CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207695Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207695 SUPPL # N/A HFD # 540

Trade Name Eucrisa®
Generic Name crisaborole ointment, 2%

Applicant Name Anacor Pharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ 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.

N/A

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

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

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

YES ☐ NO ☒

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

N/A

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:

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical

investigations submitted in the application that are essential to the approval:

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

Investigation #2		!
		!
IND #	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: Belainesh Robnett
Title: Regulatory Health Project Manager
Date: 11/30/16

Name of Division Director signing form: Jill Lindstrom, MD, FAAD
Title: Deputy Director, Division of Dermatology and Dental Products

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/

BELAINESH ROBNETT
12/07/2016

JILL A LINDSTROM
12/08/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207695	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Eucrisa, Established/Proper Name: crisaborole Dosage Form: ointment, 2%		Applicant: Anacor Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Lydia Springs/Omolara Laiyemo		Division: DDDP

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 January 7, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	N/A
❖ Application Characteristics [3]	

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

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

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

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

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

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

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

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

Comments:

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 12/14/2016
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)*	Proprietary Name Granted Letter 3/18/2016 3/10/2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 12/1/2016 DMEPA: 7/6/2016 DMPP/PLT (DRISK): 8/10/2016 OPDP: 8/15/2016 SEALD: ☒ None CSS: ☒ None Product Quality: 11/22/2016 DPMH: 8/4/2016 (Maternal) 9/29/2016 (Pediatric)
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	12/1/2016 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed 12/8/2016
❖ 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 8/10/2016 If PeRC review not necessary, explain:	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	N/A
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	N/A
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	3/21/2016 Filing letter 7/1/2016 Information Request 7/14/2016 Information Request
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	9/23/2015
• EOP2 meeting *(indicate date of mtg)*	2/26/2014
• Mid-cycle Communication *(indicate date of mtg)*	6/24/2016
• Late-cycle Meeting *(indicate date of mtg)*	9/26/2016
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ 12/13/2016
Division Director Summary Review *(indicate date for each review)*	☒ 12/13/2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 12/8/2016
PMR/PMC Development Templates *(indicate total number)*	☒ 1
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/3/2016
• 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)*	Pages 182-183 (clinical review)/ 11/3/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	DPP: 6/23/2016 DCRP: 4/20/2016 (Review) DCRP: 8/2/2016 (Addendum)
❖ 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 DRISK: 11/4/2016
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Review: 10/21/2016 VAI letter: 9/23/2016 NAI letter: 9/28/2016 NAI letter: 9/28/2016 NAI letter: 9/29/2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	N/A
Clinical Microbiology Review(s) *(indicate date for each review)*	N/A
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)*	8/19/2016
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)*	8/30/2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ 11/21/2016
• Supervisory Review(s) *(indicate date for each review)*	8/16/2016 11/17/2016
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	8/15/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ ECAC/CAC report/memo of meeting	Meeting date: 6/21/2016
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	11/28/2016
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	8/19/2016 (Review) 11/22/2016 (Addendum)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8/19/2016 (pg. 106- IQA review)
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable- 8/12/2016 (pg. 86-90 of IQA review) Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	**N/A**
• Finalize 505(b)(2) assessment	**N/A**
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	**N/A**
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	**N/A**
❖ 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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/s/

OMOLARA R LAIYEMO
12/15/2016

PeRC Meeting Minutes
August 10, 2016

PeRC Members Attending:
Lynne Yao
Jacquline Yancy
Robert “Skip” Nelson
Hari Cheryl Sachs
Wiley Chambers
Maura O’Leary
Gil Burkhart
Kevin Krudys
Gettie Audain
Thomas Smith
Freda Cooner
Shrikant pagay
Meshaun Payne
Yeruk ‘Lily’ Mulugeta
Adrienne Hornatko-Munoz
Barbara Buch
Lisa Faulcon

Agenda

9:00	NON-RESPONSIVE				
10:00					
10:10					
10:30	NDA 207695	Eucrisa (crisaborole ointment, 2%) Partial Waiver/Deferral/Plan/Assessment (with Agreed iPSP)	DDDP	Lydia Springs	Treatment of mild to moderate atopic dermatitis in patients 2 years and older
10:40	NON-RESPONSIVE				
11:00					
11:20					
11:40					

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NON-RESPONSIVE

Eucrisa (crisaborole ointment, 2%) Partial Waiver/Deferral/Plan/Assessment (with Agreed iPSP)

- Indication: Treatment of mild to moderate atopic dermatitis in patients 2 years and older.
- This product triggers PREA as a new indication, new dosage form and new route of administration.
- This product has a PDUFA goal date of January 6, 2017.
- This product is a new molecular entity (phosphodiesterase 4 inhibitor).
- The division continues to agree with the plan as presented in the agreed iPSP. An assessment will be complete for patients 2 years of age and older.
- The division clarified that there was a potential concern in other PDE4 inhibitors taken

orally that weight loss was observed. The sponsor did not provide analysis of the effect of use of this product on growth in the pediatric patients studied in the clinical trials. The PeRC recommended that the sponsor provide an analysis (by patient) of growth during the trial and follow up period. If there is evidence of poor growth in treated patients, then additional information may be required to be collected in the deferred study in patients 3 months-2 years (e.g., additional longer-term follow up).

- *PeRC Recommendations:*
  - The PeRC agreed with the assessment and plan as provide by the division. However, the PeRC also recommended additional analysis of growth in the pediatric patients studied (see discussion above). In addition, the PeRC recommends that an exploratory safety analysis of growth (i.e., weight and height) in patient subgroups age 2-10 and 10 and above also be provided.

NON-RESPONSIVE

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

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/s/

JACQULINE A YANCY
12/09/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207695

INFORMATION REQUEST

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, MSc
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Please refer to your New Drug Application (NDA) dated January 6, 2016, received January 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crisaborole ointment, 2%.

We are reviewing your NDA and have the following information requests. We ask that you respond by July 18, 2016.

- Because weight loss may be associated with the use of phosphodiesterase 4 (PDE 4) inhibitors, provide patient profiles for the following subjects with ≥ 10 % weight loss:
  302-202008
  301-139005

If you have any questions, please contact Lydia Springs, Regulatory Project Manager, at (240) 402-0078.

Sincerely,

{See appended electronic signature page}

Snezana Trajkovic, MD
Lead Medical Officer
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

LYDIA A SPRINGS
07/13/2016

SNEZANA TRAJKOVIC
07/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207695

MID-CYCLE COMMUNICATION

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, MSc
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crisaborole ointment, 2%.

We also refer to the teleconference between representatives of your firm and the FDA on June 24, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Lydia Springs, Regulatory Project Manager at (240) 402-0078.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: June 24, 2016 @ 10:00 am

Application Number: NDA 207695
Product Name: crisaborole ointment 2%.

Indication: Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.
Applicant Name: Anacor Pharmaceuticals, Inc.

Meeting Chair: Snezana Trajkovic, MD
Meeting Recorder: Lydia Springs

FDA ATTENDEES
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Lydia Springs, MSHS, Regulatory Health Project Manager, DDDP

EASTERN REASEARCH GROUP
Peggah Khorrami, Eastern Research Group

APPLICANT ATTENDEES
Carmen Rodriguez, MSc, SVP, Regulatory Affairs & Quality
Lee Zane, MD, SVP, CMO
Sanjay Chanda, PhD, SVP, Drug Development
(b) (4), Clinical/Regulatory Consultant

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

There is an information request at this time; requesting response by July 12, 2016.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Proposed Date: 9/26/2016
Format: T-con

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/s/

SNEZANA TRAJKOVIC
07/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207695

INFORMATION REQUEST

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, MSc
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Please refer to your New Drug Application (NDA) dated January 6, 2016, received January 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crisaborole topical ointment, 2%.

We also refer to your January 7, 2016 submission, containing 4 pregnancies reported in the atopic dermatitis development program.

We are reviewing the Clinical Study Reports (CSR's) and have the following comments and information requests. We ask that you respond by Tuesday, July 12, 2016.

1. There were 4 pregnancies reported in the atopic dermatitis development program. You referenced the clinical study reports (CSRs) for the detailed narratives but our reviewer was unable to locate them within the CSRs. Provide the specific location in the eCTD where the narratives for these pregnancies may be found, or resubmit copies of the full narratives to the Agency.

2. Additionally, provide detailed narratives regarding any pregnancies that have occurred in studies in the healthy volunteers and psoriasis programs listed in IND (b) (4) and IND 77537. If there are other studies where crisaborole as an active moiety was used, provide similar detailed narratives for any pregnancies that occurred. If pregnancies did not occur, clearly state that when responding.

If you have any questions, please contact Lydia Springs, Regulatory Project Manager, at (240) 402-0078.

Sincerely,

{See appended electronic signature page}

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

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/s/

SNEZANA TRAJKOVIC
07/01/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207695

(E) CAC – FINAL REPORT

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, MSc
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for crisaborole topical ointment, 2%.

Our Executive Carcinogenicity Assessment Committee ([E]CAC) reviewed your study reports on June 21, 2016. As requested in your January 7, 2016 submission, a copy of the final meeting minutes of the (E)CAC regarding crisaborole ointment, 2% is enclosed.

The recommendations made by the (E)CAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this product.

If you have any questions, call Lydia Springs, Regulatory Project Manager, at (240) 402-0078.

Sincerely,

{See appended electronic signature page}

Barbara Hill, PhD
Pharmacology Supervisor
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Executive CAC
Date of Meeting: June 21, 2016

Committee: Karen Davis-Bruno, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Barbara Hill, Ph.D., DDDP, Presenting Reviewer /Supervisor

Author of Minutes: Barbara Hill, Ph.D.

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

NDA #: 207695
Drug Name: Crisaborole ointment, 2%
Sponsor: Anacor Pharmaceuticals Inc.

Background:

Crisaborole is a PDE-4 inhibitor. Crisaborole ointment is being developed for the topical treatment of atopic dermatitis. An oral rat carcinogenicity study report and a dermal mouse carcinogenicity study report were submitted to the original NDA to support approval.

Oral Rat Carcinogenicity Study:

Oral (gavage) doses of 0 (vehicle), 30, 100 and 300 mg/kg/day crisaborole were administered to Sprague-Dawley rats (65/sex/dose) once daily for 104 weeks. The vehicle used in this study was 1% carboxymethylcellulose and the dose volume was 10 ml/kg/day.

No treatment related non neoplastic lesions were noted in this study. A drug related increased incidence of granular cell tumors in the uterus with cervix or vagina, combined, was noted in high dose female rats (vehicle control, 6/65; low dose, 7/65; mid dose, 4/65; high dose, 20/65).

Dermal Mouse Carcinogenicity Study:

Topical doses of 0 (vehicle), 2, 5 and 7% crisaborole ointment were administered to CD-1 mice (65/sex/dose) once daily for 104 weeks. The vehicle used in this study consisted of propylene glycol, (b) (4)%, butylated hydroxytoluene, (b) (4)%, (b) (4)%, (b) (4)%, (b) (4)%, (b) (4)%, (b) (4)%, white petrolatum, (b) (4)%. The dose volume was 1.1 µl/g.

No treatment related non neoplastic lesions were noted in this study. No statistically significant differences in tumor incidence were observed in mice of either sex according to the statistical criteria used by the Executive CAC.

Executive CAC Recommendations and Conclusions:

Oral Rat Carcinogenicity Study

- The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that there was a drug related increased incidence of granular cell tumors in the uterus with cervix or vagina (combined) in high dose female rats.

Dermal Mouse Carcinogenicity Study

- The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that the study was negative for drug related neoplasms.

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

cc:\
/Division File, DDDP
/BHill/Reviewer/Supervisor, DDDP
/LSprings/PM, DDDP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
06/23/2016

ABIGAIL C JACOBS
06/23/2016

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/s/

LYDIA A SPRINGS
06/29/2016

BARBARA A HILL
06/29/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207695

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, MSc
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Please refer to your New Drug Application (NDA) dated January 6, 2016, received January 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for crisaborole ointment 2%.

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 January 7, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 14, 2016. In addition, the planned date for our internal mid-cycle review meeting is June 7, 2016.

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

We request that you submit the following information:

1. We recommend that you develop an in vitro release test (IVRT) methodology and propose 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. The IVRT method development report should contain justification for the selection of the following methodology components:

    a. Diffusion apparatus
    b. Receptor medium selection
    c. Membrane selection
    d. Sampling time points
    e. Temperature

3. The IVRT method validation report should contain 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 should 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. We recommend that you provide the report by May 16, 2016.

6. Provide a detailed in vitro skin flux study report; include the study design, analytical method and in vitro permeation data along with the results.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

PROMOTIONAL MATERIAL

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

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

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

If you have any questions, call Lydia Springs, Regulatory Project Manager, at (240) 402-0078.

Sincerely,

{See appended electronic signature page}

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

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/s/

JILL A LINDSTROM
03/21/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207695

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Anacor Pharmaceuticals, Inc.
1020 East Meadow Circle
Palo Alto, CA 94303-4230

ATTENTION: Carmen R. Rodriguez, M.Sc.
Senior Vice President, Regulatory Affairs and Quality

Dear Ms. Rodriguez:

Please refer to your New Drug Application (NDA) dated and received January 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crisaborole Ointment, 2%.

We also refer to your correspondence, dated and received February 4, 2016, requesting review of your proposed proprietary name, Eucrisa.

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

If any of the proposed product characteristics as stated in your February 4, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Lydia Springs, Regulatory Project Manager in the Office of New Drugs, at (240) 402-0078.

Sincerely,

{See appended electronic signature page}

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

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/s/

LOUIS R FLOWERS
03/18/2016

IRENE Z CHAN on behalf of TODD D BRIDGES
03/18/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077537

MEETING MINUTES

Anacor Pharmaceuticals, Inc.
Attention: Sheldon Mullins
Senior Director, Regulatory Affairs
1020 East Meadow Circle
Palo Alto, CA 94303

Dear Mr. Sheldon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for crisaborole topical ointment, 2%.

We also refer to the teleconference between representatives of your firm and the FDA on September 23, 2015. The purpose of the meeting was to discuss the anticipated submission of a New Drug Application (NDA) for crisaborole topical ointment, 2%.

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 Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 23, 2015; 11:00 a.m.
Meeting Format:	Teleconference
Application Number:	IND 077537
Product Name:	crisaborole topical ointment, 2%
Proposed Indication:	Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older
Sponsor Name:	Anacor Pharmaceuticals, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	J. Paul Phillips

FDA ATTENDEES
Kendall A. Marcus, MD, Director, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Yichun Sun, PhD, Acting Quality Assessment Lead, DNDP II/NDPB V
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Roy Blay, PhD, Scientific Reviewer, DCCE/GCPAB
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Omolara Laiyemo, PharmD, Regulatory Health Project Manager, DDDP
J. Paul Phillips, MS, Team Leader (Acting), Project Management, DDDP

SPONSOR ATTENDEES
Carmen Rodriguez, MSc, SVP, Regulatory Affairs and Quality Assurance
Lee Zane, MD, MAS, SVP, Chief Medical Officer
Sheldon Mullins, Senior Director, Regulatory Affairs
(b) (4) Clinical & Regulatory Consultant
(b) (4)

Purpose of the Teleconference:
To discuss the anticipated submission of a New Drug Application (NDA) for crisaborole topical ointment, 2%

Regulatory Correspondence History

We have had the following meeting with you:
- 02/13/2008: Pre-IND meeting
- (b) (4)
- 02/26/2014: End-of-Phase 2 meeting (atopic dermatitis)

We have sent the following correspondences:
- 07/06/2011: Non-Clinical SPA agreement letter
- 08/17/2011: Advice/IR letter
- 03/23/2011: Advice/IR letter
- (b) (4)
- 09/26/2012: Advice/IR letter
- 01/31/2013: Advice/IR letter
- 05/09/2013: Advice/IR letter
- 12/31/2013: Advice/IR letter
- 02/20/2014: Advice/IR letter
- 06/16/2014: Advice/IR letter
- 06/20/2014: Advice/IR letter
- 07/07/2014: Pediatric Study Plan—Written Response letter
- 10/06/2014: Pediatric Study Plan—Initial Agreement letter
- 06/19/2015: Inadequate PPSR letter

Chemistry, Manufacturing and Controls (CMC)

Question 1.1:
Does the Agency agree that the proposed specification for crisaborole drug substance is adequate to support NDA submission and filing?

Response:
The tests listed in the drug substance specification appear reasonable to support your NDA submission. However, if the drug substance (b)(4) the drug substance should be added to the drug substance specification. The test methods and acceptance criteria of the drug substance specification will be evaluated during NDA review.

Question 1.2:
Does the Agency agree that the proposed specification for Crisaborole Topical Ointment, 2% is adequate to support NDA submission and filing?

Response:
The tests listed in the drug product specification appear reasonable to support your NDA submission. (b)(4) drug substance should be added to the drug product specification. The test methods and acceptance criteria of the drug product specification will be evaluated during NDA review.

Question 2:
Does the Agency agree that the proposed drug substance stability data package supports NDA submission and filing?

Response:
The proposed drug substance stability data package appears reasonable to support your NDA submission. The retest period of the drug substance will be determined during NDA review.

Question 3.1:
Does the Agency agree with Anacor's proposed submission strategy to submit updated drug product stability data for 100-g tubes (12-month data for 3 primary stability lots) within 30 calendar days of the original NDA submission?

Response:
Yes.

Question 3.2:
Does the Agency agree that the proposed drug product stability data package supports NDA submission and filing?

Response:
The proposed drug product stability data package appears reasonable to support your NDA submission. The expiration dating period of the drug product will determined during NDA review based on available stability data.

Additional CMC Comment:
Results of photostability studies on the drug substance and drug product should be included in your NDA submission.

Pharmacology/Toxicology

Question 4:
Does the Agency concur that the nonclinical development program is adequate to support NDA submission based on information provided in Section 9.0, Appendix 1, and Appendix 4 of the Briefing Document?

Response:
Yes, we agree.

Clinical Pharmacology

Question 5:
Does the Agency concur that the studies to characterize the clinical pharmacology of Crisaborole Topical Ointment, 2% in humans are adequate to support the NDA submission and filing?

Response:
The Clinical Pharmacology program appears reasonable. Filing determination will be made after NDA submission.

It appears that major metabolite AN7602 was not evaluated in vitro for potential to inhibit or induce cytochrome P450 enzymes. Results from trial AN2728-AD-102 showed that the exposure to metabolite AN7602 was greater than 30% of the parent AN2728. Therefore, you should provide in the NDA results of in vitro enzyme inhibition and induction studies.

Provide the following in your NDA:

1. A table listing all clinical trials and the associated formulation used in each trial. Provide a discussion of any studies conducted to bridge the formulations.
2. Pharmacokinetic (PK) datasets in SAS Transport format (.xpt).
3. Method validation report and bioanalytical reports for all trials with PK assessments.
4. Evidence of long term storage stability to support duration of PK sample storage for all trials. Include a table listing the maximum duration of sample storage for each trial. The duration can be based on time of first subject enrolled to time of last sample analysis if there is sufficient documented storage stability to support the duration.

Clinical/Biostatistics

Question 6:
Does the Agency agree that the proposed data presentation in the ISE will support the review and evaluation of efficacy data to be included in this NDA?

Response:
The ISE should include comprehensive in-depth analysis of the individual study results in addition to pooled efficacy results, and should discuss the extent to which the results of the relevant studies reinforce or do not reinforce each other. This may require additional discussion beyond individual study summaries and a pooled analysis. For additional information on the content of the ISE refer to guidance for industry *Integrated Summary of Effectiveness* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf).
Individual study-level study reports as well as the study-level datasets should be included in 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) of the NDA.

For the datasets, we have the following general comments:

1. Submit study-level electronic datasets for clinical studies in SAS transport form (.xpt). You should submit both SDTM datasets (raw data directly from the CRF in standardized format) and analysis datasets.
2. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
3. The analysis dataset documentation (define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding define.pdf files in addition to the define.xml files.
4. You plan to use the Multiple Imputation (MI) method which involves generating multiple datasets. Instead of submitting the multiple imputed datasets, please provide the code including seed number used to implement MI. In addition, statistical programs for any non-standard analyses should also be submitted.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment), and an annotated copy of the Case Report Form (which maps variables in the datasets to the CRF).

Meeting Discussion:
The Agency clarified that while an imputed variable that used a single imputation method such as Last Observation Carried Forward (LOCF) could be included in the data sets, for the data sets generated using the multiple imputation (MI) method, the sponsor should submit sufficient details concerning the MI (i.e., random seed number, SAS codes) so as to be able to reproduce the sponsor's analysis results.

Question 7.1:
Does the Agency agree that the structure of the ISS presented in this briefing document will provide adequate information to conduct a review and evaluation of the safety of the Crisaborole Topical Ointment, 2%?

Response:
In general, the structure of the ISS presented in your briefing document is acceptable to allow review and evaluation of the safety of the crisaborole topical ointment, 2%.

The primary analysis of safety to support labeling will be based on pooled data from Phase 3 trials AN2728-AD-301 and AN2728-AD-302.These two identical, randomized, vehicle-controlled, parallel group Phase 3 trials enrolled 1511 subjects with mild to moderate atopic dermatitis who applied crisaborole topical ointment, 2% twice daily for 29 days. You appear to propose (b) (4)

(b) (4)

All observations related to safety (e.g. adverse events, vital signs, ECGs, local tolerability, physical findings and laboratory assessments) should be summarized for the pooled Phase 3 datasets; all analyses of safety in special populations should be conducted using this pooled dataset.

Based on the differences in study design (e.g. bilateral comparisons of target lesions, open-label trials, microplaque assessments etc.), study populations, and indications (e.g. psoriasis versus atopic dermatitis), the safety data from the remaining trials is considered supportive.

The integrated summary of safety may provide a summary of the pooled Phase 3 safety data well as a comprehensive discussion of safety across the entire clinical program for the indications of atopic dermatitis and psoriasis, including data regarding dermal safety, bioavailability, Phase 2 and Phase 3 clinical findings.

The pooled analysis (Phase 3 trials AN2728-AD-301 and AN2728-AD-302) should include the following:

1) Adverse event tables ≥ 1% regardless of causality.
2) Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) ≥ 1%.
3) Narratives for all deaths, serious AEs regardless of causality, and all subjects who became pregnant or discontinued from the trials.
4) Case report forms (CRFs) for all deaths, serious AEs regardless of causality, or discontinued from the trials due to adverse events. A study's CRFs should be placed in a CRF folder under the applicable trial with a file tag of "case-report-forms."
5) Also provide the following:
   Electronic links for:
   a) all serious AEs
   b) all severe AEs
   c) all patients discontinued regardless of reason
   d) all deaths
6) CRF should be referenced under the trial in which it belongs and tagged as "casereportforms" in that study's stf.xml file.
7) CRFs that are not submitted should be readily available upon request.
8) Line listings for all abnormal safety findings (e.g. adverse events, vital signs etc.)
9) Shift tables for all laboratory values. 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.
10) Shift tables for all vital signs. Provide the normal range of values for all parameters
11) If the product is approved in any other jurisdiction, provide a worldwide safety update in addition to the 120 day safety update.

With regard to the long term safety trial, AN2728-AD303, provide an analysis in the ISS and final study report of those subjects who required treatment with low to mid potency topical corticosteroids because their atopic dermatitis became "intolerable", those subjects who

experienced 3 consecutive cycles without improvement and those subjects who discontinued the trial due to an adverse event.

At the time of NDA submission, submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Meeting Discussion:
The Agency clarified that the sponsor should provide narratives for all subjects who discontinued due to adverse events. Other narratives should be available upon request.

The sponsor proposed to provide Patient Profiles for subjects with abnormal findings rather than provide line listings. The Agency responded that the sponsor could provide a sample of the Patient Profile for consideration for inclusion in the NDA.

The Agency stated that shift tables for all vital signs using published standards from medical literature to define normal ranges of age and gender is acceptable.

Post meeting comment:
The sponsor provided an example of the Patient Profile. The proposal to submit Patient Profiles containing safety findings of adverse events, vital signs, and related safety data instead of submitting line listings for subjects with abnormal safety findings is acceptable. In addition, Patient Profiles may be submitted for subjects who experienced serious AEs and subjects who are discontinued from the trials due to adverse events.

Question 7.2:
Does the Agency concur with Anacor's plans for providing individual study-level safety datasets for all studies included in the ISS to support review of the safety data?

Response:
In addition to providing a pooled dataset from the Phase 3 trials, it is reasonable to provide individual study-level safety datasets for all trials in your development program because the Phase 1 and Phase 2 trials include different study designs (e.g. bilateral comparisons, open-label trials etc.), study populations, and indications (e.g. psoriasis).

Meeting Discussion:
The sponsor stated that they intend to submit data sets for the Phase 3 trials in CDISC compliant format, with data from supportive trials to be submitted in SAS data set format. The Agency stated that it was important to be able to pool data from additional (supportive) trials if a safety signal was identified. The sponsor agreed to provide data sets from supportive trials in a format that would allow pooling with Phase 3 CDISC compliant data sets.

Question 8:
Does the Agency agree that the size of the proposed safety package is acceptable to support review of the NDA?

Response:
The proposed safety package appears reasonable. See response to Question 7.2. The adequacy of the safety database is a review issue.

Question 9:
Does the Agency concur that a formal REMS proposal will not be required for NDA submission based on the overall safety profile of Crisaborole Topical Ointment, 2% in subjects with mild to moderate AD?

Response:
At this time we are not aware of a safety signal that would necessitate a REMS. Labeling and regulatory safety reporting requirements may be sufficient to mitigate risks and preserve benefits. Final determination will be a review issue.

Additional Clinical Comments:
The final study report for Study AN2728-TQT-108 (Thorough QT/QTc) should include the following:

a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
b. Electronic copy of the study report
c. Electronic or hard copy of the clinical protocol
d. Electronic or hard copy of the Investigator's Brochure
e. Annotated CRF
f. A data definition file which describes the contents of the electronic data sets
g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
i. Dataset whose QT/QTc values are the average of the above replicates at each nominal time point
j. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
l. A completed Highlights of Clinical Pharmacology Table (attached)

ISE and ISS should be submitted to the FDA in accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively). For information about the location of ISS and ISE in the CTD, the sponsor is referred to the guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* at the FDA website. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)

Regulatory

Question 10:
Anacor intends to submit a *Request For Priority Review Designation* as detailed in Section 11.3. Although Anacor realizes this will be a review issue, any comment or guidance would be appreciated.

Response:
As stated in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm358301.pdf), you may submit a request for priority review designation at the time you submit your original NDA. The FDA would notify you of a priority review designation by day 60, and a standard review designation by day 74.

You should refer to the above mentioned guidance for the content of the priority review designation request.

Administrative

Question 11:
Does the Agency agree that the proposed content of this NDA includes all required components of a complete NDA to support review?

Response:
In general, the proposed content of your planned NDA submission is acceptable. Per PDUFA V, all applications are expected to be complete at the time of original submission. The major components of the application which include the full study reports of required long-term safety trials are to be submitted with the original application and are not subject to agreement for late submission.

In addition, to support the approval of a new molecular entity, the Agency requires a comprehensive assessment of the benefits and risks of your drug product. The information needed to complete this analysis is described in the guidance for industry *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation*

Plan which is available at
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm.

Although you have addressed many of the elements of this benefit-risk assessment in your meeting package, we recommend that you provide a more granular approach in your NDA benefit- risk discussion. Your application may include the following information:

1. Analysis of the condition which includes
    - Clinical manifestations (frequency and severity) and potential for progression
    - Prevalence in the general population and subpopulations
    - Proportion of patients who experience mild, moderate or severe disease
    - Severity across subpopulations (e.g. pediatric subgroups versus adult subgroups)
    - Impact on daily living in all populations and subpopulations
    - Uncertainties in the understanding of the condition
    - Subpopulations of particular concern

2. Current treatment options
    - Standard of care: list of approved therapies, drugs used off-label, nonprescription drugs, medical and surgical procedures, and non-drug therapies
    - Efficacy information and safety / tolerability issues associated with each these therapies
    - Uncertainties in the understanding of the risks and benefits of the treatment options
    - Adequacy of current therapies to meet the medical needs of the affected population and subpopulations (e.g. patients with refractory disease etc)

3. Benefit
    - Trial design(s) and effect size
    - Limitations of the data
    - Clinical relevance of endpoints
    - Durability of benefit
    - Variation of benefit across subpopulations
    - Any exclusions in the studied population that would limit use in the general population
    - The number needed to treat (NNT) to achieve the treatment response/prevent bad outcome (e.g. likelihood of benefit)
    - Uncertainties in the evidence or about the product

4. Risk
    - Ability of the safety database to reflect expected use in the patient population
    - The most important safety concern
    - Important aspects of the safety concern (e.g. range of severity, dose relationship, prevention/mitigation, reversibility etc.)
    - Risks associated with suboptimal management of the disease
    - Uncertainties regarding risk

5. Conclusions
    - This information may be tabulated in the following framework:

Figure 1: FDA Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

Additional E-Submission (ESUB) Comments:
From a technical standpoint, the proposed format for the planned NDA is acceptable. However, please see additional comments below.

- If you are utilizing m1 v3.3 DTD, then FDA Form 3397 can be placed in m1.1.3 otherwise, please provide it in m1.2 cover letter section, with a clear leaf title.
- Do not provide duplicate heading element (e.g.m1.12.4) for sections that have more than one document. Instead, a single m1.12.4. section should be provided and referenced documents should have clear leaf title, that is indicative of the content
- Please do not create additional nodes beyond what is in the specifications (e.g. 2.2.1). If you do, it's likely that the information will not display properly. Instead the submission needs to comply with ICH and FDA specifications.
- Please refer to the Granularity Document, "Annex to M4: Organization of the CTD" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf for placement of single or multiple documents in the appropriate sections (e.g. m.2.4). Please note that single pdf files that are more than 5 pages, should include proper bookmarks, table of contents and hyperlinks.
- List of investigators (single pdf file with bookmarks, table of contents and hyperlinks) should reside in m5 (not m5.2.), under the specific study's Study Tagging File (STF) and file tagged as "list-description-investigator-site".
- For archival purposes, also submit a pdf file of any document submitted in word (e.g. labeling). 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.

Additional general information regarding your planned NDA submission may be found in Attachment 2.

Meeting Discussion:
The sponsor inquired whether they could submit a request for proprietary name review to the NDA following the filing. The Agency confirmed that a request for proposed proprietary name review can be submitted at any time during the NDA review cycle, including with the original NDA submission.

The proposed proprietary name request for review has a separate PDUFA goal date of 90 days. The sponsor should keep in mind that if the primary proposed proprietary name is denied, additional names submitted for review will each have a 90-day review cycle. Therefore, the sponsor is encouraged to submit a proposed proprietary name for review as early in the review cycle as possible.

Administrative Comments

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

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

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time FDA is not aware of a safety signal that would necessitate a REMS. Labeling and regulatory safety reporting requirements may be sufficient to mitigate risks and preserve benefits. Final determination will be a review issue.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application component may be submitted within 30 calendar days after the submission of the original application:

- Updated drug product stability data for 100-g tubes (12-month data for 3 primary stability lots) within 30 calendar days of the original NDA submission

Prominently identify the submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

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

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

c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

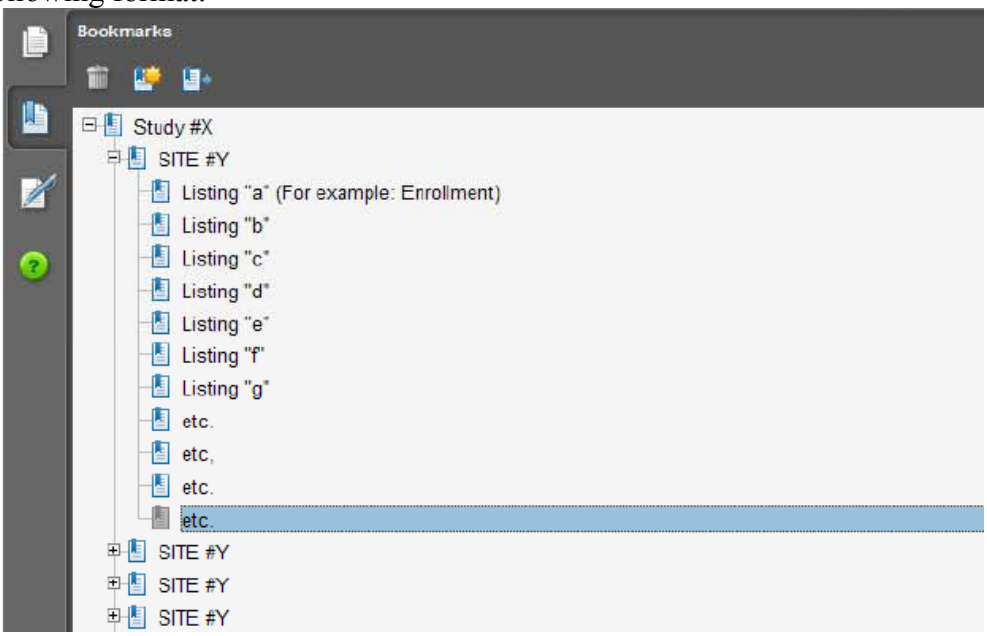
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

Attachment 2

Pre-NDA
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

The **Study Data Standards Common Issues Document** can be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

NDA/BLA content and format
CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format), if any
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset

h) listing of raw data definitions
i) analysis data definitions
j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)
k) documentation of programs

7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf).

8) Pediatric Studies:

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

9) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application

10) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

11) References:

There should be active links from lists of references to the referenced article.

Studies, Data And Analyses

12) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).

13) Provide a table with the following columns for each of the completed Phase 3 clinical trials:
a) Site number
b) Principle investigator
c) Location: City State, Country
d) Number of subjects screened
e) Number of subjects randomized
f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)

g) Number of protocol violations (Major, minor, including definition)
14) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
15) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components: a) subject age and gender b) signs and symptoms related to the adverse event being discussed c) an assessment of the relationship of exposure duration to the development of the adverse event d) pertinent medical history e) concomitant medications with start dates relative to the adverse event f) pertinent physical exam findings g) pertinent test results (for example: lab data, ECG data, biopsy data) h) discussion of the diagnosis as supported by available clinical data i) a list of the differential diagnoses, for events without a definitive diagnosis j) treatment provided k) re-challenge and de-challenge results (if performed) l) outcomes and follow-up information m) an informed discussion of the case, allowing a better understanding of what the subject experienced.
16) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request. 17) Provide reports for any autopsies conducted on study.
18) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
19) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis
20) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies

and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
b) Exposure-Response Relationships – important exposure-response assessments.
c) Less common adverse events (between 0.1% and 1%).
d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
f) Marked outliers and dropouts for laboratory abnormalities.
g) Analysis of vital signs focused on measures of central tendencies.
h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
l) Standard analyses and explorations of ECG data.
m) Overdose experience.
n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
o) Explorations for:
    i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
    ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
    iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
    iv) Drug-demographic interactions
    v) Drug-disease interactions
p) Drug-drug interactions
    i) Dosing considerations for important drug-drug interactions.

ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
Financial Disclosure Information
21) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf).

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/s/

KENDALL A MARCUS
10/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077537

MEETING MINUTES

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, MSc
Senior V.P., Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303

Dear Ms. Rodriguez:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AN2728 Topical Ointment, 2%.

We also refer to the teleconference between representatives of your firm and the FDA on February 26, 2014. The purpose of the meeting was to discuss the development program for AN2728 Topical Ointment, 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

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 Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	February 26, 2014; 8:30 a.m. ET
Meeting Location:	Teleconference
Application Number:	IND 077537
Product Name:	AN2728
Proposed Indication:	treatment of mild to moderate atopic dermatitis in patients 2 years of age and older
Sponsor Name:	Anacor Pharmaceuticals, Inc.
Meeting Chair:	Tatiana Oussova, MD, MPH
Meeting Recorder:	J. Paul Phillips

FDA ATTENDEES
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Stanka Kukich, MD, Deputy Director, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
An-Chi Lu, MS, PharmD, Clinical Pharmacology Reviewer, DCP3
Carin Kim, PhD, Biostatistics Reviewer, DB III
Julie Beitz, MD, Director, ODE III
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Belainesh Robnett, MS, Regulatory Health Project Manager, DDDP
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Carmen R. Rodriguez, MSc, SVP, Regulatory Affairs & Quality
Lee Zane, MD, MAS, SVP, Chief Medical Officer
Xiaoming Lin, Vice President, Clinical Research and Development
(b) (4)
Le-Van Nguyen, RAC, Senior Director, Regulatory Affairs
Randy Aquipel, RAC, Associate Director, Regulatory Affairs
David Perry, Chief Executive Officer and President

Purpose of the Meeting:
To discuss the development program for AN2728 Topical Ointment, 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older

Regulatory Correspondence History

We have sent the following correspondences regarding the proposed AD indication:
- 09/26/2012: Advice/IR letter
- 09/05/2013: Advice/IR letter

Chemistry, Manufacturing and Controls (CMC)

Question 1a:
Anacor has developed regulatory drug substance and drug product specifications for Phase 3 and registration batches as presented in Sections 7.1.6.1 and 7.2.4.1, respectively. The proposed acceptance criteria were established based on batch history, toxicological qualification, and applicable ICH guidelines and FDA advice.

Does the Agency concur that the proposed regulatory specification for AN2728 drug substance is adequate to support Phase 3 clinical and NDA registration batches?

Response:
Yes we concur.

Question 1b:
Does the Agency concur that the proposed specification for AN2728 Topical Ointment, 2% is adequate to support Phase 3 clinical and NDA registration lots?

Response:
Yes we concur, provided that you will replace "report results" with a meaningful numeric range as the acceptance criterion for the test on viscosity.

Question 2:
The stability program for the three drug substance registration batches also planned for use in Phase 3 clinical trial materials will be conducted in accordance with ICH Q1A(R2). Registration batches will be packaged in (b)(4) the proposed container-closure system for the commercial drug substance. (Section 7.1.11.1)

Does the Agency concur that the stability protocol proposed for the registration batches will generate the necessary data to establish the shelf life and storage conditions for AN2728 drug substance?

Response:
Yes, we concur.

Question 3:
The stability program to support registration of AN2728 Topical Ointment, 2% will be executed in accordance with ICH Q1A(R2). Registration and Phase 3 clinical stability lots will be packaged at a (b) (4)-gram minimum fill weight in the container-closure system proposed for the to-be-marketed product. (Section 7.2.6)

Does the Agency concur that the stability protocol proposed for the registration lots will generate the necessary data to establish the shelf life and storage conditions for the to-be- marketed drug product?

Response:
Yes, provided that you will include weight loss in the registration stability protocol.

Pharmacology/Toxicology

Question 4:
Anacor has conducted and is continuing to conduct thorough nonclinical safety assessments of AN2728 as recommended by ICH M3(R2). Anacor considers that the nonclinical studies completed to date, the ongoing and planned studies, and the proposed timing of these studies adequately support initiation of Phase 3 clinical trials and a complete nonclinical section of the NDA application for AN2728 Topical Ointment, 2% for topical treatment of mild to moderate AD in patients 2 years of age and older. (Section 8.0; Appendix 15)

Does the Agency agree with this nonclinical plan to support conduct of Phase 3 studies and eventual registration?

Response:
In principle we agree that the completed, ongoing, and planned studies are appropriate to meet the non-clinical safety requirements according to the current ICH guidelines. However, a final decision about the adequacy of these studies, or need for additional studies to support Phase 3 trials and eventual registration, will be made after review of full study reports.

Clinical

General Comments
To date you have conducted the following trials to evaluate AN2728 Topical Ointment, 2% for the treatment of atopic dermatitis (AD):

AN2728-AD-102 (Phase 1)
- Multicenter, open-label, maximal use, 4- week trial to assess safety and PK of AN2728 Topical Ointment, 2% applied twice per day in 34 subjects age 2-17 years.

AN2898-AD-202 (Phase 2a)
- Multicenter, randomized, double- blind, vehicle-controlled, 6-week, within- subject, bilateral lesion comparison trial of AN2898 ointment, 1% and vehicle with AN2728

Topical Ointment, 2% and vehicle applied twice per day in 46 subjects age 19 to 73 years (not conducted with the to-be-marketed formulation)

AN2728-AD-203 (Phase 2a)

- Multicenter, open-label, 4- week, non-randomized, safety, tolerability and PK trial of AN2728 Topical Ointment, 2% applied twice per day in 23 subjects age 12-17 years.

AN2728-AD-204 (Phase 2b)

- Multicenter, randomized, double- blind, 4-week, within- subject, bilateral lesion comparison trial of AN2728 Ointment, 0.5% and AN2728 ointment, 2% applied twice per day in 86 subjects age (b)(4) years to assess safety and efficacy.

Your estimates of treatment effect used for powering your Phase 3 trials are not based on Phase 2 trial(s) using the same study population, the same measure and the same definition of 'success/failure' that will be used in the Phase 3 trials.

Question 5a:
Anacor considers the study designs and assessment plans for the Phase 3 registration studies adequate to support registration for the proposed indication of the topical treatment of mild to moderate AD in patients 2 years of age and older. (Sections 9.4.1.1 and 9.4.1.2; Appendix 19)

Does the Agency agree that the design of study AN2728-AD-301, as one of two identically designed Phase 3 studies, is adequate to demonstrate the efficacy and safety of AN2728 Topical Ointment, 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older?

Response:
You proposed to conduct two similarly designed multicenter, randomized, double-blind, vehicle-controlled trials to assess the safety and efficacy of AN2728 Topical Ointment, 2% in 750 pediatric subjects (ages 2–17 years) with mild to moderate atopic dermatitis treated twice daily for 28 days.

Although the data submitted to date appears to support your proposed dosing regimen and duration of treatment, we have the following concerns:

For powering your Phase 3 trials, you assumed success rates of 20% and 10% in the active and vehicle treatment groups, respectively, and stated that the proposed sample size of 750 subjects would yield 90% power.

The Agency reiterates its previous comments in the advice letter (IND 102317; 1/23/2009) that due to the lack of control, within-subject, bilateral trials are limited in assessing dose response as well as limited in providing reliable safety and efficacy data. You are also referred to the minutes from the Pre-IND meeting (IND 77537; 2/13/2008) that in order to power future Phase 3 trials based on previously conducted Phase 2 trials, similar endpoints and patient populations intended for the Phase 3 trials should be assessed in the Phase 2 trials. The primary endpoint for Phase 2

trials (AN2728-AD-204 and AN2728-AD-202) was based on the Atopic Dermatitis Severity Index (ADSI) of the target lesion only and not on a global disease severity as whole. ADSI is calculated from a number of variables and is not used routinely in clinical settings. Therefore, taking into account that the primary endpoint in trials AN2728-AD-202 and AN2728-AD-204 was based on ADSI, and not on the ISGA scale, and that AN2728-AD-203 was a small open-label, non-randomized, safety trial, you run the risk of underpowering your Phase 3 trials.

Question 5b:
Does the Agency agree that the proposed Exclusion and Inclusion criteria for the Phase 3 studies are reasonable for the targeted population with mild to moderate AD, aged 2 years and older, as described in the TPP (Appendix 1)?

Response:
In your Phase 3 trial(s), you propose to enroll pediatric subjects aged 2 to 17 years with mild to moderate atopic dermatitis (IGSA score 2 or 3) involving ≥ 5% treatable BSA (excluding the scalp). As your target population also includes adults, you propose to extrapolate findings of efficacy and safety in the pediatric population to the adult population. Although atopic dermatitis is primarily a disease of the pediatric population, you also need to demonstrate the safety and efficacy of your product in the adult population. The indication garnered will be based upon the population studied and for whom safety and effectiveness is established. The Division recommends the inclusion of a sufficient number of adult subjects to be able to assess efficacy and safety in that age subgroup.

Meeting Discussion:
The sponsor agreed with the FDA recommendation to include adult subjects in Phase 3 trials.

Question 5c:
Does the Agency agree with the plans to stratify enrollment in the Phase 3 pivotal studies by only study center and not also by age group?

Response:
Yes. As safety/efficacy might vary across the age groups, you should ensure that a sufficient number of subjects are enrolled in the various age categories, in particular across the younger age groups.

Question 6a:
The primary efficacy endpoint for the Phase 3 studies, as stated in protocol AN2728-AD-301, is the proportion of subjects achieving treatment success in the Investigator's Static Global Assessment (ISGA) at Day 29 in the AN2728-treated group compared with the vehicle-treated group. Treatment success is defined as an ISGA score of Clear (0) or Almost Clear (1) at Day 29, with at least a 2-grade improvement from baseline. (Section 9.4.1.1)

Does the Agency concur that ISGA is an appropriate efficacy measurement tool for the pivotal studies?

Response:
The category "Clear" should indicate true absence of disease (e.g., no residual coloration other than hypo/hyperpigmentation). Modify the descriptor in the "Clear" category to include "Minor residual hypo/hyperpigmentation."

Meeting Discussion:
The sponsor agreed with the FDA recommendation to modify the descriptor in the "Clear" category.

Question 6b:
Does the agency agree that the stated primary efficacy endpoint is appropriate?

Response:
Yes. The proposed primary efficacy endpoint of the proportion of subjects achieving treatment success which is defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline is acceptable.

Question 7a:
The primary efficacy endpoint in each of the proposed Phase 3 studies is the proportion of subjects achieving success in ISGA at Day 29, which will be compared with logistic regression with factors of treatment group and analysis center. The primary method of handling missing efficacy data for the primary endpoint will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) imputation. (Appendix 19)

Does the Agency agree with the use of the Markov Chain Monte Carlo (MCMC) imputation method for handling missing efficacy data for the primary endpoint?

Response:
The Agency has the following general comment concerning your primary analysis method. For the primary analysis method, you are proposing to use logistic regression with factors of treatment group and analysis center. You are proposing to investigate the site-to-site variability after pooling those sites that did not meet the minimum enrollment. However, as the pooling process could mask center effects, you are encouraged to also investigate center-to-center variability prior to pooling.

Your proposal to use the Markov Chain Monte Carlo (MCMC) imputation method for handling missing data as the primary imputation method appears reasonable.

Meeting Discussion:
The FDA clarified that the sponsor will need to investigate the center-to-center variability on the original sites for the main effects as well as the interaction term. The sponsor agreed with the FDA recommendations.

Question 7b:
Does the Agency have any other comments regarding the endpoint and/or the analyses for study AN2728-AD-301?

Response:
No, we do not have additional comments at this stage.

Question 8a:
There are 3 secondary endpoints for the pivotal Phase 3 studies, as described in protocol AN2728-AD-301. These endpoints will be evaluated with a sequential process to control for multiplicity. The first of these endpoints is the proportion of subjects with an ISGA of Clear (0) or Almost Clear (1) at Day 29, which will be analyzed using the same methods as the primary analysis. If the first test is statistically significant, then the process will proceed to evaluate the second secondary efficacy endpoint of the time to improvement in pruritus, defined as a pruritus score of None (0) or Mild (1), which will be analyzed using Kaplan-Meier methods and the log-rank test. Finally, if both of the preceding endpoint results are statistically significant, then the third endpoint, time to success in the ISGA, will be analyzed using Kaplan-Meier methods and the log-rank test. (Appendix 19)

Does the Agency concur with the acceptability of the proposed secondary endpoints and the sequential process to control for multiplicity?

Response:
Your approach for adjusting multiplicity appears reasonable.

We have the following general comments regarding your proposed secondary endpoints:

- Secondary endpoints should be clinically meaningful and supportive of the proposed primary efficacy endpoint. The secondary endpoints that the Division recommends include an evaluation of the signs and symptoms of atopic dermatitis (e.g. erythema, induration/papulation, scaling and oozing/crusting) which should be dichotomized to success/failure *a priori* in the protocol. These signs should be evaluated globally on a 4-5 point scale and not by body region (as in the EASI score.)

- You propose to evaluate the time to improvement in pruritus, defined as a pruritus score of None (0) or Mild (1), as a secondary endpoint. However, you do not clearly identify the population that you intend to enroll with regard to baseline pruritus score. In addition, you do not provide supporting data (e.g., PRO dossier) that the instrument used to assess pruritus is reliable, valid, and able to detect clinically meaningful changes. Because of these deficiencies, the assessment of pruritus in this trial has limited regulatory utility.

  Because you propose to include patient-reported outcome (PRO) instruments {Severity of Pruritus Scale and Dermatology-related quality-of-life (QoL) questionnaires} among your assessments of treatment benefit, the Division recommends that you refer to the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to support Labeling Claims* at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

Meeting Discussion:
The sponsor agreed not to use the EASI score and will include signs and symptoms of atopic dermatitis (AD) as exploratory endpoints which are not intended for labeling.

The sponsor agreed not to use time to improvement of pruritus as a secondary endpoint. Time to improvement of pruritus will be used as an exploratory endpoint which is not intended for labeling.

Question 8b:
Does the Agency concur with the acceptability of the proposed analysis of pruritus using Kaplan-Meier methods and log-rank test?

Response:
Your analysis approach for the pruritus endpoint appears reasonable.

Question 8c:
Does the Agency concur with the acceptability of the proposed analysis of ISGA using Kaplan-Meier methods and log-rank test?

Response:
Your analysis approach for the time to success in the ISGA endpoint appears reasonable.

Question 8d:
Does the Agency have any other comments or suggestions regarding the analysis of the secondary endpoints?

Response:
No.

Question 9a:
Anacor plans to evaluate the long-term safety of treatment with AN2728 Topical Ointment, 2% in children and adolescents aged 2 to 17 years with mild to moderate AD in an open-label 48-week safety study, AN2728-AD-303. This rollover study will enroll eligible patients who completed the Phase 3 studies. Anacor believes that this study will provide adequate data to support the long-term use of AN2728 Topical Ointment, 2.
(Section 9.4.1.3; Appendix 20)

Does the Agency agree that the design of study AN2728-AD-303 is adequate for the evaluation of the long-term safety of the product and to support registration?

Response:
Refer to the response to Question 9b for general comments regarding the evaluation of the long-term safety of your product.

Question 9b:
Does the Agency have any comments on the long-term study design or analysis proposed for this study?

Response:
We have the following general comments regarding the synopsis of your long term trial:

- Stopping criteria should be established for subjects with inadequate treatment response or "treatment failures" so that these subjects may receive effective therapy.

- It is not clear whether you intend to require continued treatment of areas of atopic dermatitis which resolve with application of the study product during the On-Treatment Period. If you intend to require treatment of areas which are free of disease (especially in the youngest subjects), provide your justification.

Meeting Discussion:
The sponsor agreed to submit the subject treatment stopping criteria for the long term trial protocol.

The sponsor agreed that treatment would be discontinued in areas determined to be completely clear, in the long term trial.

Question 10:
Does FDA agree that the proposed safety evaluations for the Phase 3 studies are adequate to support registration?

Response:
In general, the proposed safety monitoring which includes adverse events, physical examinations, vital signs and laboratory assessments (hematology, serum chemistry and urine pregnancy testing in females of child bearing potential) is acceptable. In addition, an active assessment of local safety at each visit using an appropriate scale is recommended.

You included the Cardiovascular Electrographic Expert Report for TQT trial (AN2728-TQT-108) in your briefing document. As recommended in the Advice Letter dated 1/31/2012 (IND 77537), submit the final study report with the following items for Agency review:

1. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
2. Electronic copy of the study report
3. Electronic or hard copy of the clinical protocol
4. Electronic or hard copy of the latest Investigator's Brochure
5. Annotated case report forms (CRF)
6. A data definition file which describes the contents of the electronic data sets

7. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses.
8. Make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
9. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
10. Narrative summaries and case report forms for any
    a. Deaths
    b. Serious adverse events
    c. Episodes of ventricular tachycardia or fibrillation
    d. Episodes of syncope
    e. Episodes of seizure
    f. Adverse events resulting in the subject discontinuing from the study
11. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
12. A completed Highlights of Clinical Pharmacology Table (see attached)

Meeting Discussion:
The sponsor agreed to add burning and stinging at the application site, measured on a 3 point scale to an active assessment of local safety.

Question 11a:
Anacor estimates that the overall safety database supporting registration will contain ~2150 evaluable subjects exposed to AN2728. Approximately 1000 of those will be pediatric AD subjects (aged 2-17 years) treated with AN2728 Topical Ointment, 2% for 4 weeks in the two Phase 3 efficacy and safety studies. A long-term safety study is anticipated to treat a total of 500 subjects aged 2–17 years, with a minimum of 300 evaluable subjects exposed to AN2728 for at least 6 months and a minimum of 100 evaluable subjects exposed for 1 year. Enrollment in the Phase 3 studies will be stratified by center only and not by age; however, based on past enrollment in studies of other approved products with similar inclusion and exclusion criteria, Anacor anticipates that at least 20% of evaluable subjects enrolled and exposed for at least 6 months will be 2-6 years of age, which will provide an adequate representation of younger patients. (Figure 4; Section 9.4)

Does the Agency agree that the proposed size of the AD safety database, which is estimated to be 1335 subjects (~1310 of whom are pediatric), together with supportive safety data from psoriasis and healthy subjects exposed to AN2728 Topical Ointment, 2% would be adequate to support registration for the AD indication? (Figure 4)

Response:
Your proposal is reasonable. The number of subjects needed to demonstrate safety may be substantially higher than the number of subjects needed to demonstrate efficacy and as such will greatly depend on the safety data collected from previous trials and any safety signal detected.

Refer to the guideline for industry *The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long term Treatment of Non-Life-Threatening Conditions.*

Question 11b:
Does the Agency agree that the proportion of subjects in the 2-6 years age group anticipated to enroll in the Phase 3 studies (20%) will be sufficient to establish safety and efficacy in this pediatric subgroup?

Response:
In your target population, the prevalence of atopic dermatitis is the highest in the 2 to 6 year age group. You should consider enrolling a greater proportion of subjects in this pediatric subgroup.

Meeting Discussion:
The sponsor stated that it is difficult to enroll subjects in this age category despite higher prevalence of AD in this age group. The sponsor proposed to include at least 20% (i.e. 300 subjects) in the 2 to 6 year age group. The FDA agreed to this proposal.

Question 12:
Are the completed and proposed clinical studies, including total subject number and exposure duration, adequate to support FDA's review of both safety and efficacy claims as anticipated in the Target Product Profile (TPP) (Table 33 and Table 45; Appendix 1)? If not, what specific concerns does the Agency wish the sponsor to further discuss or justify?

Response:
Refer to the General Comments and response to Question 5b.

It is premature to discuss specific labeling claims reflected in the Target Product Profile (TPP). The final content of labeling will be determined by review of the data submitted in your NDA.

Additional general comments regarding the study design of the Phase 3 Trials:

- Subject stopping criteria should be clearly defined. Propose subject stopping criteria for adverse events that may develop during treatment with your product (e.g. discontinue treatment if an adverse event grade ≥ 2 according to CTCAE v.4.0 is observed and follow until resolution.)

- You permit the use of "acceptable bland emollient(s)" adjacent to the treatment areas during the Phase 3 trial(s). The use of emollients may confound the assessment of safety and efficacy of your product if subjects applied them to the treatment area and should not be permitted.

- You propose to allow short courses (≤ 14 days) of systemic antibiotics during the study if clinically necessary for the treatment of new onset infections. The Phase 3 protocols should include procedures to address suspected skin infections (e.g., bacterial cultures before the initiation of systemic antibiotics.)

- You propose to instruct subjects/caregivers to apply the study product regardless of whether the treatable area of atopic dermatitis clears prior to Day 28. The Division recommends that you discontinue treatment to areas which clear and evaluate subjects for durability of response.

Meeting Discussion:
The sponsor agreed to submit newly proposed subjects treatment stopping criteria as part of the revised Phase 3 protocols.

The sponsor agreed to provide subjects with written instructions (i.e. body diagram) on application of emollients to non-treatment areas only.

The sponsor agreed to address suspected skin infections in the amended protocols.

The FDA agreed that the sponsor can maintain treatment with the study product for the duration of the trials regardless of whether the treatable area of atopic dermatitis clears prior to Day 28.

Clinical Pharmacology/Biopharmaceutics

Question 13:
Based on (1) low systemic exposure following topical dosing, (2) a lack of AN2728 accumulation in plasma over 84 days of topical dosing, and (3) the lack of nephrotoxic or hepatotoxic effects observed in nonclinical and clinical studies to date, Anacor considers there to be no significant systemic exposure risk with this topically applied drug product and does not plan to conduct specific clinical pharmacology studies in subjects with renal insufficiency or hepatic insufficiency as a condition of registration. (Sections 9.1.3.1, 9.1.2, and 8.3)

Does the Agency concur?

Response:
Your proposal appears reasonable at this time.

Additional Comments for Sponsor:
We note that the concentration reached in the TQT trial was lower than the concentration observed in Trial AN2728-AD-102 with AD subjects. You should provide additional data, data analysis, and/or rationale regarding the potential for QT interval prolongation at drug concentrations that may be achieved in patients with AD.

Meeting Discussion:
The sponsor will provide additional data analysis to the IND.

Regulatory

Question 14:
AN2728 Topical Ointment, 2% is intended for treatment of mild to moderate AD in patients 2 years of age and older. Anacor does not plan to conduct clinical studies of AN2728 Topical Ointment, 2% in the adult AD population on the basis of disease similarity in adults and pediatrics and pharmacokinetic behavior of AN2728 in the two populations. Anacor intends to use efficacy, safety, and PK data from the pediatric AD population to extrapolate upward in age to support inclusion of the adult AD population in the label. (Section 9.5)

Does the Agency concur with this proposed approach to use pediatric clinical efficacy data from the Phase 3 AD studies together with safety and PK data from other supportive studies to support registration of AN2728 Topical Ointment, 2% for the treatment of mild to moderate AD in the adult population?

Response:
Refer to the General Comments and response to Question 5b.

Question 15:
Anacor is proposing to conduct a safety and efficacy study of AN2728 Topical Ointment, 2% in children aged 3 months up to 2 years with mild to moderate AD after approval of the marketing application for the AD indication in subjects 2 years and older has been granted. In accordance with regulations and current FDA guidances, Anacor is providing a draft Pediatric Study Plan (PSP) in this briefing package. The plan describes the basis for requesting a deferral for conducting studies in children aged 3 months up to 2 years in the initial NDA and a waiver for conducting studies in the 0 up to 3-month pediatric AD population in the initial NDA. (Section 9.6; Appendix 22)

Does the Agency concur with this proposed PSP for AN2728 Topical Ointment, 2%?

Response:
You should re-submit your proposed initial Pediatric Study Plan (iPSP) as a separate submission within 60 days following this End-of-Phase 2 meeting. The FDA will review and comment on your iPSP at that time.

See additional comments and guidance below under PREA Requirements.

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.

Meeting Discussion:
The sponsor confirmed that they will not be submitting a request for special protocol assessment (SPA).

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. 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.

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

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

PREA REQUIREMENTS

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

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

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

Meeting Discussion:
The sponsor confirmed they would submit their proposed pediatric study plan (PSP) within 60 days as required.

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/

TATIANA OUSSOVA
03/06/2014

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207695

LATE-CYCLE MEETING MINUTES

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, MSc
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Please refer to your New Drug Application (NDA) dated January 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for crisaborole ointment, 2%.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 26, 2016.

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

If you have any questions, call Omolara Laiyemo, Regulatory Project Manager at (301) 796-402-3842.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 26, 2016
Meeting Format: Teleconference

Application Number: NDA 207695
Product Name: crisaborole ointment, 2%
Applicant Name: Anacor Pharmaceuticals, Inc.

Meeting Chair: Snezana Trajkovic, MD
Meeting Recorder: Lydia Springs

FDA ATTENDEES
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Bhavishya Mittal, PhD, CMC Reviewer, DNDP
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
CDR Lydia Springs, RN, BSN, MSHS, CPHM, Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES
Azada Hafiz, Independent Assessor

APPLICANT ATTENDEES
Carmen Rodriguez, MSc, Sr. Vice President, Regulatory, Anacor
Owen Fields, PhD, Vice President, Regulatory, Pfizer
Crystal Browning, MS, Sr. Director, Regulatory, Anacor
John Groskoph, PhD, CMC/Regulatory, Pfizer
Mike Corbo, MD, Chief Development Officer, Pfizer
Vivek Purohit, PhD, Director, Clinical Pharmacology, Pfizer

1.0 BACKGROUND

NDA 207695 was submitted on January 7, 2016 for crisaborole ointment, 2%.

Proposed indication(s): treatment of mild to moderate atopic dermatitis in patients 2 years of age and older

PDUFA goal date: January 7, 2017

FDA issued a Background Package in preparation for this meeting on September 16, 2016.

2.0 DISCUSSION

1. Introductory Comments

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

2. Discussion of Substantive Review Issues

A potential review issue was identified late in the review cycle (i.e. late August) by the applicant. The issue is related to potential mutagenic impurities (b) (4) (b)(4)

Additional CMC and genotoxicity information will be provided by the applicant by the end of October 2016. The Agency will further review and consider the information at that time.

Discussion:

The applicant discussed the findings of potential mutagenic impurities (b) (4) *and presented their planned approach to address the issue.*

The applicant suggested that a teleconference be conducted to discuss their findings prior to submission; however, the Agency stated that a teleconference would be determined upon the review of submitted data.

The applicant was informed that this new information may affect the NDA review timeline or its approvability.

3. Discussion of Upcoming Advisory Committee Meeting

An Advisory Committee meeting is not planned.

Discussion:

There was no further discussion.

4. REMS or Other Risk Management Actions

No issues related to risk management have been identified to date.

Discussion:

There was no further discussion.

5. Postmarketing Requirements/Postmarketing Commitments

Discussion:

The applicant proposed revisions to the FDA language for the Pediatric Research Equity Act (PREA) Post-Marketing Requirement (PMR) (letter dated 21 Sept 2016) to conduct an open-label safety trial in 100 evaluable pediatric subjects with mild to moderate atopic dermatitis ages 3 months to < 2 years and at least 5% treatable percent body surface area (%BSA).

The Agency stated that the inclusion of (b)(4) *was an error.*

The Agency indicated that a subpopulation of at least 16 completers (not (b)(4) *was needed to fully characterize the pharmacokinetics of crisaborole in this pediatric population.*

6. Review Plans

FDA will review information to be submitted in late October and determine next steps at that time.

Discussion:

The applicant agreed.

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

SNEZANA TRAJKOVIC
11/03/2016