (b) (4)
   What is meant by this request? DMFs for the facilities themselves do not exist as the DMF's pertain to the DS. Bayer does have DMFs for the Drug Substance (DS) and these have been listed on the 356h. Please clarify
   (2) adding drug substance manufacture to the function of Bayer Pharma AG located at Berlin, Germany
   Bayer Pharma AG does not manufacture the Drug Substance (DS). This facility only performs [redacted] (b) (4) testing. In light of this information, please clarify if this addition is still required.
   (3)) describing the work performed at Bayer HealthCare LLC, Morristown, NJ to release drug product batches (i.e., Are there any tests performed?)
   -> The current description "release to market" pertains to a review of the records only prior to release. There is no physical testing performed in Morristown, NJ>.

Thank you,
Karen

Kind regards, Mit freundlichen Grüssen, Meilleures salutations,

Karen A. Costa, M.S., Ph.D.

Bayer HealthCare Pharmaceuticals Inc.
Global Regulatory Affairs
Specialty Medicine: Dermatology & Ophthalmology

Bayer HealthCare

Science For A Better Life

100 Bayer Boulevard
Bldg 200; 2B3370
Whippany, NJ 07981-0915
Telephone: 1 (862) 404-3306
Email: Karen.Costa@bayer.com

From: Simakova, Olga (CDER) [mailto:Olga.Simakova@fda.hhs.gov]
Sent: Monday, November 03, 2014 8:52 AM
To: Karen Costa
Subject: NDA 207071 finacea foam: IR

Dear Dr. Costa,

We have the following information request concerning Bayer HealthCare Pharmaceuticals Inc. 's NDA 207071. We request a prompt response to this IR request no later than **Wednesday COB November 5, 2014**.

Establishment information provided in the initial submission is incomplete and inconsistent between modules.

> Amend Modules 2 and 3 to include the following establishment information for both drug substance and drug product facilities that are involved in manufacture/testing of this NDA: name and address, FEI number, DUNS number, functions, contact information, and statement of readiness for inspection-> Bayer notes that the Name, address, FEInumber, functions is included in Module 2 and 3; DUNS number, contact information and statement of readiness for inspection is always provided via 356h. We have never put any of this information into M2 or 3 for all facilities.

2. Amend Form 356h by (1) adding DMF references for the following two facilities: Bayer Pharma AG located at Berlin, Germany, and Bayer Pharma AG located at Bergkamen, Germany; (2) adding drug substance manufacture to the function of Bayer Pharma AG located at Berlin, Germany; and (3) describing the work performed at Bayer HealthCare LLC, Morristown, NJ to release drug product batches (i.e., Are there any tests performed?).

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment. If you have any questions or comments feel free to contact me.

Thank you.

Best Regards,

Olga Simakova, PhD
Regulatory Health Project Manager
Office of New Drug Quality Assessment
FDA/CDER/OPS
10903 New Hampshire Ave.
WO21, Rm. 2667
Silver Spring, MD 20993
Olga.simakova@fda.hhs.gov
(240) 402-3814

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207071

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals Inc.
Attention: Karen A. Costa, MS, PhD
Global Regulatory Affairs, Specialty Medicine (Dermatology)
100 Bayer Boulevard
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Costa:

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: Finacea (azelaic acid) foam, 15%

Date of Application: September 30, 2014

Date of Receipt: September 30, 2014

Our Reference Number: NDA 207071

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 November 29, 2014, in accordance with 21 CFR 314.101(a).

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

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 207071** submitted on September 30, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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

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

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

If you have any questions, call Omolara Laiyemo, Regulatory Project Manager, at (240) 402-3842.

Sincerely,

{See appended electronic signature page}

Omolara Laiyemo, PharmD
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/

OMOLARA R LAIYEMO
10/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077516

MEETING MINUTES

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Karen A. Costa, MS, PhD
Global Regulatory Affairs, Specialty Medicine (Dermatology)
100 Bayer Blvd
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Costa:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (azelaic acid) foam, 15%.

We also refer to the meeting between representatives of your firm and the FDA on July 9, 2014. The purpose of the meeting was to discuss the content and format for the anticipated NDA submission for (azelaic acid) foam, 15%.

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, at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
OSI Pre-NDA/BLA Request

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 9, 2014; 9:00 AM (EST)
Meeting Location: WO Bldg. 22; Rm. 1313
Application Number: 077516
Product Name: (azelaic acid) foam, 15%
Indication: Topical treatment of [redacted] (b) (4) rosacea

Sponsor Name: Bayer HealthCare Pharmaceuticals, Inc.

Meeting Chair: Stanka Kukich, M.D.
Meeting Recorder: Belainesh Robnett

FDA ATTENDEES
Kendall A. Marcus, MD, Acting Director, DDDP
Stanka Kukich, M.D., Deputy Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Roy Blay, PhD, Reviewer, OSI/DGCAB
Felicia Duffy, RN, BSN, MSEd, Risk Management Analyst, DRISK
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP
Belainesh Robnett, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Deepika Jalota, PharmD, Head, Dermatology & Ophthalmology, GRA
Karen A. Costa, MS, PhD, Global Regulatory Lead, GRA (Dermatology)
Claudia Lerch, PhD, CMC Lead GRA
Dennis Krickau, PhD, Development CMC
Richard Nkulikiyinka, MD, Head of Dermatology, Global Clinical Development
Kaweh Shakery, MD, Lead Clinician, Clinical Development (Dermatology)
Sandra Johanssen, PhD, Lead Toxicologist, Preclinical Development

Clemens Guenther, PhD, Lead Clinical Pharmacologist
Gerald Staedtler, MS, Lead Statistician, Global Biostatistics
Aasia Bhatti, MD, Lead Pharmacovigilance
Andrea Jux, BA, Project Management

Purpose of the meeting:
To discuss the content and format for the anticipated NDA submission for (azelaic acid) foam, 15%

Regulatory Correspondence History

We have had the following meetings with you:

- 11/09/2011 End of Phase 2 Meeting
- 06/10/2009 Guidance Meeting
- 07/17/2007 Pre-IND Meeting

We have sent the following correspondences:

- 08/27/2012 Advice
- 03/30/2012 Special Protocol-Agreement
- 07/28/2011 Advice/Information Request
- 10/01/2010 Advice
- 07/28/2010 Advice/Information Request
- 05/30/2008 Advice
- 04/14/2008 Advice
- 02/06/2008 Advice/Information Request

Regulatory and Multidisciplinary

Question 14:
Bayer conducted two Phase I studies at a CRO which subsequently went bankrupt and out of business in March 2013. Specifically, the two studies included a Human Repeat Insult Patch Test (HRPIT) for skin sensitization (1401842) and a 21-day cumulative irritation test (1401841). At the point this occurred, both the studies were in data-lock and the final/draft CSR's were in existence. However, the CRO had in their possession Bayer's study data, TMF's as well as the CSR's. Bayer was able to procure all data and documents.

Does the Agency concur that it is acceptable for BHC to submit the data from these studies as part of the planned NDA for azelaic acid foam, 15%?

Response:
Clarify what is meant by "final/draft CSR".

Meeting Discussion:
The sponsor clarified what would be submitted for the Phase 1 studies. The Agency stated that it would be acceptable to submit the data from these Phase 1 studies.

Question 15:
In the EOP2 Meeting Minutes 18 Nov 2011, the Agency acknowledged that since Bayer will be cross-referencing applicable nonclinical data from NDA 021470 FINACEA® (azelaic acid) Gel, 15% (for which Bayer is the current holder), a 505(b)(1) is the appropriate regulatory pathway. Where cross-referencing takes place, Bayer will cite the date of submission and the volume.

Does the Agency concur with this approach to cross-referencing?

Response:
Your overall approach for cross-referencing the nonclinical data for FINACEA gel to support the azelaic acid foam electronic NDA submission appears reasonable. However, it would be preferable if you could include a scanned copy of the pivotal nonclinical study reports contained in the FINACEA gel NDA (i.e., chronic toxicity studies, genotoxicity studies, reproductive toxicity studies and carcinogenicity studies) in the azelaic acid foam electronic NDA submission. In addition, it is anticipated that a comprehensive summary of the available nonclinical data will be provided in Module 2 of the azelaic acid foam electronic NDA submission.

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

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (i.e. paper/eCTD and/or non- eCTD format) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document along with a hypertext link to the location of the information, when possible.

2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind,). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

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

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

Additional electronic submissions comments:

- Bookmarks were not applied to the briefing package. Since the eCTD is very granular, providing sufficient navigation using proper bookmarks, table of contents and hyperlinks is essential to help ensure an efficient review. Refer to FDA PDF Specifications, located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf.

- Providing a Reviewer's Guide with a high level overview of what is provided in modules 1 through 5 with hyperlinks can be helpful to reviewers. The Reviewer's Guide is usually submitted as a separate document in the cover letter section (m1.2), with a clear and descriptive leaf title.

- The submission needs to comply with FDA and ICH specifications. Refer to the eCTD website for eCTD Specifications and Guidance, located at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5, with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Case Report Forms (if provided), need to be referenced under the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

Chemistry, Manufacturing and Controls (CMC)

Question 1:
Bayer is the manufacturer of the drug substance (DS) azelaic acid which is used in the azelaic acid foam, 15% formulation as well as in other Bayer-marketed azelaic acid formulations around the world. (b) (4)

(b) (4)

Response:
Yes, your proposal is reasonable. (b) (4)

Question 2:
Bayer will submit stability data for three (3) full scale batches (b) (4)

Does the Agency agree with Bayer's proposal to provide 24 months data for two of the primary stability batches and 3 months data for the three supportive stability batches, within two months of the azelaic acid foam, 15% NDA submission to support a proposed shelf life of (b) (4) months?

Response:
We recommend that you provide primary stability data from <u>three</u> full scale registration stability batches in the initial NDA submission as stated in the first paragraph. Clarify why the number of primary stability batches becomes two in the second paragraph.

As to the supporting stability batches, your proposal of providing three months of data within two months of the NDA submission is acceptable.

The drug product expiration dating period to be granted will be determined in the NDA review.

Meeting Discussion:
The sponsor confirmed that they would have stability data from three primary stability batches (13 months from one batch and 18 months from two batches) at the time of NDA submission. The sponsor proposed to provide additional stability data from one more stability time point within two months after NDA submission. The Agency agreed with the proposal.

<u>Pharmacology/Toxicology</u>

Question 3:
Bayer has identified two degradants (b) (4) in the azelaic acid foam, 15%. These impurities are formed (b) (4) were assessed with respect to genotoxicity, general toxicity and dermal tolerability. A 4-week dermal toxicity study in mice has been

performed to qualify the [redacted] (b) (4) after topical administration to support a specification level of [redacted] (b) (4)%. Because of the [redacted] (b) (4) the 4-week dermal toxicity study results are also regarded as representative for [redacted] (b) (4).

Does the Agency agree that the described approach is sufficient to support release and shelf life specifications of NMT [redacted] (b) (4)% for [redacted] (b) (4) and NMT [redacted] (b) (4)% for [redacted] (b) (4)?

Response:
Yes, we agree.

<u>Additional CMC Comments</u>

1. Provide a correlation table in Section 3.2.P.2 Pharmaceutical Development to correlate formulation, drug substance supplier, drug product manufacturing site to the study numbers of clinical/toxicology/stability studies.

2. A bridging study may be necessary if the drug product manufacturing site of Phase 3 batches is different from the designated commercial site. SUPAC-SS contains bridging study examples.

3. Provide formulation characterization information in Section 3.2.P.2 Pharmaceutical Development for the formulation in the aerosol can. We would like to know whether the formulation remains as an [redacted] (b) (4)

4. [redacted] (b) (4)

Question 4:
The nonclinical safety and pharmacological properties of azelaic acid are well-characterized. In addition, the nonclinical studies supporting azelaic acid foam, 15% were previously agreed with by the Agency. Furthermore, conducting a carcinogenicity study as a Phase IV commitment was agreed to be completed for IND 077516. Nevertheless, in order to bridge from the available nonclinical studies on the azelaic acid gel and cream formulations to the currently proposed azelaic acid foam formulation, Bayer performed a number of additional studies.

Does the Agency agree that the executed nonclinical program is adequate to support the planned NDA for azelaic acid foam, 15% and that additional nonclinical studies are not needed?

Response:
Yes, we agree.

Question 5:

Does the Agency agree that the results of the Tg.AC mouse assay conducted with FINACEA® (azelaic acid) gel 15% do not need to be incorporated into the label of azelaic acid foam, 15%?

Response:
No, we do not agree. It might be possible to remove the Tg.AC mouse assay conducted with FINACEA gel from the azelaic acid foam label and replace it with the results of the postmarketing dermal carcinogenicity study conducted in mice with azelaic acid foam. This will be determined after review of the final study report.

As was relayed to you during the End of Phase 2 meeting conducted on November 9, 2011, you should include a study protocol for the dermal carcinogenicity study in mice and the 13 week dermal dose range finding study in mice in the original NDA submission for azelaic acid foam. You should also include a proposed time line for conduct of the dermal carcinogenicity study in mice and subsequent submission of the final study report in the original NDA submission for azelaic acid foam.

Question 6:
Does the Agency still agree that nonclinical studies for phototoxicity/ photocarcinogenicity are not required to support the planned NDA for azelaic acid foam, 15%?

Response:
Yes, we agree.

Question 16:
Allergan is the current NDA holder of 020428, AZELEX® (azelaic acid), cream 20%. Bayer will be referencing applicable data from NDA 020428. As such, Bayer plans to submit a 505(b)(1) application with a right-of-reference letter from Allergan.

Does the Agency agree with this approach?

Response:
Yes, we agree with your approach to submit a right of reference letter for NDA 20428 for AZELEX (azelaic acid) cream, 20%. Clarify the information which you will supply by reference to NDA 020428.

<u>Clinical/Biostatistics/Clinical Pharmacology</u>

Question 7:
For the NDA submission of azelaic acid foam, 15% it is planned to include the efficacy data from two clinical studies: Study 1403120 & Study 1401846. The design and results of these two adequate and well-controlled studies are described below.

Does the Agency agree that the clinical data package, including the two pivotal studies 1403120 and 1401846, provides sufficient evidence of efficacy to support the planned NDA for azelaic acid foam, 15% with the following indication: The topical treatment of the inflammatory papules and pustules of mild to moderate rosacea? *Although some reduction of erythema which was*

present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

Response:
Your proposed clinical package would support filing of your NDA. However, as previously stated on Nov 9, 2011 at the EOP2 meeting, Study 1403120 was designed as a Phase 2 study with 'exploratory' objectives. In order for the study to be considered an adequate and well-controlled study, the study needs to have been designed and executed with all of the characteristics of a Phase 3 study (e.g., adequate blinding, appropriate control arm, appropriate endpoints and scales, pre-defined statistical analysis plan, scientifically sound method for handling of missing data along with alternative approaches as sensitivity analyses, appropriate controls for multiplicity, sensitivity analyses, etc.). The adequacy of the study is a review issue (clinically meaningful treatment effect, appropriate patient population, consistency of findings across subgroups, etc.). Your indication will depend on the study findings.

Meeting Discussion:
The sponsor provided additional discussion about trial 1403120 and their rationale why it should be considered well-controlled. The Agency reiterated that the adequacy of this trial will be a review issue. The Agency stated that if there were any issues regarding this trial these issues will be communicated to the sponsor by mid-cycle.

Question 8:
Bayer notes that a large safety database exists for azelaic acid. Specifically in the US, this database is inclusive of NDA 021470 [FINACEA® (azelaic acid), Gel 15% approved 24 December 2002] as well as NDA 020428 [AZELEX® (azelaic acid), Cream 20% approved 13 September 1995]. Worldwide, Bayer currently markets one-hundred and six (106) azelaic acid-containing formulations under different trademarks for both acne and rosacea: 70 cream formulations and 36 gel formulations. In 2013, approximately (b) (4) units of azelaic acid formulations were sold, with an estimated 3.02 million person-months (approximately 251,710 person-years) of exposure in 2013 (Periodic Safety Update Report for the time period 03 Jan 2013 – 02 Jan 2014). A favorable risk benefit ratio for the azelaic acid containing formulations can be confirmed from the Periodic Safety Update Reports over the last 12 years. No Bayer marketing authorizations/applications for azelaic acid-containing formulations have ever been rejected, withdrawn, or suspended due to safety reasons. In support of the NDA submission for azelaic acid foam, 15% formulation, Bayer intends to rely in part on NDA 021470 for FINACEA® (azelaic acid), Gel 15% and plans to cross-reference in part to this data. Bayer notes further that the final results of the PK study did demonstrate that in patients with rosacea, cutaneous application of azelaic acid foam, 15% does not result in higher systemic drug exposure compared to cutaneous application of azelaic acid gel, 15%. The Agency stated previously that dependent upon the final results of the PK study and providing that additional studies did not raise a signal of concern, it is possible that long term safety studies with the foam formulation would not be needed (EOP2 Meeting Minutes 18 Nov 2011). Bayer deems these conditions to be fulfilled.

Taking into account the pre-existing data package for NDA 021470 [FINACEA® (azelaic acid), Gel 15%] the extensive clinical and post-marketing experience with the approved azelaic acid

formulations, and the final results of the PK study providing evidence of a similar systemic exposure to azelaic acid following cutaneous application of either the gel or foam formulation, does the Agency agree that the current safety data base is sufficient to support the planned NDA submission for azelaic acid foam, 15% and that no additional long-term safety studies are needed?

Response:
We agree that an additional long-term safety study is not needed at this time.

Question 9:
In the administrative comments of the EOP2 Meeting Minutes 18 Nov 2011, the FDA noted that it was necessary for Bayer to address the potential for QT/QTc interval prolongation. To address this issue, Bayer notes the following. Azelaic acid, a compound with a low toxicity profile, is found endogenously in humans. Additionally, azelaic acid is produced in vivo by Malassezia furfur (Pityrosporum ovale), a yeast that lives on normal skin and is involved in the degradation of nonanoic acid to azelaic acid (Ashbee and Evans, 2002). Moreover, azelaic acid is a naturally-occurring substance in plants (whole grain cereals such as wheat, rye and barley) and animals. Therefore, throughout their lifetime humans are exposed to azelaic acid from both endogenous as well as dietary sources. Data demonstrates that in patients with rosacea, cutaneous application of azelaic acid foam, 15% does not result in higher systemic drug exposure compared to cutaneous application of azelaic acid gel, 15%. Additionally, the mean systemic azelaic acid concentration after therapeutic application on human skin does not increase beyond the range derived from nutritional intake of and endogenous metabolism of azelaic acid. Still further and as noted earlier, there exists a large safety database for azelaic acid. From both the clinical & nonclinical perspective, this cumulative database has yielded no safety signals relating to cardiovascular function or QT/QTc interval prolongation. Of note is that in the preclinical cardiovascular safety pharmacology tests (*in vitro* guinea pig isolated papillary muscle), azelaic acid had no effect on the action potential up to the highest concentration tested. Furthermore, long-term toxicity studies in minipigs and dogs revealed no effects on EKGs or EKG intervals up to the highest doses tested which were 131-fold and 176-fold the maximum human dose based on mg/m^2 comparison in minipigs and dogs, respectively.

Given the endogenous nature of azelaic acid, its low toxicity profile and the extensive cumulative human and nonclinical safety database on topical azelaic acid formulations which provide no evidence of a safety signal for QT/QTc interval prolongation, does the Agency agree that formal studies are not necessary to demonstrate lack of QT/QTc interval prolongation by azelaic acid in support of the planned NDA for azelaic acid foam, 15%?

Response:
Based on the summary of results of the maximal use PK trial (1401843) and the rationale provided, a TQT trial does not seem warranted at this time. The final determination will be made following a detailed review of your study reports during your NDA submission.

Question 10:

In addition to individual study data from six clinical studies that have been conducted with the foam formulation, Bayer plans to provide integrated analyses of safety and efficacy data in the azelaic acid foam submission. The rationale for pooling of 1) safety data from three clinical trials (all phase 2 and phase 3 trials with azelaic acid foam, 15%, with an additional pool containing only the pivotal studies) and 2) efficacy data from two clinical trials (pivotal trial 1+ 2 with azelaic acid foam, 15%) is provided below in the company position for question #10.

Does the Agency agree that the pooling, and submission of the safety and efficacy data as planned for the clinical data derived from azelaic acid foam, 15% studies will be adequate to support the planned NDA for azelaic acid foam, 15%?

Response:
Your pooling strategy seems reasonable at this time. See response to Question #7.

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

Question 11:
The AzA Foam eCTD submission will contain two types of datasets, both to be submitted electronically in SAS Version 5 transport file format with corresponding documentation. The types are 1. SDTM datasets (version 3.1.3) with define.xml documentation [.xml style sheet, and an annotated CRF (blankcrf.pdf)] and 2. analysis datasets with define.pdf or define.xml documentation.

Does the Agency agree with the proposed scope, format and documentation of the electronic datasets to be submitted?

Response:
You noted that the datasets for Studies 1402140 and 1403120 were collected in an internally-defined legacy dataset structure, and that you plan to convert the legacy data structure to SDTM structure for this submission. It is important that the resulting SDTM data support the accompanying analysis data sets and your study reports. For completeness and to ensure we have access to the datasets used to construct the reports, we recommend submitting the datasets in both the legacy and converted SDTM format. If you submit any SAS programs it is important that you submit the datasets that correspond to the programs.

The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified.

Also submit define.pdf with define.xml for SDTM, ADaM, and legacy datasets. The analysis dataset documentation (define file) should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

Statistical programs for any non-standard analyses should be submitted.

For each clinical study, include the study protocol, all protocol amendments (with dates), the statistical analysis plan, an annotated copy of the case report form, generated treatment assignment lists, and the actual treatment allocations (along with date of enrollment).

Additional Comments Data Submission:

The Agency prefers sponsor to submit datasets based on the *Study Data Specifications* (currently 2.0). However, in general, the Agency accepts datasets, which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

The Agency expects sponsor to evaluate the risk involved converting study data collected to standardized data, if applicable. The Agency prefers sponsor to submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario; decision rationale for not converting or decision rationale for converting. The Agency expects sponsor's evaluation and rationale include study data scientifically relevant to the application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsor should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. Sponsor should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. Sponsor should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM*

and *ADaM* as referenced in *Study Data Specifications*). Study analyses datasets should be traceable to the tabulations datasets.

In addition, reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions.

The agency also offers a process for submitting sample standardized datasets for validation. Refer to *Submit a Sample eCTD or Standardized Data Sample*.

Additional Links:
Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)
Study Data Standards Resources

Meeting Discussion:
The sponsor noted that the legacy dataset for Phase 2 trial 1402140 do not include derived and imputed variables and inquired if this was acceptable. The Agency responded that this appears to be acceptable. However, it would be helpful if the statistical programs for computing the endpoints could be submitted.

Question 12:
The clinical pharmacokinetic maximum use study supporting azelaic acid foam, 15% was previously agreed and discussed with the Agency (Guidance Meeting Minutes 08 Jul 2009; EOP2 Meeting Minutes 18 Nov 2011; Special Protocol Assessment Agreement Letter 30 Mar 2012). Bayer would like to reconfirm that the agreement pertaining to the clinical pharmacology program is still valid and no additional studies are required.

Does the Agency agree that the clinical pharmacology program is adequate to support the planned NDA for azelaic acid foam, 15%?

Response:
Overall, the design of trial 140183 appears reasonable to support filing of your NDA. The adequacy of the data will be determined following a detailed review of your report at the time of your NDA submission.

Question 13:
The NDA will be supported by the data from two clinical studies: Study 1403120 & Study 1401846. Bayer proposes that the case report forms (CRFs) and narratives provided in the submission include only those for serious adverse events (SAEs) and discontinuation due to adverse events (AEs) from these two studies. All other CRF's would be available upon request.

Does the Agency agree with this proposal?

Response:
Submit the following case report forms (CRFs) and narratives:

- Serious Adverse Events

- Adverse Events leading to discontinuations
- Severe Adverse Events

Meeting Discussion:
The sponsor stated that there are no narratives for fifteen subjects who experienced severe adverse events since the adverse events did not meet seriousness criteria or lead to discontinuation. The sponsor proposed to submit CRFs without narratives for these cases. The Agency stated that this would acceptable and asked the sponsor to clearly identify these cases.

Question 17:
In the Guidance Meeting Minutes 08 Jul 2009, the FDA agreed that since 1) lack of a substantial number of pediatric rosacea precludes proper controlled studies from being conducted and 2) this drug is not intended to treat patients < 18 years of age, a Pediatric Waiver was appropriate. Bayer intends to submit a Pediatric Waiver.

Does the Agency still agree that pediatric studies with azelaic acid foam, 15% in (b) (4) rosacea are not required and that a Pediatric Waiver can be submitted?

Response:
Be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. Since your EOP2 meeting occurred in 2011 you should submit a PSP as soon as possible.

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

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

Meeting Discussion:
The sponsor stated they would submit an initial PSP prior to the NDA submission. The Agency stated that this would acceptable.

The Agency agreed that the OSI requirements for site selection tool (SST) could be submitted after the initial NDA submission.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).

3. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: *Qualifying for Pediatric Exclusivity for details*. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

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

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

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of

Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

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.				

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/default.htm).

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

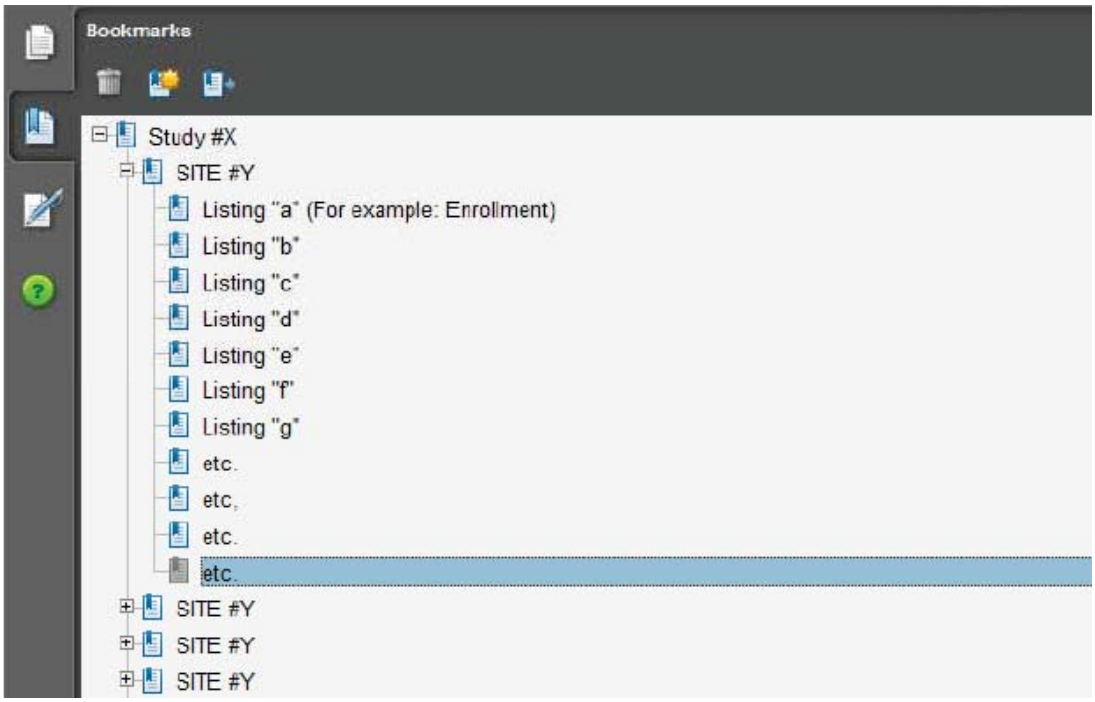
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571,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

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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

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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

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

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

/s/

STANKA KUKICH
07/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077516

ADVICE

Bayer HealthCare (Dermatology)
Attention: Karen Costa, MS, PhD
Head US Regulatory Affairs
36 Columbia Road
Morristown, NJ 07962

Dear Dr. Costa:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (azelaic acid) Foam, 15%.

We also refer to your amendment dated July 3, 2012, containing a request for clarification of the March 30, 2012 Special Protocol Agreement letter.

Question:
Does the Agency agree that the proposed endpoints are adequate to support the proposed indication of "topical treatment of (b) (4) rosacea"?

Response:
Yes, assuming an acceptable IGA that incorporates the changes recommended in the March 30, 2012 Special Protocol Agreement letter.

We have the following comments:

1. The difference between minimal and mild is the dichotomization point on this scale for achieving success for the primary endpoint. As such, it is essential that the difference between these categories represent a clinically meaningful and significant difference easily interpreted by the investigator. Revising the scale by using a distinct descriptor such as "faint" or "barely perceptible" erythema for the minimal category would improve the ability of the scale to discriminate between this category and the category of mild disease.

2. You are free to proceed with Phase 3 trials at any time. According the 21 CFR 312.30(a), a sponsor may begin any new clinical trial (subsequent to the first in man trial) provided that the protocol is submitted to the IND in a protocol amendment and the protocol has been approved by the responsible internal review board (IRB).

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of

Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

SUSAN J WALKER
08/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077516

SPECIAL PROTOCOL - AGREEMENT

Bayer HealthCare, Dermatology
c/o B & H Consulting Services, Inc.
Attention: Elizabeth Dupras, RAC
36 Columbia Road
P.O. Box 1941
Morristown, NJ 07962-1941

Dear Ms. Dupras:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for (azelaic acid) Foam, 15% for the treatment of (b) (4) rosacea.

We acknowledge your request dated and received February 17, 2012, for a special protocol assessment of a clinical protocol. The protocol is titled "A randomized, double-blind, vehicle-controlled, multicenter, parallel-group clinical trial to assess the safety and efficacy of Azelaic Acid Foam, 15% topically applied twice daily for 12 week in patients with papulopustular rosacea".

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study, with the exceptions noted below, adequately address the objectives necessary to support a regulatory submission.

As stated on page 9 in the "Guidance for Industry: Special Protocol Assessment," a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

I. Agreements

1. The general design of Study 1401846 entitled "A randomized, double-blind, vehicle-controlled, multicenter, parallel-group clinical trial to assess the safety and efficacy of Azelaic Acid Foam, 15% topically applied twice daily for 12 week in patients with papulopustular rosacea" is acceptable.

2. Your proposed co-primary efficacy endpoints of treatment success rate (defined as clear or minimal on an acceptable IGA, where subjects must have an IGA score of moderate or severe at baseline) at end of treatment and the absolute change in inflammatory lesion count from baseline to end of treatment are acceptable. See comment below for discussion of IGA.

3. Your proposed primary efficacy timepoint of 12 weeks is acceptable.

4. Your proposed dose regimen (azelaic acid foam, 15% topically applied twice daily) is acceptable.

5. Safety assessment consisting of recording of adverse events and serious adverse events (including active assessment for local cutaneous reactions and hypopigmentation) and the subject's assessment of local tolerability at the end of treatment are acceptable.

6. Follow-up visits at 4 week intervals with a 4 week post treatment follow-up period for assessment of relapse are acceptable.

7. The population you propose to study with regard to disease severity, i.e., subjects 18 years or older with a clinical diagnosis of moderate or severe papulopustular rosacea [(grade 3 or 4) on an agreed upon IGA] presenting with a minimum of 12 and no more than 50 inflammatory lesions (papules and/or pustules), is acceptable.

8. Your proposal to include pregnant and lactating women in the study if the investigator believes that the treatment is clearly indicated is acceptable.

9. Your proposal to define the full analysis set (FAS) population as all subjects randomized and dispensed investigational product is acceptable.

10. Your proposal to analyze treatment success with the Cochran-Mantel-Haenszel test stratified on center is acceptable.

11. Your proposal to analyze the absolute change in inflammatory lesions with an ANCOVA model with terms for treatment, center, and baseline lesion count is acceptable.

II. <u>Comments/Non-Agreements</u>

(b) (4)

(b) (4)

4. Because there is no universally appropriate method for handling missing data that can occur in clinical trials, you should design and conduct the study in such a way to reduce the occurrence of missing data. You have proposed imputing missing data using LOCF. Because the scientific justification for LOCF is limited, you should either provide a rationale for why LOCF is appropriate in this situation or propose an alternate method that has a reasonable justification. In addition to a primary method of handling missing data, you should also propose two or three sensitivity analyses with alternate methods of handling missing data to ensure that the results are not driven by the method of handling missing data (beyond observed-cases or per protocol analyses). The sensitivity analysis method should use alternate assumptions; for example, alternate approaches might include modeling approaches or multiple imputation.

III. Sponsor Questions

1. Does the Agency agree that the proposed endpoints are adequate to support the proposed indication of "topical treatment of (b) (4) rosacea"?

   FDA Response:
   Yes, assuming an acceptable IGA that incorporates the changes recommended above.

2. Does the Agency agree that the proposed inclusion/exclusion criteria are adequate to support the proposed indication of "topical treatment of (b) (4) rosacea"?

   FDA Response:
   Yes; however, as previously discussed, your inclusion criteria #1, which includes (b) (4)

3. Does the Agency agree that the proposed trial 1401846 will fulfill the requirements for a pivotal study and generate sufficient efficacy data to support the approval of planned NDA?

   FDA Response:
   The general design of Protocol 1401846 is acceptable. See Agency advice provided Nov 9th, 2011.

4. Does the Agency agree that no further clinical evaluation of QT/QTc interval prolongation or pro-arrhythmic potential drug effects with the foam formulation are needed for approval of the planned NDA?

   FDA Response:
   As discussed at the November 9, 2011 End of Phase 2 Meeting, "the need for long term safety studies *[Including QT/QTc studies]* cannot be determined until the final study report for Study 1401843 has been received and reviewed". As of the date of this letter, we have not received the final study report for Study 1401843.

5. Does the Agency agree that the proposed bridging approach to the gel formulation safety data (Section 3.2 and Attachment 2) in conjunction with the safety data from the expected number of subjects to be exposed in the Azelaic Acid Foam, 15% clinical program, will be adequate to support approval of the planned NDA?

   FDA Response:
   Determination of the adequacy of the safety database in your eventual NDA is beyond the scope of this special protocol assessment. As discussed during the November 9, 2011 End of Phase 2 Meeting, "the ultimate applicability of this data *[results of Study 1401843]* towards the bridging between the gel and foam formulation will be a review issue based on *[review of]* the full final study report and specific parameters that you intend to bridge".

6. Does the Agency agree with the proposed statistical analyses for Study 1401846?

   FDA Response:
   Refer to comments above and below.

   - We recommend pre-specifying the expected key protocol exclusions for the per protocol set in the protocol rather than deferring the definition until the statistical analysis plan to avoid bias.

   - We recommend specifying approximately how many centers will participate in the study. The study should be designed with a sufficient number of subjects per center so that center effects and treatment-by-center interactions can be adequately assessed.

- You have not proposed a method of assessing treatment-by-center interaction for the absolute change in lesion count endpoint. Because the analysis method is ANCOVA, we recommend conducting an analysis with the treatment-by-center interaction term in the model.

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

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
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/

SUSAN J WALKER
03/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077516

MEETING MINUTES

Intendis, Inc.
Attention: Elizabeth Dupras, RAC (Agent for Intendis)
Associate Director, CM&C and Regulatory
36 Columbia Road
Morristown, NJ 07962-1941

Dear Ms. Dupras:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (azelaic acid) Foam, 15%.

We also refer to the meeting between representatives of your firm and the FDA on November 9, 2011. The purpose of the meeting was to discuss the development program for (azelaic acid) Foam, 15%.

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

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

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: End of Phase 2 Meeting

Meeting Date and Time: November 9, 2011; 9:00 am
Meeting Location: White Oak Campus, Building 22, Room 1313

Application Number: 077516
Product Name: (azelaic acid) Foam, 15%
Indication: Topical treatment of (b) (4) rosacea
Sponsor Name: Intendis, Inc.

Meeting Chair: Stanka Kukich, M.D.
Meeting Recorder: Dawn Williams, B.S.N.

FDA ATTENDEES
Stanka Kukich, M.D., Deputy Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Jane Liedtka, M.D., Clinical Reviewer, DDDP
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP III
Chinmay Shukla, Ph.D., Clinical Pharmacology Reviewer, DCP III
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III
Roy Blay, Ph.D., Regulatory Reviewer, OC
Gene Holbert, Ph.D., Product Quality Reviewer, DNDQA II, Brach IV
Dawn Williams, B.S.N., Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Silke Freihammer, Regulatory Affairs Manager, Intendis
Andrea Jux, B.Sc., Project Director, Intendis
Dennis Krickau, Ph.D., Analytical Development, Intendis
Kaweh Shakery, Ph.D., Medical Advisor, Intendis
Gerald Staedtler, Clinical Statistician, Intendis
Elizabeth Dupras, RAC, Associate Director, CM&C and Regulatory Affairs, B&H Consulting

Regulatory Correspondence History

We have had the following meetings with you:

- June 10, 2009 Guidance Meeting
- July 17, 2007 Pre-IND Meeting

We have sent the following correspondences:

- October 1, 2010 Advice/Information Request
- July 28, 2010 Advice/Information Request
- May 30, 2008 Advice/Information Request
- April 14, 2008 Advice/Information Request
- February 6, 2008 Advice/Information Request

Regulatory

Question 1:
Does the Agency agree that a 505(b)(1) application is appropriate for approval of the proposed foam formulation of AzA, 15%?

Response:
Since you are cross referencing all applicable CMC, nonclinical and clinical data from NDA 021470 Finacea (azelaic acid) Gel, 15% for which you are the current holder, a 505(b)(1) is the appropriate regulatory pathway.

Question 2:
Does the Agency agree that a new proprietary name can be requested?

Response:
You can submit a proprietary name request for review for the foam formulation. Refer to the Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names.

Additional Comment:
Clarify the indication you intend to pursue.

Meeting Discussion:
The sponsor clarified they will seek an indication of (b) (4) rosacea.

Chemistry, Manufacturing and Controls (CMC)

Question 3:
Does the Agency agree that release testing by the drug substance supplier and identity testing by the drug product manufacturer provides appropriate quality control of the drug substance prior to the drug product manufacturing?

Response:

Your proposal of release testing by the drug substance supplier and identity testing by the drug product manufacturer appears to be reasonable. However, the adequacy of quality control over the drug substance is a review issue.

Question 4:
Does the Agency agree that the proposed drug product specifications are adequate to support approval of the planned 505(b)(1) NDA?

Response:
No, we do not agree. The adequacy of specification to support NDA approval is a review issue. Additionally, we have the following comments:

- Replace "report" with appropriate numeric limits as the acceptance criteria for the tests on particle size [redacted] (b) (4).
- Replace "report" with an appropriate numeric range as the acceptance criterion for the test on delivery rate.
- Replace "report" with an appropriate description as the acceptance criterion for the test on container compatibility.
- Revise the acceptance criterion for the test on delivered amount [redacted] (b) (4) to "average amount not less than label claim, and no single value less than [redacted] (b) (4)% of label claim for the 30 g and 50 g sizes and no single value less than [redacted] (b) (4)% of label claim for the [redacted] (b) (4) size".
- Modify the acceptance criteria for the test on [redacted] (b) (4) than or conform to the acceptance criteria given in [redacted] (b) (4).

Meeting Discussion:
The Agency recommended adding a second identity test which is specific for the drug substance.

Question 5:
Does the Agency agree that the limits for impurities/degradants in the proposed drug product specification are adequate to support approval of the planned 505(b)(1) NDA?

Response:
The adequacy of impurity limits to support NDA approval is a review issue.

Question 6:
Does the Agency agree with the Sponsor's proposal to submit available data for the single-timepoint and the ongoing leachables studies in the planned 505(b)(1) NDA, additional data during review of the application, and final data post-approval?

Response:
The proposal appears to be reasonable.

Additional Comment:

Some of the proposed excipients are described in the CMC section to function as (b) (4) in the proposed formulation (p. 28 of the briefing package). (b) (4) We recommend that you designate the function of each inactive ingredient based on its physicochemical characteristics.

Meeting Discussion:
The sponsor will address the function of the above identified excipients.

Pharmacology/Toxicology

Question 7:
Does the Agency agree that the proposed nonclinical program is adequate to support the planned 505(b)(1) NDA, and that no additional nonclinical studies are needed?

Response:
Yes, provided that you incorporate the results of the Tg.AC mouse assay conducted with Finacea (azelaic acid) Gel, 15% into the label for azelaic acid foam, 15%.

We acknowledge that you plan to include the results from a 13 week dermal mouse dose range finding study conducted with the azelaic acid pre-foam formulation in the planned NDA submission. This study is intended to support dose selection for a dermal mouse carcinogenicity study that will be conducted with the azelaic acid pre-foam formulation as a Post-Marketing Requirement. Your plan is in agreement with the advice relayed to you during the Guidance meeting conducted on June 10, 2009. You should also include a study protocol for the dermal mouse carcinogenicity study and a proposed timeline for conduct of the study and submission of the final study report for the dermal mouse carcinogenicity study in the NDA submission.

Clinical Pharmacology/Biopharmaceutics

Question 8:
Does the Agency concur that preliminary results from Study 1401843 demonstrate an adequate bridge between the gel and foam formulations, and that no further clinical pharmacology studies are required for the planned 505(b)(1) NDA?

Response:
Clarify the intent of your proposed bridge.

Based on a preliminary review of the summary of preliminary results from Study 1401843, it appears to be adequate to assess the relative systemic bioavailability of Azelaic Acid Foam, 15% and Azelaic Acid Gel, 15%. The ultimate applicability of this data towards bridging between the gel and foam formulation will be a review issue based on the full final study report and specific parameters that you intend to bridge.

Meeting Discussion:

The sponsor clarified that they intend to use the bridge to satisfy safety, but not efficacy, data needs. Specifically, they intend to use the bridge to address the risk for prolongation of cardiac repolarization and to address long-term safety. The sponsor will submit their rationale.

The sponsor clarified that they used the to-be-marketed formulation in the PK study.

The sponsor stated that they understood that their PK study needs to be conducted in subjects at the upper end of disease severity for the intended population.

Additional Comment:
Provide statistical comparison between the two formulations using gel as a reference in your NDA.

Clinical/Biostatistics

Question 9:
Does the Agency agree that no long-term safety studies with the foam formulation are needed for approval of the planned 505(b)(1) NDA?

Response:
In the meeting package submitted on Sep 23, 2011 you state that preliminary results from Study 1401843 show that "treatment of AzA Foam 15% did not result in a higher systemic exposure than the treatment with Azelaic Acid 15% gel formulation".

The need for long term safety studies cannot be determined until the final study report for Study 1401843 has been received and reviewed. However, if your preliminary findings for the PK study are correct and any additional studies you conduct (including topical safety studies) do not raise a signal of concern, it is possible that long term studies with the foam formulation will not be needed.

Question 10:
Does the Agency agree that Study 1403120 fulfills the requirements for a pivotal study?

Response:
Study 1403120 was designed as a Phase 2 study with 'exploratory' objectives. In order for the study to be considered an adequate and well-controlled study, the study needs to have been designed and executed with all of the characteristics of a Phase 3 study (e.g., adequate blinding, appropriate control arm, appropriate endpoints and scales, pre-defined statistical analysis plan, scientifically sound method for handling of missing data along with alternative approaches as sensitivity analyses, appropriate controls for multiplicity, sensitivity analyses, etc.). The adequacy of the study is a review issue (clinically meaningful treatment effect, appropriate patient population, consistency of findings across subgroups, etc.).

Meeting Discussion:

The sponsor inquired whether conduct of sample size calculation is a key factor defining an adequate and well-controlled trial. The Agency responded that sample size calculation is not typically an element in determining the adequacy of a trial. The sponsor will need to submit 2 adequate and well-controlled trials.

Question 11:
Does the Agency agree that the clinical development program demonstrates safety and efficacy of the proposed foam formulation, and is sufficient to support approval of the planned 505(b)(1) NDA?

Response:
You have conducted two Phase 2 studies: Study 1402140, a 12 week study in 83 subjects (41 on Azelaic Acid Foam 15% and 42 on placebo) and Study 1403120, a 12 week study in 401 subjects (198 on Azelaic Acid Foam 15% and 203 on placebo).

You have stated that Study 1403120 meets the criteria for establishing efficacy. See the response to Question 10 regarding some of the characteristics of an adequate and well-controlled study. Your other Phase 2 study (1402140) did not provide evidence of efficacy in the whole study population. Your post-hoc subset analysis of subjects with higher baseline lesion counts is not adequate for providing evidence of efficacy. As noted above in the answer to Question #10, the adequacy of study 1403120 is yet to be determined. It is unlikely that Study 1403120, even if it were determined to be an adequate and well controlled study, would meet the criteria for a single study submission, including robust statistical findings and consistency in findings across subgroups and centers. You will need to submit two adequate and well controlled studies to support your application for approval.

Study 1402140 enrolled 41 subjects in the active arm. Study 1403120 enrolled 198 subjects in the active arm of which 177 completed the study. Study 1401843 (your phase 1 PK study) enrolled 24 subjects. Your current database does not appear to be adequate to inform on the safety of your product.

Meeting Discussion:
The sponsor stated that they are considering submission of a protocol for a Special Protocol Assessment, possibly by the end of the year.

<u>Administrative Comments</u>

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of

protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

6. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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/s/

STANKA KUKICH
11/18/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 77,516

Intendis, Inc.
Attention: Elena Serbinova, Ph.D., RAC
Director, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Pine Brook, NJ 07058-1000

Dear Dr. Serbinova:

Please refer to your Investigational New Drug Application (IND) file for Azelaic Acid, 15% Foam for the treatment of (b) (4) rosacea.

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2009. The purpose of the meeting was to discuss the questions outlined in your briefing document, dated May 8, 2009.

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

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 10, 2009
TIME: 9:00AM
LOCATION: WO, Bldg 22, Room 1313
APPLICATION: IND 77,516
DRUG NAME: Azelaic Acid 15% Foam
SPONSOR: Intendis, Inc.
TYPE OF MEETING: Guidance Meeting

MEETING CHAIR: Susan J. Walker, M.D., F.A.A.D.

MEETING RECORDER: Catherine Carr, MSc.

FDA ATTENDEES (Title and Office/Division)**:**

Susan Walker, M.D., Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Jane Liedtka, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Catherine Carr, M.S., Regulatory Health Project Manager, DDDP
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III
Dennis Bashaw, Pharm.D., Director, DCP III
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPMA II, Branch III
Yubing Tang, Product Quality Reviewer, DPMA II, Branch III

EXTERNAL CONSTITUENT ATTENDEES:

Ulrike Ebert, M.D., Clinical Development, INTENDIS GmbH
Silke Freihammer, Regulatory Affairs, INTENDIS GmbH
Clemens Guenther, Ph.D., Preclinical Development, INTENDIS GmbH
Claudia Hartisch, Ph.D., Project Management, INTENDIS GmbH
Timm Schmidt, Ph.D., Pharmaceutical Development, INTENDIS GmbH
Elena Serbinova, Ph.D., RAC, Regulatory Affairs, INTENDIS Inc.
Gerald Staedtler, Clinical Statistician, INTENDIS GmbH
Eugene OKeefe, M.D., INTENDIS GmbH

BACKGROUND:

The sponsor submitted a briefing document, dated May 8, 2009, which included background information and questions for discussion. Preliminary responses were sent to the sponsor on June 9, 2009.

DISCUSSION POINTS:

The Agency asked the sponsor to clarify the purpose for pursuing development of this product based on the data provided in the briefing package. The Agency noted that the product has not shown even a trend toward treatment effect compared to vehicle. Prior to agreeing to Phase 3 studies or reviewing an SPA, the Agency would like to have information that supports a Phase 3 program. Adequate information would include data showing a treatment effect to inform agreements pursuant to a successful clinical developmental program.

The sponsor stated that they have a successful franchise for their gel product and would like to extend the franchise in the U.S., as the gel product is their only U.S. marketed product. They also stated that based upon consumer research, patients like foam products so they would like to develop the foam product as a "line extension". (b) (4)

The Agency informed the sponsor that this meeting would be considered a Guidance Meeting as the sponsor has not provided adequate information to provide a basis for the Agency to reach Phase 3 agreements with the sponsor.

The sponsor stated that they understand the risk of proceeding to Phase 3 clinical trial.

Chemistry, Manufacturing and Controls:

Question 1:

Does the Division agree on the upgraded specification for drug product release and the upgraded drug product shelf specification?

Response:

No, we do not agree.

Please further upgrade drug product specification for Phase 3 development for the following:

1. Add a test to stability specification to evaluate potential (b) (4) . The test can be a simple visual examination on the physical appearance (b) (4) .

2. The acceptance criterion for (b) (4) should be further upgraded by reporting a percentage of (b) (4) present in the formulation instead of the current criterion of "(b) (4)

3. The acceptance criteria of particle size should be further upgraded to include (1) a notion on agglomeration, and (2) a numeric number (b) (4)

4. The acceptance criteria of degradation product should be further upgraded from "report" to quantitative limits for specified, unspecified and total degradants/impurities. Please structure the specification in compliance with **ICH Guideline Q3B**: ***Impurities in New Drug Products***.

Question 2:

Extractable study on container compounds in contact with the formulation during storage revealed a number of extracted substances. Critical components will be defined and monitored if detected as leachables during storage according to argumentation provided in the Briefing Documentation. Does the Agency agree?

Response:

We concur with your approach in principle. The adequacy of a leachable study to support NDA is a review issue. Please refer to **FDA's Guidance for Industry**: ***Container Closure Systems for Packaging Human Drugs and Biologics*** for specific guidance.

Question 3:

Method development and validation of the test for (b) (4) during storage showed that the (b) (4) Given this finding, does the Agency agree to terminate the stability testing (b) (4)?

Response:

No we do not agree. (b) (4) needs to be verified in the registration stability studies.

Other CMC comments:

1. If the proposed to-be-marketed packaging configurations involve various can sizes in addition to fill sizes, you should include both can and fill sizes as factors in designing registration stability study protocol. Please refer to the ICH Guideline **Q1D:** ***Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*** for detail information.

2. The passing of *Antimicrobial Effectiveness Testing* (USP <51>) needs to be demonstrated in at least one registration stability batch throughout the expiration dating period of the drug product.

3. We note the use of "conform" in multiple places of the stability tables. Report the actual readings for stability results instead of "pass" or "conform".

4. (b) (4)

Meeting Discussion:

The Agency acknowledged receipt of the foam dosage formulation samples provided via mail by the sponsor.

Pharmacology/Toxicology:

Question 4:

Intendis has the right of reference to the complete set of toxicology and pharmacology studies for earlier approved formulations of AzA, and has performed several bridging studies (including a 3 month minipig study) with the new foam formulation. Does the Division concur that the nonclinical studies conducted with AzA drug substance, those with earlier formulations, and the ones with the pre-foam emulsion are sufficient, and that no additional studies are needed to support the NDA filing for AzA Foam, 15%?

Response:

The overall nonclinical toxicology study package available for azelaic acid appears acceptable to support NDA filing for azelaic acid foam provided that the issues raised in the responses to the following two questions are adequately addressed prior to a NDA submission for azelaic acid foam.

Question 5:

AzA drug substance was negative for carcinogenic potential in the Tg.AC mice, and all excipients of the AzA Foam, 15% formulation are used in previously FDA approved dermal formulation. AzA is an endogenously occurring compound. The Sponsor anticipates in analogy to Finacea® 15% Gel that human systemic levels of AzA are not increased above their endogenous levels following repeated dosing with our topical foam products. Intendis believes that there is no need for additional long-term carcinogenicity studies with the AzA Foam, 15%. Does the Agency concur?

Response:

We acknowledge receipt of a labeling supplement for Finacea (azelaic acid) gel, 15% (SLR 005) on April 6, 2009 that incorporates the results of the Tg.AC mouse assay conducted with azelaic acid gel. The adequacy of this labeling supplement is currently under review.

You are reminded that the Exec CAC concluded on September 11, 2007 that the Tg.AC mouse assay conducted with azelaic acid gel was negative for female mice and positive for male mice, noting a statistically significant increase in the incidence of males with papillomas in the vehicle and high dose groups compared to untreated control. The Exec CAC noted that there was no statistically significant difference in the incidence of males with papillomas in the vehicle and

high dose groups which suggested that the positive effect may be due to the vehicle only. There was no statistically significant increase in the incidence of treated females with papillomas compared to vehicle or untreated females.

We have concerns about the positive response noted in male mice in the Tg.AC mouse assay. A final determination for the possible need for additional dermal carcinogenicity studies conducted with either the azelaic acid gel or azelaic acid foam formulation has not been reached at this point in time.

Question 6:

The Sponsor would like to follow-up on nonclinical question 3 of the pre-IND meeting from July 17, 2007 where no conclusions could be drawn regarding the need for photoco-carcinogenicity studies (b) (4)

(b) (4)

Response:

We can not provide agreement that no further investigations for the photoco-carcinogenic potential associated with azelaic acid foam, 15% would be needed, at this time. (b) (4)

Addendum to Minutes

(b) (4)

In addition, it has been determined after consultation with the Pharmacology/Toxicology Associate Director that a 2 year dermal mouse carcinogenicity study should be conducted as a post-marketing commitment for azelaic acid foam (b) (4) *In addition, you should include a time line for initiation of the dermal carcinogenicity study and submission of the final study report with the NDA for the azelaic acid foam formulation.*

Clinical Pharmacology:

Question 7:

Does the assessment of systemic exposure provided in Section 4.4.1 and in the study synopsis included in Section 4.4.3 of the Briefing Documentation meet the FDA requirements as specified in the official pre-IND meeting minutes dated August 2, 2007 and the Clinical Pharmacology Reviewer's comments regarding IND 77,516 for Azelaic acid dated on May 30, 2008?

Response:

No, while this application is a 505(b)(1) application, as you are relying on data from your previously approved product vis a vis pharm/tox data, a single arm trial is insufficient for assessment of bioavailability. In such a situation, much as with a 505(b)(2) application, you would need to utilize a randomized cross-over design study using your currently approved product (dose per current labeling) as the "reference" product. This would allow us to link the two formulations and allow for the use of data relative to the other formulation of Azelaic Acid. In addition we also recommend that the sample size be increased from 12-15 to 15-20 due to the expected effects of dietary intake. An increased sample size would better inform the variability due to dietary considerations. Also we would encourage the inclusion of a 6 hour sampling time point at steady-state (day 10).

As for the use of a vehicle control arm and the need for a double-blind, a vehicle control arm would be of limited benefit here for assessment of topical safety as the numbers of subjects employed would be too few to allow for safety/tolerability conclusions to be drawn. As for the double-blind nature of the trial, as pk endpoints are objective rather than subjective, there is not a compelling need to utilize a double-blind design here.

Meeting Discussion:

The Agency stated that a parallel trial or a cross over study design could be used for this trial. The protocol should include a rationale for the wash out period and how the baseline was established.

Clinical:

Question 8:

Does the Agency concur that the results obtained from the Phase 2 study together with the available clinical data from AzA Gel, 15% (NDA 21-470) provide an appropriate basis for the design of the Phase 3 clinical studies?

Response:

We are concerned that no relevant difference in effectiveness was seen for AzA Foam, 15% and its vehicle. You have identified a subgroup of subjects (>14 lesions at baseline) that showed a slightly larger effect. However, the observed treatment effect for the absolute reduction in lesions in the subgroup (2.3) was not much better than in the whole population (0.9). Differences between the results in percent reduction and absolute reduction in lesions in the more severe subgroup may be due to the small number of subjects and the influence of a few outliers. Consequently the results might not be generalizable to the broader study population. When subgroups of interest are not pre-specified, the 'most favorable' subgroup findings from one study may not always be replicated in future studies.

Before committing to Phase 3 studies, we recommend additional exploration in Phase 2 to identify the best dose and patient population. The phase 2 study compared AzA Foam 15% to its vehicle. Ideally in Phases 1 and 2, dose ranging studies should be performed to investigate safety and efficacy of the drug product in the intended population at ranges in concentration, frequency, and duration of therapy which bracket response and allow determination of the dose most likely to succeed in Phase 3. You selected the dose of 15% applied twice daily based on the precedent of topical azelaic acid formulations currently approved and marketed in the U.S. (gel and cream) and the known safety and efficacy in the concentration range of 15% to 20% for the gel and cream formulations. In the absence of Phase 2 dose ranging studies with your formulation (foam), you take risk in presuming that your proposed dosage (15% concentration and twice daily application) is the most optimal with the new dosage form.

Question 9:

Does the Agency agree with the Phase 3 program while the discussion of the Phase 3 protocol will be subject to the SPA?

Response:

No, we do not agree. We recommend additional Phase 2 studies before proceeding to Phase 3 to identify the most appropriate dose and patient population (see response to Question 8). It is premature to provide detailed comments on Phase 3 protocols at this time; however we have the following general comments on study exclusion criteria and endpoints.

1. (b) (4) . We continue to recommend using the co-primary efficacy endpoints of clear/minimal on the IGA (when all subjects will have a baseline IGA of

moderate or severe), and *absolute* change from baseline in inflammatory lesions (see response to Question 12). Percent reduction in lesions can be evaluated as a secondary endpoint.

2. The current IGA Scale lists [redacted] (b) (4) under the category clear. The category clear should represent total absence of disease [redacted] (b) (4). Please revise the IGA Scale appropriately.

3. You propose "response rate" as a secondary efficacy variable. You propose

   [redacted] (b) (4)

   We do not agree with [redacted] (b) (4)

4. We do not agree with [redacted] (b) (4) .

5. Please add Minocycline to the list of systemic medications under the exclusion criteria.

<u>*Meeting Discussion:*</u>

The sponsor indicated that they do not intend to include [redacted] (b) (4) *in the labeling.*

The Agency indicated that with the close treatment response of the active and the vehicle, the sponsor should consider the active ingredient(s) in their product and whether the combination drug policy would be applicable.

Question 10:

Does the Agency concur that the Phase 2 clinical study performed, together with the planned Phase 1 and Phase 3 studies will be sufficient for the approval and marketing of the new product?

Response:

In general, the framework that you provide, dermal safety studies, 2 multicenter, randomized, vehicle-controlled trials and one pk maximum use study may be acceptable to support the filing of an NDA for your topical drug product. Approval of a marketing application, however, depends on the demonstration of safety and efficacy of your topical drug product in an appropriate population. Note that in order to make the best use of Phase 3 resources, we recommend additional Phase 2 studies to identify the most appropriate dose and patient population.

Given the chronic nature of the indication acne rosacea, you will need to demonstrate the safety of long term use of your product. Please consult the E1A Guideline for Industry in the development of your chronic use product. The number of subjects needed to demonstrate safety may be substantially higher than the number of subjects needed to demonstrate efficacy.

In the absence of a thorough QT/QTc study demonstrating no effect on cardiac repolarization (or a definitive PK study demonstrating no systemic exposure under maximum use conditions in diseased subjects), please perform ECG monitoring to ensure subject safety, at a minimum at baseline, when drug concentration has reached steady state, and at end of treatment. Please consult the Guidance for Industry ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Anti-arrhythmic Drugs.

Question 11:

Does the Agency concur to the 5-point Investigators Global Assessment (IGA) score for the Phase 3 clinical studies, although a 7-point IGA score was used in the Phase 2 clinical trial?

Response:

As noted under response to Question #9, please remove (b) (4) from the category of (b) (4). Final discussion of scales should occur at an EOP2 meeting and be presented in a SPA.

Question 12:

Does the Agency concur that (b) (4) can be used as a primary variable (absolute reduction will be used as a supporting endpoint)?

Response:

The Division once again recommends using absolute change in lesion count as a co-primary endpoint (b) (4). The reason for this recommendation is that the absolute

change is expected to have better distributional properties (more symmetry and less influenced by extreme outliers [redacted] (b) (4)).

Question 13:

Does the Agency concur that no pediatric study with AzA Foam, 15% in [redacted] (b) (4) rosacea is required?

Response:

Yes, please submit a waiver request to either the IND or the NDA.

Meeting Discussion:

The sponsor stated that they are considering submission as a 505(b)(2) and requested Agency comment. The Agency recommended that they submit their proposal for review.

Project Management:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

3. You are encouraged to request an End of Phase 2 Meeting and a Pre-NDA Meeting at the appropriate time.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 77516	INTENDIS INC	AZELAIC ACID 15%

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

/s/

SUSAN J WALKER
07/08/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 77,516

Intendis, Inc.
Attention: Elena Serbinova, PhD, RAC
Director, Drug Regulatory Affairs
PO Box 1000
Pine Brook, NJ 07058

Dear Dr. Serbinova:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Azelaic Acid Foam, 15%.

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2007. The purpose of the meeting was to obtain the Agency's agreement regarding the overall development strategy for the foam formulation of Azelaic Acid for the treatment of (b) (4) rosacea.

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

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Division Deputy Director
Division of Dermatologic and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 17, 2007 **Time:** 2:00

Location: WO/22 Room 1315 **Meeting ID:** 21863

Topic: Guidance Meeting for Azelaic Acid Foam, 15% for the treatment of [redacted] (b) (4) rosacea

Subject: Pre-IND meeting

Sponsor: Intendis, Inc.

Meeting Chair: Stanka Kukich, M.D./Deputy Division Director, DDDP

Meeting Recorder: Catherine Carr/Regulatory Project Manager, DDDP

FDA Attendees:

Stanka Kukich, M.D./Deputy Division Director, DDDP
Jill Lindstrom, M.D./Team Leader, Clinical, DDDP, HFD-540
Patricia Brown, M.D./Clinical Reviewer, DDDP, HFD-540
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP, HFD-540
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDP, HFD-540
Shulin Ding, Ph.D./ Pharmaceutical Assessment Lead, ONDQA
Kathleen Fritsch, Ph.D./Biostatistian, DBIII, HFD-725
Tien-Mien Chen, Ph.D./Pharmacology Reviewer, DDDP
Catherine Carr, M.S./Regulatory Project Manager, DDDP, HFD-540
Victoria Lutwak/Regulatory Project Manager, DDDP, HFD-540
Tamika White, MPH/Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Intendis, Inc.

Claudia Hartisch; Ph.D., Project Management, Intendis GmbH
Eugene O'Keefe; M.D., Head Development, Intendis GmbH
Elena Serbinova; Ph.D., Director Drug Regulatory Affairs, Intendis Inc.
Hartwig Steckel; Ph.D., Head Pharmaceutical Development, Intendis GmbH
Klaus Graupe; M.D., Ph.D., Clinical Development, Intendis GmbH
Sandra Johanssen; DVM, Ph.D., Preclinical Development, Intendis GmbH
Guenther Clemens Ph.D., Head Nonclinical Development, Intendis GmbH
Susanne Schertling DVM, Head Regulatory Affairs, Intendis GmbH

Purpose:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted June 12, 2007) provides background and questions for discussion. The sponsor requests input from the Agency on the CMC, clinical, and non-clinical issues outlined in the briefing book.

Chemistry, Manufacturing and Controls:

Question 1:

Does the Agency concur that all excipients used can be regarded as safe and qualified for topical administration?

Response:

Yes, we concur.

The Division notes that the concentrations of the excipients in the proposed azelaic acid 15% foam formulation are below what have been used in previously approved chronic use drug products. Therefore, the concentration of each excipient proposed for the azelaic acid 15% foam is acceptable from a pharmacological/toxicological perspective.

Question 2:

Does the Agency concur with the use of formulation where the active drug substance is substituted by water as a vehicle in the phase 1 and phase 3 clinical studies?

Response:

Because the concentration of azelaic acid in the formulation is quite high, we are concerned with a potential change in consistency of the foam (b) (4) . We would concur if you can show a comparable appearance and consistency between the active and the placebo formulations.

Question 3:

Does the Agency concur with the proposed quality specification for dimethyl isosorbide?

Response:

Yes, we concur.

Question 4:

Does the Agency concur with the proposed stability program until NDA submission, validation and commercial supply?

Response:

No, we do not concur. We have the following recommendations: (1) the product should be stored in both upright and inverted positions, (2) potential extractables should be monitored, and (3) no change in (b) (4) should be verified. We may raise other questions during NDA review.

Meeting Discussion:

The proposal for registration stability protocol is consistent with our recommendation. The stability protocol for post-approval and validation lots is a review issue.

The Agency commented that the extractable results from the screening study using a pseudo formulation needs to be verified in the registration stability study.

The Agency commented that the need for a (b) (4) specification is a review issue. Sponsor should monitor (b) (4) in registration stability batch.

Question 5:

Does the Agency concur with the proposed packaging materials?

Response:

The concurrence with the proposed packaging material is a review issue.

Additional CMC Comments:

a. Please identify all animal sourced excipients.
b. Please clarify the function of propylene glycol in the formulation.
c. Please add delivered amount to the drug product release specification.
d. Please add delivered amount, (b) (4) and product/packaging interaction to the drug product shelf specification.
e. The acceptance criteria for the test on appearance should be upgraded by the addition of a description on the color and appearance (b) (4)

Meeting Discussion:

The Agency indicated that the (b) (4) change needs to be verified in the stability protocol.

The Agency indicated that potential discoloration of the formulation is a concern.

Sponsor will submit samples for the reviewers to see as well as data sets.

Pharmacology/Toxicology:

Question 1:

Does the Agency concur that the nonclinical studies planned with the pre-foam emulsion, together with the other nonclinical data available from NDA 21-470 and the literature will be sufficient to support the marketing approval of azelaic acid 15% foam?

Response:

The nonclinical studies that the sponsor has proposed for azelaic acid 15% foam in the briefing package together with the nonclinical data contained in NDA 21-470 for azelaic gel 15% gel and the literature may be acceptable to support the safety of azelaic acid 15% foam. The determination of the adequacy of the conducted nonclinical studies to support marketing approval will be determined after review of the final study reports.

It is acceptable to conduct the nonclinical studies with azelaic acid 15% foam as a pre-foam emulsion minus the propellant. If azelaic acid 15% foam is a primary skin irritant in rabbits, then it will be labeled as an ocular irritant as well. However, if azelaic acid 15% foam is not a primary skin irritant in rabbits, then conduct of an ocular irritation study in rabbits should be performed with azelaic acid 15% foam. The need for a nonclinical photoirritation study is waived since no absorption was noted in the UVB/UVA/VIS spectrum (290 – 700 nm) for either azelaic acid or azelaic acid 15% foam.

The adequacy of the proposed design for the 3 month dermal minipig toxicology study to be conducted with azelaic acid 15% foam is addressed under nonclinical question 2. (b) (4) The possibility that the dermal carcinogenicity study conducted in Tg.AC mice with azelaic acid 15% gel can be used to support the safety of azelaic acid 15% foam is addressed under nonclinical question 3.

Question 2:

Does the Agency concur with the proposed design of the 3 month minipig study?

Response:

No. The design of repeat dose dermal toxicology studies should keep the treatment area constant (i.e., 10% body surface area) and vary the concentration of the active in the clinical formulation for the three dose groups. The high dose group should be the maximum feasible dose (i.e., maximum feasible concentration and maximum feasible volume), if tolerated. Each dose group should incorporate use of at least 4 animals/sex/dose. Dermal toxicology studies should include complete clinical pathology, histopathology and toxicokinetic analysis. The sponsor's proposal for incorporation of an untreated and vehicle control group in the 3 month dermal minipig toxicology study is common practice for repeat dose dermal toxicology studies.

Question 3:

Does the Agency concur, that based on the rationale provided, no carcinogenicity/photo-co-carcinogenicity studies with azelaic acid 15% foam need to be performed?

Response:

No. (b) (4) .

(b) (4)

Clinical:

Question 1:

The Sponsor seeks the Agency's concurrence that conducting the three phase 1 studies in Europe is acceptable.

Response:

Please clarify whether the three Phase 1 studies described under section 5.3.4 of the sponsor's Pre-IND/End of Phase 2 Information Package will be conducted under the IND. If they are to be conducted under the IND, protocols should be submitted to the IND prior to initiation. If they are not to be conducted under the IND, the sponsor is advised that the acceptability of foreign clinical studies not conducted under an IND is addressed in 21 CFR 312.120. The sponsor is also referred to the Guidance Documents entitled "Acceptance of Foreign Clinical Studies" and "Ethnic Factors in the Acceptability of Foreign Clinical Data."

Additionally, we have the following comments on the proposed Phase 1 PK study.

The proposed human pharmacokinetics (systemic absorption) study No. 1401843 (p.100/253) is acceptable provided the following revisions/considerations are incorporated as follows:

Instead of employing healthy volunteers, you should enroll patients with papulopustular rosacea at the upper range of disease severity as anticipated in both your clinical trials and (b) (4).

It should be noted that the to-be-marketed 15% foam formulation should be used and the trial should attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

a. Frequency of dosing
b. Duration of dosing
c. Use of highest proposed strength
d. Total involved surface area to be treated at one time
e. Amount applied per square centimeter
f. Method of application/site preparation

Additionally, the assay methods should be sensitive for the purpose.

Depending on the study results on systemic exposure, we may recommend additional clinical pharmacology studies.

Meeting Discussion:

The Agency indicated that it is acceptable to use the pre-foam solution in the dermal safety studies as long as this is the same as the final-to-be marketed formulation less the propellant.

Question 2:

The Sponsor seeks the Agency's concurence that no clinical photoirritation / photoallergy studies are required for azelaic acid 15% foam.

Response:

The sponsor's briefing package includes absorption spectra for the drug substance and for the drug product. Because there is no absorption in the UVB, UVA, or visible light spectrum, the need for clinical photoirritation and photoallergy studies is waived.

Question 3:

Does the Agency agree that no additional phase 2 studies will be necessary for azelaic acid 15% foam?

Response:

Ideally in Phases 1 and 2, dose ranging studies should be performed to investigate safety and efficacy of the drug product in the intended population at ranges in concentration, frequency, and duration of therapy which bracket response and allow determination of the dose most likely to succeed in Phase 3. In the early phases of drug development, it is also important to study PK parameters, refine endpoints, and explore treatment effects for powering Phase 3 studies.

The sponsor selected the dose of 15% applied twice daily based on the precedent of topical azelaic acid formulations currently approved and marketed in the U.S. (gel and cream) and the known safety and efficacy in the concentration range of 15% to 20%. In the absence of Phase 2 dose ranging studies with the sponsor's formulation (foam), the sponsor takes the risk in presuming that their proposed dosage (15% concentration and twice daily application) is the most optimal with the new dosage form.

Although previous studies of azelaic acid gel have been conducted, using efficacy estimates from one study of azelaic acid gel to power the proposed Phase 3 studies could lead to underpowered studies. Different vehicles can have substantive impact on treatment effects and additionally, estimated treatment effects can also vary from study to study even when they are conducted under similar conditions. The Agency recommends conducting a small Phase 2 study to preliminarily assess the impact of the proposed vehicle before proceeding to Phase 3 trials. The Agency also recommends taking potential study-to-study variability into account when identifying estimates for calculating sample sizes.

The sponsor is proposing a Phase 1 pharmacokinetic study; however, the subjects will be healthy volunteers. To study systemic exposure, a PK study in subjects with diseased skin under conditions of maximal use and using the final to-be-marketed formulation is needed.

Meeting Discussion:

The Agency indicated that Phase 2 studies can generally be small and do not need to demonstrate statistical significance.

Sponsor agreed to submit a protocol for a Phase 2 dose-ranging study with the IND.

Sponsor inquired whether the Phase 1 studies on irritancy, sensitization, and pharmacokinetics could be conducted simultaneously with the Phase 3 studies.

The Agency agreed.

The Agency indicated that sponsor should explore erythema completely in Phase 2 to adequately provide data for Phase 3 study discussions.

Sponsor indicated that erythema will be evaluated in the Phase 2 protocol.

Question 4:

Does the Agency concur that the performance of two adequate and well-controlled phase 3 trials will be sufficient to support efficacy and safety for NDA 505(b)(1) filing for the azelaic acid 15% foam formulation?

Response:

It would be appropriate to discuss the specifics of a Phase 3 program at an End-of- Phase 2 meeting and of an NDA at a Pre-NDA meeting.

The sponsor is encouraged to conduct Phase 2 study(ies) to investigate dose ranging and treatment effect. Additionally PK data will be needed from the study of diseased subjects under conditions of maximal use. Please also see response to question 3.

Question 5:

Does the Agency concur with the general phase 3 clinical study design? Details will be discussed during the SPA meeting.

Response:

The Agency has concerns regarding the lack of Phase 2 data. However, we have the following preliminary comments on your submitted protocol.

The overall design of the trials as multi-center, double-blind, randomized, parallel group comparisons may be acceptable. The general scheme of evaluation at 4 week intervals with a total duration of 12 weeks is similar to that of previous studies for this type of indication.

a. The Agency recommends using absolute reduction in inflammatory lesions as the primary endpoint, (b) (4)

b. The Agency recommends using a 5-point IGA rather than a 7-point IGA. (b) (4)

   Subjects with IGA scores of clear or minimal should also have at least 2 grades reduction from baseline to be considered successes. The inclusion criteria should also specify acceptable baseline scores for the IGA.

c. (b) (4)

d. Washout periods should be sufficient to ensure that prior treatments will not impact baseline disease assessment.

e. Safety assessment is to consist of recording of AEs and SAEs and the patient's opinion on local tolerability at the end of therapy. Please include active assessment for local cutaneous reactions and hypopigmentation.

Project Management:

1. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.

2. Your pre-IND has been assigned #77,516. Please reference this number on all submissions and correspondence. Please note, studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).

3. The Sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

4. The sponsor is encouraged to request an End of Phase 2 Meeting at the appropriate time.

5. Per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

6. The sponsor is reminded that all new NDAs/BLAs and efficacy supplements submitted on or after June 30, 2006 must include content and format of prescribing information based on the new Physicians Labeling Rule at the time of submission (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details)

Action Items:

Item	Responsible Person	Due Date
1. Sponsor will request separate End of Phase 2 meeting and Special Protocol Assessment. No timeframe provided.		

Minutes Preparer: _____
Catherine Carr/Regulatory Project Manager DDDP

Chair Concurrence: _____
Stanka Kukich, M.D./Division /Deputy Director, DDDP

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

/s/

Catherine Carr
7/25/2007 02:55:06 PM
CSO

Stanka Kukich
7/25/2007 03:45:57 PM
MEDICAL OFFICER