CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207154Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207154 SUPPL # NA HFD # 540

Trade Name Aczone

Generic Name dapsone gel, 7.5%

Applicant Name Allergan, Inc.

Approval Date, If Known February 24, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ 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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3

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

YES ☐ NO ☒

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

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).

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

NA

(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:

NA

(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:

NA

(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:

1. 225678-006: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris (Phase 3)

2. 225678-007: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris (Phase 3)

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 (225678-006) YES ☐ NO ☒

Investigation #2 (225678-007) 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:

NA

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 (225678-006) YES ☐ NO ☒

Investigation #2 (225678-007) 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"):

1. 225678-006: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris (Phase 3)

2. 225678-007: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris (Phase 3)

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 (225678-006) !
!
IND # 054440 YES ☒ ! NO ☐
! Explain:

Investigation #2 (225678-007) !
!
IND # 054440 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: Strother D. Dixon
Title: Sr. Regulatory Project Manager
Date: January XX, 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/

CRISTINA Petruccelli Attinello
02/24/2016

KENDALL A MARCUS
02/24/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207154 BLA # NA	NDA Supplement # NA BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: ACZONE Established/Proper Name: dapsone Dosage Form: Gel, 7.5%		Applicant: Allergan, Inc. Agent for Applicant (if applicable): NA
RPM: Strother D. Dixon		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 February 28, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

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

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

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

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

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

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

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

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

Comments:

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AP, 2-24-16
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)*	7/18/15 7/10/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 6/29/15 DMEPA: ☐ None 2/12/16, 11/30/15 DMPP/PLT (DRISK): ☐ None 12/10/15 OPDP: ☐ None 12/15/15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	7/24/15 ☒ 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 ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC December 2, 2015 If PeRC review not necessary, explain: NA	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)*	N = 7
❖ 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)	September 28, 2015 November 23, 2015
❖ 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 11/19/14
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 8/28/13
• 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)*	NA
❖ 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 2-17-16
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 1-27-16
PMR/PMC Development Templates *(indicate total number)*	☐ None 1
Clinical	
❖ Clinical Reviews	

• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review Same as CDTL
• Clinical review(s) *(indicate date for each review)*	1-21-16
• 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)*	pg. 21
❖ 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)*	N/A N/A ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested N = 4
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 1/14/16
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 1/11/16
❖ 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 11/12/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 2/17/16, 1/13/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None NA
❖ 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)*	1/13/16
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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

/s/

CRISTINA Petruccelli Attinello
02/26/2016

Attinello, Cristina

From: Attinello, Cristina
Sent: Monday, February 22, 2016 8:19 AM
To: 'Mccumber_Jeremy'
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager
Attachments: draft-labeling-text 2 22 16.docx

Hello,

We have identified two additional, small revisions in the draft PI. Please see attached and return by noon tomorrow.

Please confirm receipt of this email and its attachment.

Thanks,

Cristina

From: Attinello, Cristina
Sent: Tuesday, February 16, 2016 3:09 PM
To: 'Mccumber_Jeremy'
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi,

Nothing needed at present.

Thanks,

Cristina

From: Mccumber_Jeremy [mailto:Mccumber_Jeremy@Allergan.com]
Sent: Tuesday, February 16, 2016 2:12 PM
To: Attinello, Cristina
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina,
I just wanted to reach out and ask if you had any updates or needed any additional information regarding the pending Aczone 7.5% application? Please let me know if I can be of any assistance.

Looking forward to hearing from you.

Best regards,
Jeremy

From: Attinello, Cristina [mailto:Cristina.Attinello@fda.hhs.gov]
Sent: Friday, February 12, 2016 4:43 AM
To: Mccumber_Jeremy
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi,

Confirming receipt of both.

Thanks,

Cristina

From: Mccumber_Jeremy [mailto:Mccumber_Jeremy@Allergan.com]
Sent: Thursday, February 11, 2016 8:07 PM
To: Attinello, Cristina
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina,
The UPSI and Carton/Container updates were submitted to NDA 207154 today, February 11, 2016 as Sequence 0013. Can you please confirm receipt of the submission and this email?

Please feel free to contact me by phone or email if you have any questions.

Best regards,
Jeremy

From: Mccumber_Jeremy
Sent: Wednesday, February 10, 2016 10:48 AM
To: 'Attinello, Cristina'
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina,
I'm confirming receipt of your email and the attachment. We're working on the changes and should be able to submit them tomorrow. Note the container label for the Sample does not contain this language and will not be re-submitted.

Best regards,
Jeremy

From: Attinello, Cristina [mailto:Cristina.Attinello@fda.hhs.gov]
Sent: Wednesday, February 10, 2016 9:19 AM
To: Mccumber_Jeremy
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hello,

Please see the attached. Please return by COB tomorrow, if possible.

Please address the following comment. Please return labels by COB tomorrow, if possible.

- Remove the statement [redacted] (b) (4) " from the "Storage" description on all container/carton labels.

Please confirm receipt of this email and attachment.

Thanks,

Cristina

From: Attinello, Cristina
Sent: Friday, February 05, 2016 9:16 AM
To: 'Mccumber_Jeremy'
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi,

Confirming receipt of both.

Thanks,

Cristina

From: Mccumber_Jeremy [mailto:Mccumber_Jeremy@Allergan.com]
Sent: Thursday, February 04, 2016 5:30 PM
To: Attinello, Cristina
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina,
As mentioned in the email below, Allergan's response to the proposed PMR and updates to the UPSI/Carton/Container labels were submitted to the NDA today, February 4, 2016 (Sequence Number 0012).

Can you please confirm receipt of the submission and this email?

Best regards,
Jeremy

From: Mccumber_Jeremy
Sent: Wednesday, February 03, 2016 4:54 PM
To: 'Attinello, Cristina'
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina,
Thank you for the PMR and the additional comments on the UPSI and the Carton/Container labels. Our team is working to ensure a submission goes in by Friday. There is a slight chance it may go in Thursday. I will update you tomorrow with a final submission date.

Best regards,
Jeremy

From: Attinello, Cristina [mailto:Cristina.Attinello@fda.hhs.gov]
Sent: Wednesday, February 03, 2016 11:19 AM
To: Mccumber_Jeremy
Cc: Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hello,

Please see the attached draft PI and PPI, with edits. Please review and return by COB Friday.

With regard to carton and container labels:

1. On the side panel, increase the prominence of the usual dosage statement by increasing the font size and possibly using color to improve readability of pertinent information. Consider moving the statement to above the warning statement as currently presented the information is not prominent.

   We note you made the above change on the carton labeling, but did not make the change on the container label. Relocate the usual dosage statement on the container label for consistency.

2. Also, the pdf's most recently submitted for the carton and container labels were mislabeled. You labeled the container label pdf as the carton, and vice versa. Provide appropriate labels in your next response.

Please submit carton and container labels, correctly labeled, by COB Friday.

Please review and provide concurrence on the following language and schedule:

Conduct an open-label study to assess safety, pharmacokinetics, and treatment effect of ACZONE (dapsone) Gel, 7.5% in 100 pediatric subjects aged 9 years to 11 years 11 months with acne vulgaris. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

Final Protocol Submission:	06/2016
Study Completion:	03/2019
Final Report Submission:	11/2019

Please state your concurrence in a submission to the NDA, by COB Friday.

Thanks,

Cristina

From: Attinello, Cristina
Sent: Tuesday, February 02, 2016 9:51 AM
To: 'Mccumber_Jeremy'
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Received.

From: Mccumber_Jeremy [mailto:Mccumber_Jeremy@Allergan.com]
Sent: Monday, February 01, 2016 4:51 PM
To: Attinello, Cristina
Cc: Gould, Barbara; Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina,
As we are nearing the February 28, 2016 PDUFA action date for NDA 207154, I wanted reach out and make myself available for any questions or information you may need. Please feel free to contact me at any time.

The only outstanding item at this time is Allergan's response/edits to the label that was provided to you on January 21, 2016.

Can you please confirm receipt of this email?

Best regards,
Jeremy
714-246-2343

From: Attinello, Cristina [mailto:Cristina.Attinello@fda.hhs.gov]
Sent: Friday, January 22, 2016 8:23 AM
To: Mccumber_Jeremy
Cc: Gould, Barbara; Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hello,

Confirming receipt of both.

Thanks,

Cristina

From: Mccumber_Jeremy [mailto:Mccumber_Jeremy@Allergan.com]
Sent: Friday, January 22, 2016 11:07 AM
To: Attinello, Cristina
Cc: Gould, Barbara; Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina,
I just wanted to reach out and ensure you received both the email below and the formal submission through the Electronic Gateway (Sequence No. 0011).

Can you please confirm receipt?

Best regards,
Jeremy

From: Mccumber_Jeremy
Sent: Thursday, January 21, 2016 2:01 PM
To: 'Attinello, Cristina'
Cc: Gould, Barbara; Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Cristina/Strother,
Attached is the draft USPI (Clean and Track Changes) with Allergan's comments and edits. The proposed changes to the Carton/Container labels have been implemented and will be provided in the electronic submission scheduled for later today (Sequence 0011). The majority of the proposed changes have been incorporated in the draft USPI and an updated version will be provided in the Sequence as well. As noted in Section 6 - Adverse Reactions of the draft USPI, Allergan would like to clarify the Agency's position regarding the use of treatment-related TEAEs instead of all TEAEs.

The Sequence is scheduled for submission later today and will include both the USPI edits and the updated Carton/Container labels. Please let me know if you are not in receipt of it by tomorrow morning.

As always, feel free to contact me by phone or email should you need anything.

Best regards,

Jeremy

From: Attinello, Cristina [mailto:Cristina.Attinello@fda.hhs.gov]
Sent: Thursday, January 14, 2016 12:04 PM
To: Mccumber_Jeremy
Cc: Gould, Barbara; Dixon, Strother
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hello,

Attached, please find the Agency proposed labeling (Package Insert and Patient Package Insert) for NDA 207154 dapsone gel, 7.5%. Below, please find the recommended changes for the 3 g (sample), 30 g, 60 g and 90 g container and carton labels.

Immediate container labels:

The 30 g, 60 g and 90 g pump labels should be revised to include the following information:

1. Display "Lot:" and "Exp:"
2. Display a barcode to the container label as it is currently not present per 21 CFR 201.25(c)(2).
3. Revise the Storage statement as follows:
   - Store at 20ºC-25ºC (68ºF-77ºF), excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]. Protect from freezing.
4. List ingredients as shown below:
   - Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water.
5. In the drug product title display "%" after the strength and in the same font and size as the established name.

The 3 g sample tube labels should be revised to include the following information:

6. Display "Lot:" and "Exp:"
7. Revise the Storage statement as follows:
   - Store at 20ºC-25ºC (68ºF-77ºF), excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]. Protect from freezing.
8. In the drug product title display "%"after the strength and in the same font and size as the established name.
9. Display appropriate NDC number
10. Include "Manufactured for: and by:" same as pump labels.

Carton labels:

The 8 x 3 g sample tubes, 30 g, 60 g and 90 g pump carton labels should be revised to include the following information:

11. List ingredients as shown below:
    - Each gram of gel contains 75 mg of dapsone, diethylene glycol monoethyl ether, methyl paraben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80 and purified water.
12. Revise the Storage statement as follows:
    - Store at 20ºC-25ºC (68ºF-77ºF), excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]. Protect from freezing.
13. In the drug product title display "%" in the same font and size as the established name.
14. On the side panel, increase the prominence of the usual dosage statement by increasing the font size and possibly using color to improve readability of pertinent information. Consider moving the statement to above the warning statement as currently presented the information is not prominent.

The 8 x 3 g sample tube carton labels should be revised to include the following information:

15. Display "Lot:" and "Exp:"

16. In the drug product title display “%” after the strength and in the same font and size as the established name.
17. Place the dosage information on the carton label of the sample below the net
18. quantity as currently presented the information is not prominent.

Please submit agreed upon labeling to the NDA and provide a courtesy copy of the submission (e.g., labels, 356h and cover letter) to me via email by Thursday, January 21, 2016. If you have additional edits, please convey those in track changes.

Please confirm receipt of this email.

If you require additional information or have questions, please do not hesitate to contact me directly.

Regards,

Cristina Attinello, MPH
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology & Dental Products
White Oak, Bldg. 22, Room 5350
Phone: 301-796-3986
Fax: 301-796-9895

From: Mccumber_Jeremy [mailto:Mccumber_Jeremy@Allergan.com]
Sent: Thursday, January 14, 2016 11:55 AM
To: Dixon, Strother
Cc: Attinello, Cristina; Gould, Barbara
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Thank you, Strother.

From: Dixon, Strother [mailto:Strother.Dixon@fda.hhs.gov]
Sent: Thursday, January 14, 2016 4:27 AM
To: Mccumber_Jeremy
Cc: Attinello, Cristina; Gould, Barbara
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Greetings. Cristina is aware of the PDUFA date and will forward the labeling to you as soon as the review of the labeling is complete.

Best wishes,
Strother

From: Mccumber_Jeremy [mailto:Mccumber_Jeremy@Allergan.com]
Sent: Wednesday, January 13, 2016 6:46 PM
To: Dixon, Strother
Cc: Attinello, Cristina; Gould, Barbara
Subject: RE: NDA 207154 - Temporary Change in Regulatory Project Manager

Hi Strother,
Thank you for letting me know. It’s been a pleasure working with you on this application. I hope all is well.

Cristina,
I look forward to working together. As you know, the PDUFA date for this application is February 28th. Please feel free to contact me either by email or by phone should you need anything from me. My contact information is provided below. Our team is waiting and ready for any requests you may have. Do you have an estimate on when we may receive the Agency's comments on the proposed label?

Best regards,
Jeremy

Jeremy McCumber, M.S.
Director, Global Regulatory Affairs
Ph: 714-246-2343

From: Dixon, Strother [mailto:Strother.Dixon@fda.hhs.gov]
Sent: Wednesday, January 13, 2016 3:22 PM
To: Mccumber_Jeremy
Cc: Attinello, Cristina; Gould, Barbara
Subject: NDA 207154 - Temporary Change in Regulatory Project Manager

Greetings. I will be going on leave on January 22, 2016, therefore, NDA 207154 will be temporarily managed by Cristina Attinello. Please send communications to her and cc me until further notice.

Thank you in advance.

Best wishes,
Strother

Strother D. Dixon
Sr. Regulatory Health Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: strother.dixon@fda.hhs.gov
Phone: 301.796.1015
Fax: 301.796.9895

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/s/

CRISTINA Petruccelli Attinello
02/22/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 23, 2015

Application Number: NDA 207154
Product Name: dapsone gel, 7.5%
Sponsor/Applicant Name: Allergan, Inc.

Subject: Proposed Post Marketing Requirement (PMR) to change the upper limit from < 12 years of age to < 9 years of age

FDA Participants
Jill Lindstrom, Deputy Director, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Patricia Brown, MD, Clinical Reviewer, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Sponsor Participants
Peter Aquino, MD, Director, Medical Safety
David Berk, MD, Director, Clinical Development
David Hoveland, PhD, Vice President, Global Regulatory Affairs
Alexandre Kaoukhov, MD, Senior Director, Clinical Development
Joan-En Lin, PhD, Senior Manager, Clinical Development
Jeremy McCumber, MS, Director, Global Regulatory Affairs
Warren Tong, PharmD, MS, Senior Scientist, Translational Drug Metabolism, Pharmacokinetics and Immunology

1.0 BACKGROUND:

Although there is an Agreed Initial Pediatric Study Plan (iPSP) with the sponsor, letter date March 24, 2014, the Division plans to issue a PMR due to the changing epidemiology of acne (i.e., occurring in younger age groups). The Division plans to change the upper age limit for waiver from < 12 years of age to < 9 years of age.

2.0 DISCUSSION:

The Division acknowledged the sponsor's Agreed iPSP. However, the Division is currently asking sponsors of acne indications, unless there is a safety signal to study down to nine years of age. The Division also informed the sponsor that the application would be presented to Pediatric Review Committee (PeRC). The Division informed the sponsor that the patient population should be 9 – 11 year 11 months, include safety data from at least 100 subjects, and at least 16 in maximum use pharmacokinetic (PK). The details could be discussed in the protocol.

The sponsor asked could PeRC approve without a PMR. The Division responded due to the epidemiology changes, unless there is a safety signal, we would request the sponsor to study down to 9 years of age.

The sponsor also inquired on the potential to broaden the indication and on submitting a Proposed Pediatric Study Request. The Division responded, "Yes."

The sponsor was asked to provide a timeline with the PMR milestone dates. The sponsor agreed.

3.0 ACTION ITEMS:

The sponsor agreed to propose dates for the PMR and submit to their application.

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/s/

STROTHER D DIXON
01/19/2016

Reference ID: 3875312

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207154

GENERAL ADVICE

Allergan, Inc.
Attention: Jeremy McCumber, M.S.
Director of Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. McCumber:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACZONE (dapsone), 7.5% gel.

We also refer to your April 28, 2015, submission, containing your new NDA.

We have the following request:

Submit the IVRT method validation report, and provide your proposed in vitro release acceptance criteria based on the data from at least 6 production batches, to the Agency at your earliest convenience, but by the first Annual Report at the latest.

If you have any questions, call Dr. Maria Cowan, Regulatory Project Manager, at (240)-402-8615.

Sincerely,

{See appended electronic signature page}

Maria Cowan, Pharm.D.
Regulatory Business Process Manager
Division of Dermatology and Dental Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

MARIA A COWAN
12/23/2015

PeRC Meeting Minutes
December 2, 2015

PeRC Members Attending:
Lynne Yao
Linda Lewis
Lily Mulugeta
Thomas Smith
Dionna Green
Gerri Baer
Daiva Shetty
Meshaun Payne
Shrikant Pagay
Belinda Hayes
Michelle Roth-Cline
George Greeley
Hari Cheryl Sachs NON-RESPONSIVE
Dianne Murphy NON-RESPONSIVE)
Barbara Buch NON-RESPONSIVE
Adrienne Hornatko-Munoz NON-RESPONSIVE
Wiley Chambers
Greg Reaman NON-RESPONSIVE
Maura O'Leary NON-RESPONSIVE

Agenda

NON-RESPONSIVE

11:20	NDA 207154	Aczone (dapsone) Topical Gel (Assessment) with Agreed iPSP	DDDP	Strother Dixon	Acne

NON-RESPONSIVE

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NON-RESPONSIVE

Aczone (dapsone) Topical Gel Assessment (with Agreed iPSP)

- Proposed Indication: Acne
- The division noted that the sponsor is contemplating a submission of a PPSR.
- The PeRC noted that the timeline dates will need to be added to the PeRC template. The PeRC also noted that the stated ages for waiver in the pediatric plan were incorrect—the waiver should include patients 0-9 years of age, not 0-9 months of age.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a partial waiver in patients ages birth to less than 9 years of age and to the deferral in patients 9 to 17 years of age.

NON-RESPONSIVE

3 Pages have been Withheld in Full as NON-RESPONSIVE immediately following this page

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/s/

GEORGE E GREELEY
12/15/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 28, 2015

Application Number: NDA 207154
Product Name: dapsone topical gel, 7.5%
Sponsor/Applicant Name: Allergan, Inc.

Subject: Labeling submitted on September 15, 2015 in response to the June 30, 2015 74-Day Letter.

FDA Participants
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Patricia Brown, MD, Clinical Reviewer, DDDP
Nancy Xu, MD, Acting Associate Director for Labeling, DDDP
Tamara Johnson, MD, MS, Acting Maternal Health Team Leader, DPMH
Carol H. Kasten, MD, Medical Officer, DPMH
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Sponsor Participants
Alexandre Kaoukhov, MD, Senior Director, Clinical Development
David Berk, MD, Director, Clinical Development
Lang Narasaki, PharmD, Senior Specialist, Global Labeling Compliance
Warren Tong, PharmD, MS, Senior Scientist, Translational Drug Metabolism, Pharmacokinetics and Immunology
Diana Auyeung-Kim, PhD, MBA, DABT, Director, Toxicology
Peter Aquino, MD, Director, Medical Safety

1.0 BACKGROUND:

The sponsor submitted labeling with proposed PLLR language on September 15, 2015 in response to the June 30, 2015 74-Day Letter.

2.0 DISCUSSION:

The Agency informed the sponsor that we were in receipt of the labeling with proposed PLLR language in response to the 74 Day Letter. However, the submission lacked supporting data such as a review and summary of the relevant published literature, a summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable) to support the proposed PLLR language. The sponsor was presented the options of deferring the implementation of PLLR until June 30, 2019 or providing the supporting data along with published literature during the current review cycle. The sponsor inquired whether submission of the requested data would be a major amendment and was told that it might be. The sponsor then stated they would prefer to submit the labeling as a postmarketing submission.

The sponsor asked if they would be required to resubmit the labeling for the current application or could the Agency reject the proposed PLLR language. The Agency stated that an additional submission would not be required and that the Agency would reject the proposed PLLR language.

The sponsor inquired about the data requirements for PLLR. The Agency provided a general overview of the requirements:

- a review and summary of all available published literature regarding dapsone,
- a review and summary from your pharmacovigilance database,
- revised labeling incorporating the above information

The sponsor was also referred to www.fda.gov and the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* published on December 14, 2015 for additional information.

The sponsor asked if the pregnancy data should come from their clinical trials and postmarketing. The Agency responded that pregnancy and lactation data should come from their development program as well as postmarketing.

The sponsor inquired if any additional regulatory action was required since the Agency requested the PLLR language in the 74-Day Letter. The Agency responded there was no additional action required.

The sponsor also inquired if the general presentation of the PLLR language in the September 15, 2015 label was adequate. The Agency provided preliminary comments and referred to the draft guidance *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* especially regarding human data.

3.0 ACTION ITEMS:

The Agency will reject the proposed PLLR language in the September 15, 2015 submission. The sponsor will implement PLLR postmarketing prior to June 30, 2019.

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

/s/

STROTHER D DIXON
10/02/2015

PATRICIA C BROWN
10/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207154

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Allergan, Inc.
Attention: Jeremy McCumber, MS
Senior Manager, U.S. Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. McCumber:

Please refer to your New Drug Application (NDA) dated and received April 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for dapsone topical gel, 7.5%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is February 28, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 18, 2016.

We request that you submit the following information:

Chemistry, Manufacturing and Controls

1. We recommend that you develop an *in vitro* release test (IVRT) methodology and propose *in vitro* release acceptance criteria (range) for your drug product to be used at release and during stability as a quality control parameter. Your proposed acceptance

criteria should be based on generated data for the final to-be-marketed batches. Submit all the generated data in electronic format.

2. Also, along with the proposed *in vitro* release specification, include the IVRT method development and validation report. Include in the IVRT method development report justification for the selection of the following methodology components:
    a. Diffusion apparatus
    b. Receptor medium selection
    c. Membrane selection
    d. Sampling time points
    e. Temperature

3. Include in the IVRT method validation report the following validation components:
    a. Linearity and Range
    b. Accuracy/Precision and Reproducibility
    c. Mass Balance
    d. Sensitivity and Specificity
    e. Selectivity
    f. Robustness
    g. Membrane Inertness
    h. Receptor Solution Solubility/Stability

4. The IVRT method's sensitivity, specificity, selectivity and robustness need to be performed with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.

5. Section 3.2.P.5.2 of the application outlines the test for the absence of *Burkholderia cepacia* in the drug product. Provide the following:
    a. A detailed description of the test method that specifies the growth conditions (i.e., growth medium, incubation time and temperature).
    b. Validation studies to confirm that the test method is suitable for detection of *B. cepacia* in the drug product. Include pre-incubation conditions for the *B. cepacia* test strain and enumeration of inoculated organisms.

Clinical

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

pregnancy and lactation. The PLLR implementation date is June 30, 2015; however, we encourage you to comply with PLLR with your current submission. See Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). PLLR requires the Risk Summary statements for 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential be based on available human and nonclinical data.

7. Provide your rationale for the applicability of foreign data to the U.S. population, or identify the location of this information in your application.

8. Describe the steps taken to minimize potential bias from investigators with disclosable financial interests or arrangements, or identify the location of this information in your application..

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

1. Format to ensure there is a minimum of 1/2 inch margin between the Highlights (HL) columns.
2. In the HL, the Dosage and Administration right line is shorter than the Indications and Usage and the Dosage Forms and Strengths right lines.
3. There is no numerical identifier after "None." under Contraindications. Add "(4.0)" after "None."
4. Change the revision date to "MM/YYYY" until approval.
5. In the first paragraph of section 6.1 Clinical Trials Experience of the Full Prescribing Information (FPI), change "studies" to "trials".
6. When postmarketing adverse reaction data are included, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 15, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We reference the partial waiver granted on March 24, 2014, for the pediatric study requirement for this application for pediatric patients younger than 12 years of age.

If you have any questions, call Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Acting Deputy 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 ignature.

/s/

JILL A LINDSTROM
06/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207154

NDA ACKNOWLEDGMENT

Allergan Inc.
Attention: Jeremy McCumber, MS
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19543
Irvine, CA 92623-9534

Dear Mr. McCumber:

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: Aczone® (dapsone) gel, 7.5%

Date of Application: April 28, 2015

Date of Receipt: April 28, 2015

Our Reference Number: NDA 207154

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 June 27, 2015, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

If you have any questions, call me at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Strother D. Dixon
Senior Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

STROTHER D DIXON
04/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 054440

MEETING MINUTES

Allergan, Inc.
Attention: Jeremy McCumber, MS
Senior Manager, U.S. Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. McCumber:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dapsone topical gel, 7.5%.

We also refer to the teleconference between representatives of your firm and the FDA on November 19, 2014. The purpose of the meeting was to discuss the development plan for dapsone topical gel, 7.5%.

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

If you have any questions, call Strother D. Dixon, Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
Allergan Response to Pre-Meeting Communication

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:	November 19, 2014, 10:30 AM EST
Meeting Location:	Teleconference
Application Number:	IND 054440
Product Name:	dapsone topical gel, 7.5%
Proposed Indication:	For the treatment of acne vulgaris
Sponsor Name:	Allergan, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Kendall A. Marcus, MD, Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Amy Woitach, DO, MS, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
An-Chi Lu, MS, PharmD, Clinical Pharmacology Reviewer, DCP3
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Roy Blay, PhD, Reviewer, DGCAB
John W. Metcalfe, PhD, Senior Microbiology Reviewer, OPS
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Strother D. Dixon, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Diana Auyeung-Kim, PhD, Senior Manager, Toxicology
David Berk, MD, Director, Clinical Development
Eric Carter, MD, PhD, Senior Vice President, Chief Medical Officer, Head Global Drug Development
Andre Daniels, MD, Vice President, Global Safety and Epidemiology
Jacqueline Dombroski, PhD, Director, Global Regulatory Affairs

Alexandre Kaoukhov, MD, Senior Director, Clinical Development
Pan-yu Lai, PhD, Senior Director, Biostatistics
Joan-En Lin, PhD, Senior Manager, Clinical Development
Vince Lin, PhD, Manager, Biostatistics
Jeremy McCumber, MS, Senior Manager, US Regulatory Affairs
Karen Smith, MD, PhD, MBA, LLM, Senior Vice President, Global Medical Affairs and Interim Therapeutic Area Head, Dermatology
Paul Stone, PhD, Senior Director, Global Regulatory Affairs
Warren Tong, PharmD, MS, Senior Scientist, Pharmacokinetics and Pharmacodynamics
Kevin Warner, PhD, Principal Scientist, Pharmaceutical Science
Pramod Sarpotdar, PhD, Senior Director, Dermal Product Development
Peter Aquino, MD, MPhil MSc, Director, Medical Safety Physician

General Comment:
The sponsor was provided the Agency's preliminary responses in the draft premeeting communication on November 12, 2014. The sponsor sent a response to the draft premeeting communication via email on November 17, 2014 titled "Allergan Response to Pre-Meeting Communication" which is appended to this document.

Purpose of the Teleconference:
To discuss the development plan for dapsone topical gel, 7.5%

Regulatory Correspondence History
We had the following meeting with you:
- August 28, 2013 – End-of-Phase 2

We have sent the following correspondences:
- June 13, 2014 – Advice
- March 24, 2014 – Advice
- March 13, 2014 – Advice
- January 15, 2014 – Advice/Information Request
- June 15, 2014 – Advice

Regulatory

Question 1:
A draft Electronic Common Technical Document (eCTD) Table of Contents (TOC) for the proposed NDA, including details on the planned submission of specific study reports for Module 4 and Module 5, is provided in Section 12.1.

Does the Agency agree that the proposed organization of the submission is acceptable?

If the Agency does not agree, please provide any recommendations.

Response:
Yes, the proposed organization of the submission is acceptable. However, please see additional comments, below.

- For archival purposes, also submit a pdf file of the labeling document submitted in word. When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.

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

- No need to include Section numbering in your leaf title (e.g. 16.1.1-Protocol-and-Protocol Amendments). Instead, it will be preferred that you include the study number on the leaf titles to help differentiate one study protocol from another (e.g. 225678-009-protocol, 225678-004-study-report or something similar).

- Note that Study Tagging Files (STF) files 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 properly file tagged and placed under the study's STF, including case report forms (crfs). Individual Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

- The Patient Reported Outcomes (PRO) should be placed in eCTD section 5.3.5.3 with a file tag of **"study-report-body"** and a leaf title similar to **"PRO Dossier"**, so reviewers could easily identify the document

Question 2:
NDA 207154 for ACZONE 7.5% will cross-reference NDA 21-794 (approved on 07 July 2005) for ACZONE 5% to support the new product. A table of cross-references will be provided in Module 1.4.4 of the NDA, and the study reports will be cited in the text of each document as required by the FDA's *Guidance for Industry: Providing Regulatory Submissions in Electronic Format.*

NDA 21-794 was submitted as a paper NDA, therefore, the study reports that will be cross-referenced are not currently accessible to the FDA as electronic files. As is typical for paper NDAs, the study reports that will be cross-referenced may occupy multiple volumes. Allergan will be converting the study reports that will be cross-referenced to an electronic, submission ready, legacy-file format independent of the submission of the ACZONE 7.5% application (NDA 207154). Allergan proposes to resubmit the converted electronic study reports to NDA 21-794.

Does the Agency agree with Allergan's proposal to resubmit study reports that were part of the paper application for ACZONE 5% as electronic study reports to NDA 21-794?

Response:
Yes. The reports could be file tagged as "legacy-clinical-study-report" under the respective study's STF.

Question 3:
Allergan plans to generate a pooled analysis for both efficacy and safety (an Integrated Summary of Efficacy [ISE] and an Integrated Summary of Safety [ISS]). The text portions of the ISS and ISE will be placed in Module 2, Sections 2.7.3 and 2.7.4, respectively. Summary tables and data listings of the pooled data, along with the respective statistical analysis plans (SAPs), will be provided in Module 5, Section 5.3.5.3.

Does the Agency agree?

Response:
Yes, please see response to question number 8.

Question 4:
Allergan plans to provide Case Report Forms (CRFs) for the following categories of patients: deaths, serious adverse events (SAEs), and discontinuations due to adverse events. Based on *ICH E3, Structure and Content of Clinical Study Reports (CSRs)*, Allergan proposes that the CRFs be organized and submitted by study in Module 5.3.5.1. All CRFs will have their respective study's accompanying study tagging file.

Does the Agency agree?

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

Question 5:
Allergan intends to include patient narratives for deaths, serious adverse events, and discontinuation due to adverse events within each CSR submitted with the NDA and also in Module 5.3.5.3, as a separate file separated by event type (death, serious adverse event, discontinuation due to adverse event), and study number.

Does the Agency agree?

Response:
Yes, for your product this approach appears reasonable. Additional information may be requested during the NDA review.

Reference ID: 3883259

Question 6:
At the time of the NDA submission, the phase 3 clinical trials will have been completed. No additional trials will be ongoing during the NDA review period. Therefore, Allergan plans to submit a letter stating that there are no new data available, in lieu of the 120 day safety update.

Does the Agency agree?

Response:
All required information that would be included in the 120 day safety update must be included in your submission. Note that your letter stating that there are no new data available should reference the 120 day safety update in the subject line of your cover letter.

Question 7:
As stated in the Request for Advice regarding Pediatric Exclusivity submitted to IND 54,440 on 19 September 2014, Allergan intends to request an (b) (4) (b) (4) (b) (4) and the provisions for pediatric exclusivity set forth in Section 505A of the Federal Food, Drug, and Cosmetic Act.

Does the Agency agree that, if approved, NDA 207154 would qualify for an (b) (4) (b) (4)

(b) (4)

Response:
No, we do not agree. The Pediatric Exclusivity provision under the Best Pharmaceuticals for Children Act allows sponsors to qualify for an (b) (4) (b) (4) It is not a stand-alone exclusivity. To qualify for pediatric exclusivity, a sponsor must:

1) be in receipt of a Written Request from FDA;
2) submit study reports to the NDA **after** receipt of the Written Request; and
3) meet the terms of the Written Request.

If you wish to qualify for pediatric exclusivity, submit a "Proposed Pediatric Study Request" requesting a Written Request from FDA. For further information, refer to the guidance for industry *Qualifying for Pediatric Exclusivity* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078751.pdf .

Chemistry, Manufacturing and Controls (CMC)

Question 12:
Allergan will seek a shelf life of 24 months at the preferred storage condition of 25°C for ACZONE 7.5%. To support the shelf life and storage recommendation, primary stability data on 3 batches stored through 12 months at 25°C and 6 months stored at 40°C in the to-be-marketed product configuration will be submitted in NDA 207154. Additional stability data (18 months) for these batches will become available after the NDA has been submitted but prior to the anticipated conclusion of the review period. Allergan proposes to submit the 18 months stability data during the NDA review. Twenty-four month data will be provided in the first Annual Report.

Does the Agency agree that Allergan may submit the additional 18 months primary stability data to support the 24 month shelf life and storage conditions for the product during the NDA review period without impacting the review timeline?

Response:
Yes, provided that the stability update will be provided within 4 months after the receipt of the NDA.

Additional Comments

1. Pump functionality (number of prime, amount dispensed per actuation, and total deliverable) should be included in drug product specification for pump configurations.
2. The analytical samples for a pump configuration should be taken from the pumped-out formulation.
3. Include an examination of the interior surface in the test on package appearance. This is to evaluate potential interaction between the formulation and the fabrication materials of the container/closure system. It is necessary for both pump and tube configurations.
4. The registration stability study results supporting the pump configurations should include the following data: pump functionality (number of prime, amount dispensed per actuation, and total deliverable), weight loss, and package integrity.
5. In-use stability studies should be conducted for pump configurations and the results should be provided in the initial submission to demonstrate that the pumped out formulation can consistently meet the proposed product specification throughout the in-use period. If a bracketing approach is applied to the design of the in-use stability studies, provide acceptable justification.
6. In addition to critical product attributes such as assay, related substances, pH, viscosity, particle size distribution, etc., the in-use stability studies should include the following tests: pump functionality (number of prime, amount dispensed per actuation, and total deliverable), weight loss, and package integrity (interior, exterior, and leakage).
7. Since drug substance is suspended in the gel vehicle, add particle size distribution to drug product specification. You will also need to demonstrate that the drug substance does not undergo [redacted] (b) (4) change during the registration stability studies.

8. If the designated commercial manufacturing site for drug product is different from the Phase 3 site, appropriate bridging studies would be required. SUPAC-SS contains examples for bridging different sites
9. Provide the following documents in the initial submission of the proposed NDA:
   - Master Batch Records for the drug product;
   - A correlation table (in Pharmaceutical Development section) correlating drug product batch numbers and drug substance lot numbers with clinical, toxicological, pharmacokinetic, and stability studies.

Meeting Discussion:
Sponsor stated that the pump is not metered and does not intend to provide pump functionality assessments. The Agency acknowledged that the proposed pump is not a metered pump; however, the pump functionality test with its three elements should be added to the drug product specification. The Agency expects proper functioning of the pump at time of batch release and throughout the product shelf-life. This is a standard request for dermatological products packaged in non-metered pumps.

Sponsor proposed [redacted (b) (4)] The Agency agrees with the proposal, and requests that the sponsor provide justification in the proposed NDA.

Question 13:
Allergan is removing the specific reference to [redacted (b) (4)] from the proposed commercial drug product specification. The proposed specification for "Microbial Enumeration Tests and Tests for Specified Organisms" is provided in Table 2.

Table 2 Proposed Commercial Specification for Microbial Enumeration Tests

Test Parameter	Method No.	Specification Presented in IND	Proposed Commercial Specification
Microbial Enumeration Tests and Tests for Specified Organisms	USP <61> and USP <62>	Total Combined Yeasts and Molds NMT [redacted (b) (4)] CFU/g Total Aerobic Microbial Count NMT [redacted (b) (4)] CFU/g Absence of Specified Microorganisms: *Staphylococcus aureus* and *Pseudomonas*	Total Combined Yeasts and Molds NMT [redacted (b) (4)] CFU/g Total Aerobic Microbial Count NMT [redacted (b) (4)] CFU/g Absence of Specified Microorganisms: *Staphylococcus aureus* and *Pseudomonas*

	aeruginosa [redacted] (b) (4) *Burkholderia cepacia* *Serratia marcescens*	*aeruginosa*

During development, Allergan developed methodologies to meet the requirements of USP Chapter <61> (Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests) and Chapter <62> (Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms), including the absence of the specified microorganisms *Staphylococcus aureus and Pseudomonas aeruginosa*.

Allergan also developed methodologies to confirm the absence of *Burkholderia cepacia* and *Serratia marcescens*, which is testing that exceeds the USP requirements. While neither *B. cepacia* nor *S. marcescens* presents a significant pathogenic risk when the topical dermal route of administration and the intended patient population are considered, ten batches of ACZONE 7.5% were tested. Test results confirmed the lack of *B. cepacia* and *S. marcescens*. The Environmental Monitoring data over the past year at the intended commercial manufacturing site, DPT Laboratories, San Antonio, Texas, also showed the lack of *B. cepacia* and *S. marcescens* in the manufacturing environment. Allergan is therefore removing [redacted] (b) (4) from the proposed commercial drug product specification.

Does the Agency agree with Allergan's proposal to remove the specific reference to [redacted] (b) (4) from the proposed commercial drug product specification?

Response:
We agree that changing the release specification phrase "[redacted] (b) (4) (*B. cepacia* and *S. marcescens*)" to "Absence of Specified Microorganisms" is acceptable. However, since the drug product is aqueous and may be applied to non-intact skin, it should not contain *B. cepacia*. The NDA should address how Allergan intends to control for the presence of *B. cepacia* in the final drug product. Control strategies may include [redacted] (b) (4) additional controls to exclude this organism from the manufacturing process, or finished product *B. cepacia* release testing.

Pharmacology/Toxicology

Question 11:
The proposed organization of Module 4 of NDA 207154 for ACZONE 7.5% is presented in the eCTD TOC provided in Section 12.1. Allergan will be submitting the nonclinical study reports for the additional studies that were conducted to support the new formulation in NDA 207154.

The nonclinical development program to support the new formulation for phase 3 clinical studies was agreed upon by the Agency at the EOP2 Meeting held on 28 August 2013. At that time, Allergan also proposed to cross-reference the study reports in the ACZONE 5% NDA (NDA 21-794) to support the new formulation.

Does the Agency agree with the proposed organization of Module 4?
Does the Agency agree with Allergan's proposal to cross-reference the nonclinical data in the ACZONE 5% NDA (NDA 21-794)?

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

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

2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. In this case, the applications are on the same server. The applications need to include the appropriate prefix in the hypertext reference (href) links (e.g. nda, mf, ind). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to nda XXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

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

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

Clinical Pharmacology

There are no questions for clinical pharmacology; however, we have the following comments:

1. At the time of your NDA submission, you should include bioanalytical reports and associated method validation reports for all trials with pharmacokinetic (PK) assessment. The bioanalytical report for each trial should outline the duration of sample storage and supporting long-term storage stability information.
2. Provide in the NDA raw and calculated PK parameters for all trials with PK assessments in SAS Transport format (.xpt). Include a data definition file.

Meeting Discussion:
The sponsor agreed with the Agency's request.

Clinical/Biostatistics

Question 8:
Allergan has conducted four phase 1 studies (three dermal tolerability studies and one PK study) and two identical, pivotal phase 3 studies to support the NDA submission for ACZONE 7.5%. Allergan plans to integrate the two pivotal phase 3 studies for the ISS and ISE. The four phase 1 studies will not be part of the integrated analysis because the design, treatment exposures, and objectives of those studies were different than the phase 3 studies. The proposed SAPs for the ISS and ISE are provided in Section 12.3.

Does the Agency agree with the data integration strategy for the analysis for the ISS and ISE?

Does the Agency have any additional recommendations on the proposed SAPs for the ISS and ISE?

Response:
Your proposed approach for the ISS and ISE appears reasonable.

Your ISS should include the following:

- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) $\geq 1\%$.
- Adverse event tables $\geq 1\%$ regardless of causality.
- Shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

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).

It should be noted that establishing an efficacy claim would be based on efficacy data from individual Phase 3 trials along with a replication of study findings.

Meeting Discussion:
The sponsor wanted to discuss the requested shift tables for laboratory values. The sponsor did not conduct laboratory assessments in Phase 3 trials. The sponsor is proposing to rely on PK data demonstrating lower systemic levels in the 7.5% product administered once daily as compared to the 5% product administered twice daily. The sponsor will provide their supporting rationale for not conducting Phase 3 laboratory assessments within the ISS.

Question 9:
Allergan plans to submit the following for each of the two pivotal phase 3 studies (Studies 225678-006 and 225678-007) in the NDA:

1. Raw dataset definition file
2. Analysis dataset (ADS) definition file
3. Raw data Statistical Analysis Software (SAS) transport file
4. ADS SAS transport files
5. Annotated CRFs

The draft raw dataset file (item #1), ADS definition file (item #2), and annotated CRFs (item #5) for protocol 225678-006 are provided in Section 12.4, Section 12.5, and Section 12.6, respectively. The raw dataset file, ADS definition files, and annotated CRFs for protocol 225678-007 will be identical to those for protocol 225678-006.

The ADS SAS transport files and ADS definition file from the ISE and ISS will also be submitted in the NDA.

The ADS and tables, listings, and graphs are developed by using SAS programs. The SAS programs will be available upon request by the Agency.

Does the Agency agree with the proposed package of datasets and the corresponding documentation to be provided in the proposed NDA?

Response:
Your proposal appears reasonable at this time. The Agency also prefers the sponsor to submit datasets based on the *Study Data Specifications* (currently 2.0), which is not noted in your meeting package.

In addition, we would prefer combined Tabulation Datasets for the pivotal trials for safety analysis.

Question 10:
In July of 2014, Allergan became aware of a site-specific issue concerning the phase 3 Clinical Study 225678-006 and Principal Investigator Dr. Ellen Marmur (Site 16078, located at Marmur Medical in New York City, New York). Allergan investigated the issue, which culminated in an

on-site assessment 11-12 September 2014, and confirmed the existence of Good Clinical Practice (GCP) compliance issues in the areas of Protocol Adherence and Clinical Study Management. Due to concerns over the overall data integrity for Dr. Marmur's site, Allergan has made the decision to exclude all patients randomized at the site (51 patients) from the Intent-to-Treat (ITT) analysis. All patients seen at Dr. Marmur's site will be included in the safety analysis for the NDA. The concerns are based upon the following instances of serious non-compliance:

- Numerous inconsistencies in documentation indicating that Dr. Marmur conducted patient assessments when it was confirmed she was not present in the office
- Consenting, screening, and enrolling patients into the study, as well as efficacy and safety assessments, conducted by a study coordinator who was not eligible to conduct the assessments, per protocol, and not listed on the Investigator's Form FDA 1572
- Lack of documentation for numerous patients who were randomized but who do not appear to have returned for any follow-up visits

Due to the issues identified, the site has been terminated from the study and all ongoing patients at the site have been discontinued from the study. Allergan will conduct additional sensitivity analyses of the primary efficacy endpoints (change from baseline at week 12 in Global Acne Assessment Score [GAAS] and absolute change from baseline at week 12 in lesion counts for inflammatory and noninflammatory lesions) based on the ITT population that includes all patients seen at Dr. Marmur's site. Allergan also proposes to modify the SAP for this study to include the sensitivity analysis proposed and will submit it to IND 54,440 prior to database lock.

Does the Agency agree with Allergan's proposal?

Response:
Specific recommendations from Office of Scientific Investigations (OSI) regarding this study site are pending at the current time and will be forthcoming from the Agency. Given the potential seriousness of the violations described, data from this investigative site should not be included in the primary efficacy analysis. Line listings should be provided for any safety data collected at this site, but should not be included in analyses.

Further, while you proposed that the primary analysis be stratified by gender, it should be noted that the Agency is interested in investigating the site to site variability in efficacy. Therefore, we prefer that that the primary analysis be stratified by center. If you have justification that efficacy varies by gender, you may present your findings as subgroup analyses.

Note that your planned multiplicity approach of using the gatekeeping along with a Hochberg's Step-up method does not control the Type I error rate. In addition, as previously commented (January 15, 2014), as you are analyzing the percent change of inflammatory as well as the noninflammatory lesions, the percent change of total lesion count might not provide additional information meaningful for labeling.

Meeting Discussion:
The Agency noted the sponsor justification, in the "Allergan Response to Pre-Meeting Communication" submitted via email on November 17, 2014 and appended at the end of these

minutes, for stratifying the analysis by gender by using modeling for data for NDA 21-794 submitted to the Agency on September 7, 2004. In response the Agency noted that higher response rate in lesion counts for female was due to smaller number of lesion counts for female compared to male at the baseline for both clinical trials 203 and 204. However, the treatment effect as assessed by percent change in lesion counts for both genders is similar.

As for the analysis, in principle, the statistical analysis should follow the randomization. As your randomization was stratified by center as well as gender we recommend you conduct your analyses stratified by both factors with and without pooling. Ultimately, you may submit the analyses you desire and the Agency will conduct its own analyses and review.

The Agency agreed with the sponsor proposal of using the gatekeeping approach without the Hochberg's Step-up method when controlling for multiplicity after the sponsor clarified that the testing would be done sequentially for total lesion counts followed by inflammatory and noninflammatory lesion counts before testing the next secondary endpoints.

Administrative Comments

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

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

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

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 9, 2014 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a

complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement. Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

development, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI)

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

Reference ID: 3883159

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

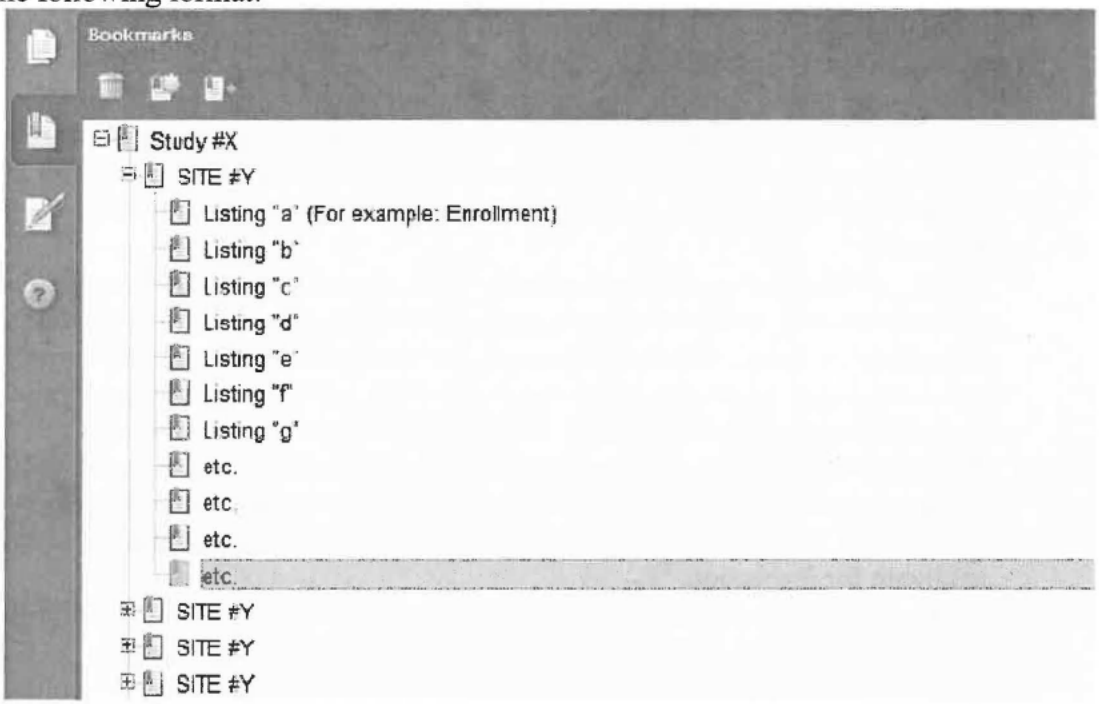
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

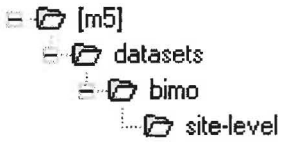
I. Attachment 1

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

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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/

KENDALL A MARCUS
11/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 054440

MEETING MINUTES

Allergan, Inc.
Attention: Giles Hulley
Senior Manager
2525 Dupont Drive
Irvine, CA 92623-9534

Dear Mr. Hulley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (dapsone) Topical Gel, 7.5%.

We also refer to the meeting between representatives of your firm and the FDA on August 28, 2013. The purpose of the meeting was to discuss the development plan for (dapsone) Topical Gel, 7.5% for the treatment of acne vulgaris.

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 Strother D. Dixon, Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	August 28, 2013, 10:00 AM
Meeting Location:	FDA, White Oak
Application Number:	IND 054440
Product Name:	(dapsone) Topical Gel, 7.5%
Proposed Indication:	For the treatment of acne vulgaris
Sponsor Name:	Allergan, Inc.
Meeting Chair:	Susan J. Walker, MD, FAAD
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES

Susan J. Walker, MD, FAAD, Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Amy Woitach, DO, MS, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Roy Blay, PhD, Reviewer, DGCAB
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP
Strother D. Dixon, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Eric Carter, MD, PhD, Sr. Vice President, Chief Medical Officer, Head Global Drug Development
Karen Smith, M.D., Ph.D., MBA, LLM, Sr. Vice President, Global Medical Affairs and Interim Therapeutic Area Head, Dermatology
Gary Charbonneau, M.S., Vice President, Global Regulatory Affairs
Alexandre Kaoukhov, M.D., Sr. Director, Clinical Development
Jacqueline A. Dombroski, Ph.D., Director, Global Regulatory Affairs
Cheyi (Vince) Lin, M.S., Manager I, Biostatistics
David Berk, M.D, Director, Clinical Development
Giles Hulley, Sr. Manager, U.S. Regulatory Affairs

Purpose of the Meeting:
To discuss the development plan for (dapsone) Topical Gel, 7.5% for the treatment of acne vulgaris

Regulatory

Question 9:
Allergan obtained a waiver for the requirement to perform pediatric clinical studies in children from birth to (b)(4) years of age for ACZONE (under NDA 21-794). The company does not plan to perform studies in children from birth to (b)(4) years of age with dapsone 7.5% topical gel or market the product for that pediatric age group.

a. Is it necessary for Allergan to request a waiver of the requirement for pediatric studies for children from birth to (b)(4) years of age for dapsone 7.5% topical gel?
b. What is the appropriate timing for submission of a waiver request, should it be necessary?
c. If the Agency deems it necessary for Allergan to request a waiver, does the Division agree that Allergan's rationale for requesting the waiver to study dapsone 7.5% topical gel in pediatric subjects from birth to (b)(4) years of age is acceptable?

Response:
Sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (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. See comments on PREA requirements below.

Your rationale for requesting the waiver to study (dapsone) Topical Gel, 7.5% in pediatric subjects from birth to (b)(4) years of age may be reasonable. (b)(4)

We recommend that you provide data on the incidence, prevalence, and drug use to support your rationale that studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed) in the population for which you seek a waiver.

Question 10:
Does the Division agree that Allergan's rationale for requesting a waiver from additional clinical studies with dapsone 7.5% topical gel in pediatric subjects from (b)(4) years of age is acceptable?

If the Division does not agree that the rationale is adequate, Allergan would appreciate a discussion about any additional information that will be required in order to address the Division's expectations.

Response:
You propose to include pediatric subjects [redacted] years of age in your Phase 3 studies. Your development program should provide sufficient data in order to make a determination of safety and effectiveness in pediatric subjects between ages [redacted]. There should be a reasonable distribution of subjects across the proposed age spectrum, including at the [redacted] adolescent population.

Question 11:
Does the Division have any comments or additional expectations regarding the enrollment, treatment, statistical analyses, or number of pediatric subjects from [redacted] years of age in the proposed phase 3 clinical study program for dapsone 7.5% topical gel?

Response:
We have no additional comments.

Chemistry, Manufacturing and Controls

No CMC questions were submitted. After reviewing the limited CMC information provided in the briefing package, we have the following comment:

1. The dosage form of the proposed Formulation 11080X can not be assessed due to inadequate information. It appears that Formulation 11080X is [redacted] The Agency normally recommends "cream" as the dosage form for [redacted]. Please provide the following information to assist in dosage form determination:
   - A representative sample
   - Quantitative composition information [redacted]
   - Justification to support your proposed dosage form

2. The proposed formulation 11080X contains [redacted] (diethylene monoethyl ether). Assess the [redacted] of the proposed formulation 11080X. If deemed necessary, a warning statement should be placed on the labels.

Pharmacology/Toxicology

Question 6:
Allergan proposes that the human pharmacokinetic data and the nonclinical assessments should allow for the conduct of phase 3 clinical evaluation of dapsone 7.5% topical gel with formulations containing the impurity [redacted] at or below the threshold levels currently recommended in the "Guidance for Industry: Q3B(R2) Impurities in New Drug Products" [July 2006].

Does the Agency agree?

If the Division does not agree, Allergan would appreciate a discussion of any additional data required in order to address the Division's expectations.

Response:
The Division has no objections to this proposal.

Question 7:
Allergan believes that the current nonclinical package for ACZONE (dapsone) Gel 5% is adequate to support phase 3 clinical evaluation of the new single agent dapsone 7.5% formulation based upon the expected lower systemic exposure of the proposed formulation and the prior long-term dermal/systemic toxicity evaluation of dapsone at concentrations up to 10% in rats and rabbits.

Does the Agency agree that phase 3 studies may proceed? If the Division does not agree, Allergan would appreciate a discussion of the additional study or studies and data required in order to address the Division's expectations.

Response:
With respect to nonclinical issues, the database described in the briefing package should acceptably support conduct of the Phase 3 studies that are described in the package.

Question 8:
Allergan plans to conduct a 13-week dermal toxicity study in rats to both support registration of the final clinical formulation as well as qualify allowable levels of the impurity (b) (4) in the formulation.

Does the Agency agree with this approach?

If the Division does not agree, Allergan would appreciate a discussion about any additional information required from nonclinical toxicology studies in order to address the Division's expectations.

Response:
The Division has no objection to conduct of a 13-week dermal toxicity study in rats. A properly designed and executed study may help to qualify proposed exposures associated with the new product, including excipients and impurities. If properly conducted, the rat study may be useful in this regard. It is suggested that the study include both a vehicle-treated control group and an untreated control group, to permit inferences to be made regarding the effects of exposure to the vehicle. If a goal of the study is to qualify exposure to (b) (4) then it may be appropriate for selected animals in that study to receive materials that have been spiked with (b) (4) (as supported by data from suitable preliminary studies).

Although you are responsible for the design and conduct of nonclinical studies, the Division offers the following general comments in regard to the design of topical dermal repeat-dose toxicity studies:

It is recommended that skin at the treatment site in topical repeated-dose toxicity studies not be deliberately lesioned (i.e., that the skin not be abraded or surgically lesioned). The data should include adequate clinical pathology, histopathology of a full range of tissues, and toxicokinetic analysis. A preferable study design may include use of test materials that vary in drug substance content over an appropriate range of concentrations, as supported by data from preliminary studies. If acceptably tolerated, the test materials should include the clinical formulation, as well as enriched formulations (materials that contain a higher concentration of drug substance than the most concentrated clinical formulation, if it is pharmaceutically feasible to formulate such materials).

If a certain concentration is implied to be the maximum feasible concentration in the clinical vehicle, e.g., on the basis of solubility or stability constraints, then this should be documented under the IND. The study should include use of materials of subclinical concentration, as appropriate. Typically, nonclinical topical general repeat-dose toxicity studies are expected to include exposures to the drug substance that either induce dose-limiting toxicity, without reducing survival or inducing excessive local irritation, or that were associated with the maximum feasible dose (MFD), under appropriate circumstances, or as otherwise discussed under the ICH M3(R2) document.

The MFD in a repeat-dose nonclinical study that involves topical administration to the skin typically involves application of approximately 2 mL/kg/dose of the most concentrated formulation that is pharmaceutically feasible, applied to approximately 10% of the body surface area. Use of a substantially different dose volume should be well justified, and will be subject to review. In general, it is recommended that nonclinical topical dermal toxicology studies be designed such that the test materials remain in contact with skin at the application site (i.e., that the materials are not removed) for at least 20 hours per day. It is suggested that the test materials utilize the vehicle of the clinical formulation, that the test materials be applied only once per day, that the animals be individually housed, and that all treated animals receive the same volume per dose.

Clinical Pharmacology

Question 5:
Allergan's position is that no additional pharmacokinetic studies should be required for dapsone 7.5% topical gel. Does the agency agree?

If the Division does not agree, Allergan would appreciate a discussion of any key data that the Division would require in order to address the Division's expectations.

Response:
Your plan regarding no additional pharmacokinetic assessment for (dapsone) Topical Gel, 7.5% appears reasonable. This assumes that the PK studies were conducted with the to-be-marketed formulation.

Clinical/Biostatistics

Question 1:
Does the Division agree that the proposed phase 3 studies will meet the requirements for the potential approval of an NDA Supplement?

Allergan would appreciate a discussion of any points of disagreement or alternative proposals in order to address the Division's concerns.

Response:
We anticipate that the development program you outline would be sufficient for filing if you adequately address the Agency comments provided.

Question 2:
Allergan requests a waiver from the requirement to conduct a dedicated 21-day cumulative irritation study. Does the Division agree?

If the Division does not agree, Allergan would appreciate a discussion about the Division's concerns.

Response:
Your proposed 7.5% dapsone gel product differs from the approved Aczone Gel, 5% in both concentration of the active ingredient as well as excipients in the formulation. Additionally, provocative dermal testing with Aczone Gel, 5%, resulted in moderate erythema in some subjects. Cumulative irritation should be assessed for your proposed higher strength (7.5%). Cumulative irritation can be assessed as part of the induction phase of the repeated insult patch test (RIPT). Typically, daily patch application for 21 days during this induction phase is recommended for products that are proposed for daily application.
Provocative dermal safety studies should be conducted with the final, to be marketed product.

Question 3:
Does the Division agree to a waiver of the thorough QT/QTc study for dapsone 7.5% topical gel for treatment of acne vulgaris?

If the Division does not agree to a waiver, Allergan would appreciate a discussion of any key features of potential study design and analysis in order to address the Division's expectations.

Response:
Your rationale based on low plasma concentration, historical clinical use and relative bioavailability data to (dapsone) Gel, 5% seems reasonable to support a waiver to conduct a thorough QT/QTc study for (dapsone) Topical Gel, 7.5%.

Question 4:
Does the Agency agree with the proposed primary and secondary efficacy measures, variables, and analyses?

If the Division does not agree, Allergan would appreciate a discussion in order to fully understand and address the Division's expectations.

Response:
You submitted the protocol for two identical Phase 3 trials.

- For the co-primary endpoints of PGA and absolute change in lesion counts, you proposed 2 out of 3 absolute change from baseline in lesion count (inflammatory, noninflammatory, and total). It should be noted that for assessing efficacy for acne indication, the co-primary endpoints regarding the lesion counts recommended by the division is the absolute change in inflammatory and non-inflammatory lesion counts from baseline. Facial counts should include lesions on the nose.
- You listed several secondary endpoints which are closely related to each other. Some of your proposed secondary endpoints might not be clinically relevant for labeling. It should be noted that secondary endpoints intended for labeling should be clinically meaningful, limited in number, and adjusted for multiplicity to control the type I error rate. Your proposed secondary efficacy endpoints of percentage change in inflammatory and non-inflammatory lesion counts from baseline to week 12 are acceptable. Patient reported outcomes may have limited utility for eventual product labeling.
- For handling missing data, you proposed to impute missing value using last observation carried forward (LOCF) as the primary method. However, as the scientific rationale for LOCF method is weak, you should provide either a justification that the LOCF is appropriate for your application or propose a more scientifically sound methodology, e.g. multiple imputation or modeling approach, as the primary imputation method. In addition, the two sensitivity approaches for success in GAAS and change in lesion counts are not consistent, which makes it difficult to interpret their findings. You should propose approaches for sensitivity analyses which are consistent across the co-primary endpoints.

General Meeting Discussion:
The sponsor stated that they plan to submit an IND amendment to address CMC comments. The Agency advised the sponsor to resolve the dosage form issue before Phase 3.

There was focused discussion and clarification for the sponsor regarding the Pediatric Study Plan, study endpoints and the handling of missing data.

The sponsor outlined a combination irritation/RIPT study that appeared reasonable. The sponsor will submit the study protocol to the IND for review.

Administrative Comments

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

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

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

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

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.

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 held on or after November 6, 2012. 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.

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

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/s/

SUSAN J WALKER
09/03/2013

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