

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202833Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202833

SUPPL # 000

HFD # 540

Trade Name Picato

Generic Name ingenol mebutate

Applicant Name Leo Pharma

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)

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

YES NO

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

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

d) 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

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

YES NO

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

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).

NDA#

NDA#

NDA#

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:

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: J. Paul Phillips
Title: Regulatory Health Project Manager, DDDP
Date: January 10, 2012

Name of Office/Division Director signing form: Susan J. Walker, M.D., F.A.A.D.
Title: Director, DDDP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

J P PHILLIPS
01/13/2012

SUSAN J WALKER
01/20/2012

PEP005 (ingenol mebutate) Gel, NDA 202833
1.3.3 Debarment Certification

3-May-2011

LEO Pharma A/S

Debarment Certification

LEO Pharma A/S hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application for PEP005 Gel 0.015% and PEP005 Gel 0.05%.

Counter-signature

Date:

Date:

May 3, 2011

Jesper Kilil

Cheri Jones

Jesper Kilil
Corporate Vice President
Regulatory Affairs & Safety
LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup, Denmark
Telephone: +45 44 94 58 88

Cheri Jones, MS., RAC, FRAPS
Jones Regulatory Consulting, LLC
481 Haven Point Drive
Treasure Island, FL 33706
USA

Telephone: 727-940-4535



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From: Phillips, J. Paul
Sent: Friday, January 13, 2012 6:05 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'; Gould, Barbara
Subject: NDA 202833 (Picato)

Ms. Jones,

Please see the attached version of the PPI (track changes) for your response on Monday (1/16/2012), instead of the one attached to my earlier email of today (1/13/2012).



Picato (ingenol
mebutate) Draf...

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: Phillips, J. Paul
Sent: Friday, January 13, 2012 5:20 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'; Gould, Barbara
Subject: NDA 202833 (Picato) Labeling

Ms. Jones,

We have noted some additional minor edits/corrections to the labeling for NDA 202833 (Picato). Please see the attached labeling in track changes.



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...

We ask that you respond by C.O.B. on Monday, January 16, 2012.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

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/s/

J P PHILLIPS
01/13/2012

From: Phillips, J. Paul
Sent: Thursday, January 12, 2012 3:17 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'; Gould, Barbara
Subject: NDA 202833 (Picato) Labeling

Ms. Jones,

Thank you for your prompt response to our 1/10/2012 labeling edits. I have attached the labeling with some minor edits/corrections.



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...

Please respond by C.O.B. tomorrow (1/13/2012).

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

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/s/

J P PHILLIPS
01/13/2012

From: Phillips, J. Paul
Sent: Tuesday, January 10, 2012 5:49 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'; Gould, Barbara
Subject: RE: NDA 202833 Picato Labeling

Ms. Jones,

I noticed that the PPI did not appear to be attached properly so I am resending the PPI with edits attached here.



Picato (ingenol
mebutate) Draf...

J. Paul Phillips, MS
Regulatory Health Project Manager

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/s/

J P PHILLIPS
01/11/2012

From: Phillips, J. Paul
Sent: Tuesday, January 10, 2012 5:42 PM
To: 'Cheri Jones'
Cc: Cheri Jones; Gould, Barbara
Subject: NDA 202833 Picato Labeling

Ms. Jones,

Please see the attached draft labeling with FDA edits for NDA 202833 (Picato).



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...

In addition, we have the following comments regarding your carton/container labels:

- Change the font color of the numbers only for the two different strengths (i.e. 0.015% and 0.05%) and ensure that two different colors are utilized that are dissimilar (one color can remain black but the other should be different).
- Utilize a different color of font to highlight the following statements "For Topical Use on Trunk and Extremities Only" and "For Topical Use on Face and Scalp Only". Ensure that two different colors are used for highlighting these statements that do not overlap with any other colors utilized on the labels and labeling.

Please respond by C.O.B. on Thursday, Jan. 12, 2011.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

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/s/

J P PHILLIPS
01/11/2012



MEMORANDUM OF TCON

Date of Teleconference: January 3, 2012

Time: 2:00 p.m. (EDT)

Application: NDA 202833

Product: Picato[®] (ingenol mebutate) Gel, 0.015% and 0.05%

Sponsor/Applicant: Leo Pharma

FDA Participants:

Jill Lindstrom, M.D., Clinical Team Leader, DDDP

Joanna Ku, M.D., Clinical Reviewer, DDDP (chair)

Barbara Hill, Ph.D., Pharm/Tox Supervisor, DDDP

Jiaqin Yao, Ph.D., Pharm/Tox Reviewer, DDDP

Carin Kim, Ph.D., Biostatistics Reviewer, DBIII

Doanh Tran, Ph.D., Clinical Pharmacology Reviewer, DCPIII

Barbara J. Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP

J. Paul Phillips, M.S., Regulatory Project Manager, DDDP

Sponsor/Applicant Participants:

Jesper Kihl, Corporate Vice President, Regulatory Affairs

Nina Christiansen, Director, Corporate Regulatory Affairs

Trine Thing Oesterby, Regulatory Affairs Specialist

Katrine Bennedsen Fugmann, Regulatory Affairs Professional

Malene Kjaer Mueller, Director, Regulatory Affairs

Thomas Nedergaard Jensen, LEO Project Director

John R. Zibert, Ph.D., Research Scientist

Anita Melgaard, Senior R&D Scientist/ Statistician

Bjarke Naver, Principal Pharmacovigilance Scientist

Torsten Skov, Senior Medical Advisor

Deborah Eickhoff, Senior Manager, Regulatory Affairs

Cheri Jones, M.S., U.S. Agent

Thomas Larsson, Senior Medical Advisor

Joergen Schuetzsack, Senior Toxicologist

Lene Thomsen, Senior Scientific Advisor

Purpose:

Discuss labeling

Discussion Summary:

The FDA (Agency) verbally presented their labeling edits and supporting rationale in sequential order, stopping after each section to allow the applicant an opportunity to respond. In some instances the Agency accepted the applicant proposed edits, while in others, the applicant accepted the Agency proposed edits. Following discussion of each of the points, all edits were agreed upon with the exception of the Adverse Reaction tables. The applicant agreed to the Agency's two category version, with the request that the Agency consider a foot note which indicated the inclusion of mild, moderate, and severe reactions. The Agency agreed to review the proposal upon submission by the applicant. The applicant agreed to submit the revised label and foot note proposal within two business days.

The conversation ended amicably.

JPP 1/3/12
BJG 1/11/12

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/s/

J P PHILLIPS
01/12/2012

From: Phillips, J. Paul
Sent: Wednesday, December 21, 2011 7:11 PM
To: 'cherijonesrac@gmail.com'
Cc: Cheri Jones; Gould, Barbara
Subject: RE: NDA 202833 (Picato) Labeling

Ms. Jones,

I have attached a document which supports the FDA calculations and basis for some of the numbers included in tables 3 and 4 of the labeling.



FDA calculations AR
tables.doc

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
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/s/

J P PHILLIPS
12/21/2011

From: Phillips, J. Paul
Sent: Wednesday, December 21, 2011 6:30 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'; Gould, Barbara
Subject: NDA 202833 (Picato) Labeling

Ms. Jones,

In response to your submission dated December 16, 2011, please see the attached edits to labeling for NDA 202833 (Picato).



Picato (ingenol
mebutate) Draf...

Please respond by C.O.B. on Friday, Dec. 23, 2011.

I will be out of the office from Dec. 22- Dec.26. In my absence, please send a courtesy copy of your response and any inquiries to Ms. Barbara Gould (barbara.gould@fda.hhs.gov).

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
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/s/

J P PHILLIPS
12/21/2011



MEMORANDUM OF TELECONFERENCE MINUTES

TYPE OF MEETING: FDA-requested, scheduled CMC teleconference
MEETING DATE: December 19, 2011
TIME: 8:45 – 9:15 AM EST
LOCATION: White Oak, Building 21, Room 1539
APPLICATION: **NDA 202833**
DRUG NAME: **Picato (ingenol mebutate) Gel, 0.015% and 0.05%**
NDA APPLICANT: Leo Pharma A/S
Jones Regulatory Consulting, LLC, U.S. Agent
MEETING RECORDER: Jeannie David, M.S.

FDA Participants:

- Nina Ni, Ph.D., Review Chemist
- Shulin Ding, Ph.D., CMC Lead
- Jeannie David, M.S., Regulatory Project Manager

Sponsor/Applicant Participants:

- Jesper Kihl, Corporate Vice President, Regulatory Affairs and Safety, Leo Pharma A/S
- Thomas Nedergaard Jensen, Project Director, Leo Pharma A/S
- Marianne Gundel, Senior R&D Scientist, Leo Pharma A/S
- Torsten K Askland, R&D Scientist, Leo Pharma A/S
- Gitte Petersen, Head of Department, Chemical Control Department, Leo Pharma A/S
- Karen Wibe Enevoldsen, Head, Pharmaceutical Product Development, Leo Pharma A/S
- Lene Thomsen, Senior Scientific Adviser, Leo Pharma A/S
- Tina Lorentsen, Head of Section, Microbiological Control Department, Leo Pharma A/S
- Kirsten Broenum-Hansen, Head of Department, New Products, Leo Pharma A/S
- Gitte Marianne Schönwandt, Senior Regulatory Affairs Specialist, Leo Pharma A/S
- Lene Ejstrup Soerensen, Regulatory Affairs Professional, Leo Pharma A/S
- Trine Oesterby, Regulatory Affairs Specialist, Leo Pharma A/S
- Cheri Jones, Jones Regulatory Consulting, LLC, U.S. Agent

BACKGROUND:

Leo Pharma A/S submitted original NDA 202833 on March 25, 2011. A consult request on the method validation of NDA 202833 was sent by ONDQA to FDA Office of Testing and Research (OTR) on July 8, 2011. The method validation evaluation was completed with a Report Summary filed in DARRTS on December 13, 2011. The Report Summary indicates that the organic impurities portion of the drug product UPLC method (AP_000449) was unacceptable for

quality control and regulatory purposes, and the primary reason for unacceptability is that (b) (4) peak could not be reliably identified. Additional comments are also provided by OTR in the report for both drug substance HPLC method AP_000459 and drug product UPLC method AP_000449.

MEETING OBJECTIVES:

To convey FDA OTR's comments on the analytical method validation for both drug substance and drug product, and request information to address the comments.

DISCUSSION POINTS:

1) Drug substance HPLC method AP_000459:

FDA OTR could not reproduce the UV spectrum reported in the NDA (Figure 1 of the NDA HPLC method (AP_000459) for the API peak. The spectrum generated by FDA OTR for the API peak using the drug substance method for both test sample and the reference standard more resembled that generated from the drug product method (Figure 3 of the UPLC method AP_000449).

- Leo Pharma A/S suggested that the discrepancy might be due to software differences in background subtraction. Figure 1 of the drug substance method AP-000459 is the spectrum of the API peak after background subtraction. Since the mobile phase of the method contains (b) (4) which contributes a significant absorption up to (b) (4) a subtraction of the absorption spectrum of the mobile phase from the API peak spectrum was carried out to produce a spectrum believed to be more reflective of the absorption characteristics of the API.
- Leo stated that the spectrum of the API peak of test samples is the same as that of reference standard regardless background subtraction.
- Leo Pharma A/S agreed to submit HPLC chromatograms with the UV spectra for the drug substance samples and reference standard obtained in the same HPLC run, with and without the automated background subtraction.

2) Drug product UPLC method AP_000449:

FDA OTR recommends to expand the relevant chromatographic retention time window from (b) (4) in order to include a peak formed in the forced degradation sample.

- Leo Pharma A/S agreed to expand the retention time window to (b) (4)

3) Impurity (b) (4) detected by drug product UPLC method AP_000449:

The relative retention time (RRT) of (b) (4) is reported in the NDA at (b) (4). However FDA OTR did not detect a peak at RRT= (b) (4). Instead, two peaks at RRT values of (b) (4) were detected. In order to positively identify (b) (4) peak, FDA requested the submission of a UV spectrum of (b) (4) to the NDA.

- Leo Pharma A/S agreed to submit the UV spectrum for Impurity (b) (4) and to report on what range of relative retention times they have observed for Impurity (b) (4).

4) (b) (4)

(b) (4)

(b) (4)

Leo Pharma A/S agreed to submit the requested information/data in an amendment to NDA 202833 by the end of this week, Friday, December 23, 2011.

The call ended amicably.

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/s/

JEANNIE C DAVID
12/23/2011

From: Phillips, J. Paul
Sent: Thursday, December 15, 2011 4:18 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'; Gould, Barbara
Subject: NDA 202833 Picato (ingenol mebutate)

Ms. Jones,

Regarding your Dec. 2, 2011 submission to NDA 202833 (Picato), it is our understanding from your cover letter that you are requesting a temporary waiver of the barcode requirements for your product labels. If this understanding is correct, we refer you to 21 CFR 201.25(d)(2), wherein, applicants are directed to send all waiver requests for barcode requirements directly to the Office of Compliance. The contact information and address can be found in the regulation just cited. If you intend to pursue a waiver request, we recommend that you send it within the next week given the time necessary for processing. Please inform the Division if such a request is sent to Compliance.

Regarding the proposed carton/container labeling, we have identified one additional edit as outlined below:

Container Labels for both 0.05% & 0.015%:

- Relocate the route of administration "For Topical Use..." to appear after the strength presentation and prior to the "Distributed by..." statement.

A diagram illustrating the above request is attached for your reference.



Picato.doc (65 KB)

You may contact me if you have any questions.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
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e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
12/16/2011

Phillips, J. Paul

From: Gould, Barbara
Sent: Tuesday, December 13, 2011 1:18 PM
To: 'Cheri Jones'; Phillips, J. Paul
Cc: Gould, Barbara
Subject: RE: NDA 202833 Picato (Draft Labeling)
Importance: High

Ms. Jones,

Thank you for taking my call this afternoon re: draft labeling for the pending NDA 202833. As discussed this product is **pending** review and the final decision regarding this application will be communicated via written correspondence. Final decisions regarding individual sections of the applications such as labeling are **not** communicated separately. The decision as to whether the production may be market is based on the totality of the application. An overall decision regarding the adequacy of the application for marketing (i.e. data, label, and labeling) will be communicated in a single correspondence prior to or on the PDUFA date of January 25, 2012..

As mentioned during the call, there are additional labeling edits for the carton and container that will be provided to you shortly. Paul will be providing this information to you prior to COB Wednesday, Dec. 14th in order that the review of this application may continue.

Please include me all future email.

Thanks,

Barbara Gould
Chief, Project Management Staff
Division of Dermatology and Dental Products

301 796-4224

From: Cheri Jones [mailto:cherijonesrac@gmail.com]
Sent: Tuesday, December 13, 2011 10:17 AM
To: Phillips, J. Paul
Cc: Gould, Barbara
Subject: Re: NDA 202833 Picato (Draft Labeling)

Dear Mr. Phillips:

The sponsor has queried me on the response to the email below. Can you provide a response? The preparation of the response is in progress.

Thank you,
Cheri Jones

On Fri, Dec 9, 2011 at 3:42 AM, Cheri Jones <cherijonesrac@gmail.com> wrote:
Dear Mr. Phillips:

I confirm receipt of your email below with the draft labeling pieces. Thank you.

Can you please advise the process you would like us to follow if sponsor wishes to discuss some points with reviewers after meeting and discussing internally at LEO?

Also, can you please give guidance on format of next draft labeling submission. Should we use your track change document to make edits as the clearest way to pick up LEO changes? Should this exchange take place via email and as an official submission to the NDA?

The sponsor would also like to know if there has been time to review the tubes and cartons submitted in SN026 of Dec 2nd. i.e. are the cartons submitted acceptable?

We would appreciate any guidance you can give.
Best regards,
Cheri

On Wed, Dec 7, 2011 at 5:57 PM, Phillips, J. Paul <Paul.Phillips@fda.hhs.gov> wrote:

Ms. Jones,

As indicated in our June 3, 2011 filing letter, we are communicating proposed draft labeling (see attached).

Please respond by C.O.B. on Dec.16, 2011.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

Phillips, J. Paul

From: Phillips, J. Paul
Sent: Tuesday, December 13, 2011 6:00 PM
To: 'Cheri Jones'
Cc: Gould, Barbara
Subject: RE: NDA 202833 Picato (Draft Labeling)

Ms. Jones,

You may use the WORD document which I sent to you to make any changes you wish to propose. The best way would be to accept all track changes from our documents and then make track changes with your proposed edits.

It would be appreciated if you did send a courtesy copy of your proposed edits via email; however, your formal response should be a submission to your NDA.

Regarding the carton/container labeling, I refer you to Ms. Gould's email of earlier today (12/13/11).

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: Cheri Jones [mailto:cherijonesrac@gmail.com]
Sent: Friday, December 09, 2011 3:43 AM
To: Phillips, J. Paul
Subject: Re: NDA 202833 Picato (Draft Labeling)

Dear Mr. Phillips:

I confirm receipt of your email below with the draft labeling pieces. Thank you.

Can you please advise the process you would like us to follow if sponsor wishes to discuss some points with reviewers after meeting and discussing internally at LEO?

Also, can you please give guidance on format of next draft labeling submission. Should we use your track change document to make edits as the clearest way to pick up LEO changes? Should this exchange take place via email and as an official submission to the NDA?

1/24/2012

The sponsor would also like to know if there has been time to review the tubes and cartons submitted in SN026 of Dec 2nd. i.e. are the cartons submitted acceptable?

We would appreciate any guidance you can give.

Best regards,
Cheri

On Wed, Dec 7, 2011 at 5:57 PM, Phillips, J. Paul <Paul.Phillips@fda.hhs.gov> wrote:
Ms. Jones,

As indicated in our June 3, 2011 filing letter, we are communicating proposed draft labeling (see attached).

Please respond by C.O.B. on Dec.16, 2011.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: Phillips, J. Paul
Sent: Wednesday, December 07, 2011 5:57 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'
Subject: NDA 202833 Picato (Draft Labeling)

Ms. Jones,

As indicated in our June 3, 2011 filing letter, we are communicating proposed draft labeling (see attached).



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...



Picato (ingenol
mebutate) Draf...

Please respond by C.O.B. on Dec.16, 2011.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
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/s/

J P PHILLIPS
12/07/2011

From: Phillips, J. Paul
Sent: Tuesday, November 29, 2011 4:22 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'
Subject: NDA 202833 Picato (ingenol mebutate) Gel, 0.015% and 0.05%

Ms. Jones,

Please see below for edits to the carton/container labels for NDA 202833 Picato.

1) For consistency with standard naming convention, change established name and dosage form to lower case in all instances on *carton* and *container* labels:

"Picato (ingenol mebutate) gel"

2) Change all instances of the following on the *carton* labels:

"3 Unit Dose Tubes each containing 0.47 g"

to

"3 Unit Dose Tubes
Net Wt. 0.47 g in each tube"

3) Change all instances of the following on the *carton* labels:

"Protection from freezing."

to

"Protect from freezing."

4) Per 21 CFR 201.25, add a barcode to the *container* labels.

You may contact me if you have any questions.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
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e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
11/29/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Products

****PRE-DECISIONAL AGENCY MEMO****

Date: November 23, 2011

To: J. Paul Phillips, DDDP

From: Lynn Panholzer, PharmD, OPDP, Division of Prescription Drug Promotion
Sheetal Patel, PharmD, OPDP, Division of Direct-To-Consumer Promotion

Re: NDA# 202833
Picato (ingenol mebutate) gel, 0.015% and 0.05%

As requested in your consult dated May 2, 2011, OPDP has reviewed the draft labeling (package insert [PI], patient package insert [PPI], Instructions for Use, and carton labeling) for Picato (ingenol mebutate) gel, 0.015% and 0.05%. OPDP's comments are based on the proposed, substantially complete, marked-up version of the PI and PPI, and on the Instructions for Use and carton labeling, sent to OPDP by DDDP via e-mail on November 10, 2011.

OPDP's comments on the PI and PPI are provided directly in the attached, marked-up copy of the labeling. OPDP's comments on the Instructions for Use are also provided directly in the attached copies of the instructions. We have the following comment on the carton labels:

1. Both carton labels state, (b) (4)
Similarly, the presentation of administration of the product on the inside of the labels states, (b) (4). These statements imply that the entire tube should be used. While the PI suggests that the entire tube would be necessary for a 25 cm² treatment area, it isn't clear that patients will always be treating an area this large. If not, would less product be applied, or would the entire tube still be applied? If a full tube is not always appropriate, we recommend that the wording of these statements be revised. We also recommend that (b) (4) be changed to "affected area" to be consistent with the changes made to the PI.
2. If appropriate, we recommend that the duration of therapy (3 and 2 consecutive days for the 0.015% and 0.05% strengths, respectively) be included in the Dosage section of the carton labeling.

If you have any questions about OPDP's comments on the PI or carton labeling, please contact Lynn Panholzer at 6-0616 or at Lynn.Panholzer@fda.hhs.gov. If you have any

questions about our comments on the PPI or Instructions for Use, please contact Sheetal Patel at 6-5167 or at [Sheetal.Patel @fda.hhs.gov](mailto:Sheetal.Patel@fda.hhs.gov).

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

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/s/

LYNN M PANHOLZER
11/23/2011

SHEETAL PATEL
11/23/2011

From: Phillips, J. Paul
Sent: Friday, November 04, 2011 7:49 AM
To: 'Cheri Jones'
Subject: RE: Follow-up to your email of October 27th, Labeling Comments

Ms. Jones,

Your understanding appears to be accurate. The PPI and IFU should be included inside the carton. Making the PI available by including it with the product in shipment also appears to be acceptable.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: Cheri Jones [mailto:cherijonesrac@gmail.com]
Sent: Tuesday, November 01, 2011 8:49 AM
To: Phillips, J. Paul
Subject: Follow-up to your email of October 27th, Labeling Comments

Dear Mr. Phillips:

The sponsor, in reviewing the comments in your email of 10/27/2011, wishes to confirm that their interpretation of your email is correct.

Both the PPI and the IFU are to be included inside the carton. (We believe this is clear and can be accommodated).

The question arises with regard to the USPI. Three pieces of insert labeling would be very difficult to accommodated in the carton for this size product. We believe, based upon precedent in the industry, that including a USPI in the shipment with the packaged product is sufficient. It does not have to be physically attached or within the product carton but rather available with the product. Can you please confirm that this understanding is in agreement with the intention of your email comments. It would be most appreciated.
Sincerely,

Cheri

Cheri Jones, M.S., RAC, FRAPS

Jones Regulatory Consulting, LLC

481 Haven Point Drive

Treasure Island, FL 33706

970-232-8150 (mobile)

727-954-0556 (office)

cherijonesrac@gmail.com

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/s/

J P PHILLIPS
11/08/2011



NDA 202833

INFORMATION REQUEST

Leo Pharma
c/o Jones Regulatory Consulting, U.S. Agent
Attention: Cheri Jones, M.S., RAC, FRAPS
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) and Biopharmaceutics sections of your submission and have the following comments and information requests. We request a prompt written response by November 3, 2011, in order to continue our evaluation of your NDA.

We acknowledge receipt of your In-Vitro Drug Release Method Development and Validation of Ingenol Mebutate (PEP005) in PEP005 Gel, 0.015% and 0.05% (Report # 69METH2003.00). While the report describes your approach on the selection of the receptor medium, the report needs to describe justification for the following:

- Choice of amount of sample to be used and maintenance of sink condition
- Choice of rotation speed
- Choice of (b) (4)
- (b) (4)
- Choice of sampling times and temperature

Please submit the above information as part of your *in-vitro* release method development and validation report.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and J. Paul Phillips, Regulatory Project Manager the Office of New Drugs (Paul.Phillips@fda.hhs.gov).

If you have any questions regarding this CMC letter, please contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
10/28/2011
Chief, Branch IV

From: Phillips, J. Paul
Sent: Thursday, October 27, 2011 1:25 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'
Subject: NDA 202833 (Picato)

Ms. Jones,

Please see below for some comments and requests related to labeling for NDA 202833 (Picato):

Instructions for Use

Develop "Instructions for Use" (IFU) to instruct patients about how to apply TRADEMARK Gel.

1. The information that is currently in the proposed Patient Package Insert (PPI) section "Applying TRADEMARK Gel" should be incorporated into the new IFU. (b) (4)
2. In the PPI under the Section "How should I use TRADEMARK?" please add a bullet that refers the reader to the Instructions for Use (IFU), such as, "See the Instructions for Use for information about how to apply TRADEMARK gel."
3. The IFU should be on a separate document from the PPI. Two individual IFUs should be developed, one for each strength of TRADEMARK Gel. To reduce the chances of medication errors, patients should only receive the IFU that is appropriate for the strength of the product and the indication for which the product is prescribed for them-- either the face/scalp indication (0.015% TRADEMARK Gel), or the trunk/extremities indication (0.05% TRADEMARK Gel).
4. Each IFU should be packaged in the appropriate carton to be distributed to the patient. Ideally, the PPI should also be packaged inside the carton.
5. We recommend the following when developing the Instructions for Use (IFU):
 - Patient Instructions that are sequential should be numbered as Step 1, Step 2, etc.
 - Patient instructions that are not sequential should be bulleted.

Incorporate the four figures (Step A to Step D) that are located on the inside flap of the proposed carton into the IFU.

- When incorporating the figures, they should be labeled sequentially as Figure A, Figure B, etc. The figures should be placed adjacent to the appropriate text and should be referenced in the text.
- The figures should be re-sized to a larger font/size for easy readability.
- Additional wording and other changes may be necessary to accommodate incorporation of these figures into the IFU.

Carton

1. Replace the (b) (4) with "or" in the "Manufactured by" statement (i.e. LEO or DPT not LEO (b) (4) DPT)
2. Modify storage statement to read "Store in a refrigerator at 36°F – 46°F (2°C – 8°C); excursions permitted between 32°F – 59°F (0°C – 15°C) (see USP for controlled cold temperature). Protection from freezing. Discard after single use."
3. (b) (4) from the "sodium citrate" listed under Composition, to comply with USP/NF name
4. Add NDC number

5. (b) (4), change the word (b) (4) to "Intravaginal" and move the "or" in the statement "Not for Oral, Ophthalmic, or Intravaginal (b) (4)-Use"

Container

1. Add barcode

Please respond by C.O.B. on November 11, 2011. Feel free to contact me if you have any questions.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
10/27/2011



NDA 202833

INFORMATION REQUEST

Leo Pharma
c/o Jones Regulatory Consulting, U.S. Agent
Attention: Cheri Jones, M.S., RAC, FRAPS
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) sections of your submission and have the following comments and information requests. We request a prompt written response by October 21, 2011, in order to continue our evaluation of your NDA.

1. Revise the proposed specification for (b) (4) (Module 3.S.2.4, Table 11) by the addition of appropriate acceptance criteria on impurities (b) (4) with proper justification.
2. The proposed specification for primary packaging component is not adequate. As per 21 CFR 211.84, at least one specific test shall be conducted to verify the identity of each component. Therefore, revise the proposed specification for primary packaging component to include at least one specific identity test for each primary packaging component.
3. Provide a representative certificate of analysis of each packaging component from the supplier.
4. Provide qualitative and quantitative compositions for the (b) (4) and inks (black, blue, and green) used for the drug product tubes.
5. Provide detailed manufacturing process for drug product tube filling, sealing, label printing, and (b) (4)
6. Upon further review, we recommend to revise the acceptance criterion for the drug product description test to the following: clear, colorless gel, free of particulates and lumps. Revise the drug product specification table in Module 3, Section P.5.1 and any other relevant sections accordingly.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and J. Paul Phillips, Regulatory Project Manager the Office of New Drugs (Paul.Phillips@fda.hhs.gov).

If you have any questions regarding this CMC letter, please contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
10/13/2011
Chief, Branch IV



NDA 202833

INFORMATION REQUEST

Leo Pharma
c/o Jones Regulatory Consulting
Attention: Sheri Jones, MS, RAC
U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

We are reviewing the Clinical and Chemistry, Manufacturing and Control sections of your submission and have the following comments and information requests. We request a prompt written response by September 30, 2011 in order to continue our evaluation of your NDA.

Drug Substance:

The information provided to Module 3 Section S.2 Manufacture is inadequate to assure the purity and quality of the drug substance. Provide the following information:

1. Detailed description of each chromatographic operation, including the acceptance criteria for fraction selection and combination as well as the endpoint of (b) (4) process.
2. Specifications with justifications (including batch analysis data along with chromatograms) for all the intermediates (b) (4) Include a descriptive acceptance criterion for appearance test of each intermediate.

Drug Product:

The following information request is pertinent to extractables/leachables from the container closure:

3. Provide study results from a controlled extractable study using (b) (4)

monitored in this study using a validated analytic method which is capable of adequate separation of all major extractables.

4. Provide study results from a leachable study where potential leachables are monitored in the drug product through out its shelf life using the analytic method developed/validated for the quantitation of leachables in drug product.
5. Provide safety assessment for each observed leachables in drug product.

Additional CMC Comments:

6. The drug substance is known to be (b) (4). Please describe control strategy for minimizing the degradation of the drug substance during the drug product manufacturing process.
7. Provide data to support your statement of deliverable amount of 0.25 g per tube from the fill weight of 0.47 g per tube.
8. Provide technical report 69.METH2003 for the method development and validation of IVRT for PEP gels. If you have already submitted it to the NDA, provide the location/link.
9. Resubmit the letter of authorization (LOA) for DMF (b) (4). The letter should contain information that clearly indicates the exact name, ID, and/or code, letter date, section and page numbers for the referenced items, including the tube, all layers of laminates, cap, ink, and external lacquer.
10. Revise the acceptance criterion of description for drug product from “clear, colorless gel” to (b) (4).
11. It is noted that the analytical method of AP_00049 cannot adequately separate (b) (4) from the leachables from container closure, including (b) (4). Clarify if the concentrations of (b) (4) reported in the batch analysis and stability data were calculated using the combined peak areas of the merged peaks of (b) (4) and the leachables. Revise Method AP_00049 by adding a statement that the calculation of the concentration of (b) (4) should use the combined area of the merged peaks of (b) (4) and the leachables unless the two peaks are well separated.

Clinical:

12. Regarding the ocular and periocular adverse events, clarify whether the events were unilateral or bilateral, what was the spatial relationship with the treatment area (e.g., within, adjacent, proximal, distant), and whether ophthalmologic care was provided.

13. Based on documentations available (including photographs), clarify the relationship between local skin reactions and AK lesions (e.g., were the local skin reactions located on the AK lesions or in the inter-lesion areas?).
14. Clarify whether any of the local skin reactions required additional medical care (e.g., pharmacologic treatment, local wound care, etc).

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, M.D.
Clinical Team Leader
Division of Dermatology and Dental Product
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JILL A LINDSTROM
09/16/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: September 15, 2011

From: Raanan A. Bloom, Ph.D.
OPS/IO/SRS

To: Jeannie David
OPS/ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS

Subject: NDA 202-833
Ingenol Mebutate Gel 0.015% and 0.05%
Request for Categorical Exclusion

Submission Date: March 25, 2011

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

Background

LEO Pharma A/S has filed a new drug application, NDA 202-833, to gain approval for Ingenol Mebutate Gel 0.015% and 0.05% (PEP005 Gel), indicated for the topical treatment of actinic keratosis on the face and scalp and on the trunk and extremities.

The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(b), based on 1) an estimated concentration of the active moiety, ingenol mebutate, at the point of entry into the aquatic environment (expected introduction concentration, EIC) below 1 part per billion; and 2) that no wild *Euphorbia peplus* is utilized. The supplier maintains and cultivates only its own cultivars of *Euphorbia peplus* (The active moiety is derived from plant sources).

Review of the Current Submission

The applicant has calculated the EIC based on five-year maximum projected amounts of products in the US containing ingenol mebutate produced by LEO Pharma.

An EIC-Aquatic of (b) (4) is calculated as follows:

$$\frac{(b) (4)}{1.22 \times 10^{11} \text{ liters per day} \times 1 \text{ year} / 365 \text{ days} \times 10^9 \text{ } \mu\text{g/kg}} = (b) (4)$$

This calculation is correct.

The applicant provides information indicating that no wild *Euphorbia peplus* is utilized and states that the supplier maintains and cultivates only its own cultivars of *Euphorbia peplus*.

In addition, the following information is provided: "*Euphorbia peplus* is a small annual, herbaceous plant that grows to 30 cm high. It is a common garden weed, which originated from Central Europe but is now found in most areas of the world. It is not (a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), (b) entitled to special protection under any Federal law or international treaty to which the United States is a party, or (c) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or (d) is entitled to special protection under some other Federal law or international treaty to which the United States is a party."

Queries of the CITES and ESA databases did not find *Euphorbia peplus* as a listed species.

The applicant also states that "To the applicant's knowledge, no extraordinary circumstances exist, as described in 21CFR 25.21 that indicate that approval of PEP005 Gel will significantly affect the quality of the human environment."

Conclusion

This application qualifies for a categorical exclusion under 21 CFR 25.31(b). The sponsor has provided information indicating that ingenol mebutate is derived from cultivated plant sources and that the EIC is below 1 ppb.

Comments and Conclusions

Based on an evaluation of the provided information, FDA regulations at 21CFR25 and FDA guidance (GFI: Environmental Assessment), this application qualifies for a categorical exclusion under 21 CFR 25.31 (b).

This determination was previously provided to Nina Ni, ONDQA/DNDQA II, CMC Reviewer, in a 9/1/2011 e-mail.

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/s/

RAANAN A BLOOM
09/15/2011

NAKISSA SADRIEH
09/16/2011



NDA 202833

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

LEO Pharma A/S
c/o Jones Regulatory Consulting
Attention: Cheri Jones, MS, RAC
U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Barbara Gould, Chief, Project Staff Management, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

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

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/s/

BARBARA J GOULD

09/15/2011

p.p. DIVISION DIRECTOR Susan J. Walker

From: Phillips, J. Paul
Sent: Thursday, September 08, 2011 1:14 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'
Subject: NDA 202833 (ingenol mebutate)

Ms. Jones,

We received your 09/06/2011 submission to NDA 202833 (ingenol mebutate) in response to the Agency's IR letter dated 09/02/2011.

Regarding the proposed carton/container labeling, we have the following additional comments:

Proposed Container Label (0.015% and 0.05%)

The company name 'LEO' appearing at the bottom of the container label is more prominent than the established name. Decrease the size of the company name.

Proposed Carton Labeling (0.015% and 0.05%)

The proposed carton labeling for the two strengths utilize similar colors (aqua green and blue) on the carton making it difficult to differentiate between the different strengths. To avoid selection errors, revise the labels to ensure that the color selected to represent each strength is unique and different from each other.

Please respond by close of business on September 19, 2011.

If you have any questions, feel free to contact me.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
09/08/2011

From: Phillips, J. Paul
Sent: Friday, September 02, 2011 3:50 PM
To: 'Cheri Jones'
Cc: 'Cheri Jones'
Subject: NDA 202833

Ms. Jones,

Please see the attached information request letter and the below comments regarding the carton/container labeling for NDA 202833 (ingenol mebutate).

<< File: IR Letter_NDA 202833_9-2-11.pdf >>

Proposed Container Label (0.015% and 0.05%)

1. The proposed labels for the two strengths utilize similar colors (aqua green and blue) on the principal display panel making it difficult to differentiate between the different strengths. To avoid selection errors, revise the labels to ensure that the color selected to highlight each strength presentation is unique and different from the other.
2. Increase the prominence of the strength and relocate it to appear after the established name as shown below:
TRADEMARKTM
(Ingenol Mebutate) Gel
0.05%
3. Revise the proprietary name presentation so that it is presented in title case and not in capital letters.
4. Remove the RX Only statement from the box to decrease its prominence.
5. Revise the proprietary name presentation so that the symbol 'TM' is superscripted as follows: TRADEMARKTM
6. The company name and distributor information is more prominent than the established name. Decrease the size of the company name and distributor information.
7. Add a statement "For Topical Use on Face and Scalp Only" on the principal display panel the 0.015% container label.
8. Add a statement "For Topical Use on Trunk and Extremities Only" on the principal display panel the 0.05% container label.

Proposed Carton Labeling (0.015% and 0.05%)

1. See comment 1, 2, 3, 4, and 5 above from Container Label.
2. The graphic on the bottom right side of the top panel is distracting and makes the labeling for both strengths appear similar. Delete this graphic.
3. We note the established name is ½ the size of the proprietary name, but it lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
4. Revise the (b) (4) statement as follows "For Topical Use on Face and Scalp Only" for the 0.015% carton labeling and "For Topical Use on Trunk and Extremities Only" for the 0.05% carton labeling. This statement should

be more prominent than the (b) (4) statement.

5. Relocate the (b) (4) statement to appear after the route and revise as follows: “2 Unit Dose Tubes each containing 0.47 gm.” Present this information in unbolded text.
6. Delete the (b) (4) statements that appear above the company logo.
7. Decrease the size of the company logo and relocate it to the side panel.
8. The information on the back panel of the carton labeling is difficult to read, increase the font size and the contrast to increase the readability.
9. Revise the dosage statement on the back panel to read as follows:
 - For the 0.015 %**
Dosage: Apply one tube per day to the treatment area on the face and scalp.
See insert for complete information.
 - For the 0.05 %**
Dosage: Apply one tube per day to the treatment area on the trunk and extremities.
See insert for complete information.

If you have any questions please feel free to contact me.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
09/06/2011



NDA 202833

INFORMATION REQUEST

Leo Pharma
c/o Jones Regulatory Consulting
Attention: Sheri Jones, MS, RAC
U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

We are reviewing the carton/container labeling of your submission and have the following comments and information requests. We request a prompt written response by Friday, September 09, 2011 in order to continue our evaluation of your pending NDA.

1. Provide clinical narratives for subjects who had the AE 'Application Site Infection'. Include information on whether cultures were obtained, the results, and the final outcome.
2. Provide your rationale for the choice of the PEP005 Gel concentration used in the dermal safety provocative trials, as the concentration tested (0.01%) is lower than that of the proposed: 0.015% for the head locations; 0.05% for the non-head locations.
3. Regarding the interim efficacy data and your dynamic randomization used in Study 014:

While the protocols state that evaluation was performed on Day 57, the studies also included planned interim visits on Days 3, 8, 15 and 29. In general, the investigators assess subjects for adverse events as well as for the number of AK lesions at all visits. However, you did not submit efficacy data for the interim visits, and only provided data for the primary time point visit (Day 57). We would like to know whether you collected such efficacy data during the course of the trial (i.e., at each interim visit), and if so, such interim efficacy data at each visit should be submitted as the data will be helpful in reviewing the application.

In the SPA letter dated June 2, 2008, Nonagreement #1 was related to the randomization method. You submitted revised Phase 3 protocols for Agency comments and proposed to use dynamic randomization. In an Advice Letter dated May 13, 2009, we stated that you

should "consider a simpler randomization procedure which stratifies by site allocating subjects in blocks". However, because Study 014 had already been enrolling subjects when you received our comments, you did not address our comments for Study 014. We would like additional detail regarding the dynamic randomization including the score for each factor, as well as the computer program with the randomized subject listing to include the score, factors and the treatment assignment.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, 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/

JILL A LINDSTROM
09/02/2011



NDA 202833

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Leo Pharma A/S
c/o Jones Regulatory Consulting, LLC
481 Haven Point Drive
Treasure Island, FL 33706

ATTENTION: Cheri Jones, M.S., RAC, FRAPS
Regulatory Consultant, U.S. Agent

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) dated March 25, 2011, received March 25, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ingenol Mebutate Topical Gel, 0.015% and 0.05%.

We also refer to your May 30, 2011, correspondence, received on May 31, 2011, requesting review of your proposed proprietary name, Picato. We have completed our review of the proposed proprietary name, Picato and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your May 30, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Paul Phillips at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

CAROL A HOLQUIST
08/10/2011



NDA 202833

**METHODS VALIDATION
MATERIALS RECEIVED**

Leo Pharma A/S
Attention: Cheri Jones, M.S., RAC, FRAPS
U.S. Agent
481 Haven Point Drive
Treasure Island, Florida 33706

Dear Cheri Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Picato (ingenol mebutate) gel, 0.015% and to our 07/14/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 8/2/2011 and 8/8/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
08/08/2011



NDA 202833

INFORMATION REQUEST

Leo Pharma
c/o Jones Regulatory Consulting
Attention: Sheri Jones, MS, RAC
U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

We are reviewing the Clinical section of your submission and have the following information requests. We request a prompt written response by August 12, 2011.

1. Clarify why the following AEs were not coded as SAEs.

Table 1

USUBJID	AEDECOD	AESER	EXTRT	AESTDY
PEP005-014-50019	MYOCARDIAL INFARCTION	N	INGENOL MEBUTATE 0.05%	6
PEP005-014-52003	MYOCARDIAL INFARCTION	N	VEHICLE	3
PEP005-014-59009	MYOCARDIAL INFARCTION	N	VEHICLE	8
PEP005-014-63004	ARTERIOSCLEROSIS	N	INGENOL MEBUTATE 0.05%	132
PEP005-014-65004	POSTOPERATIVE WOUND INFECTION	N	VEHICLE	14
PEP005-014-66011	POSTOPERATIVE WOUND INFECTION	N	INGENOL MEBUTATE 0.05%	29
PEP005-014-68018	MYOCARDIAL INFARCTION	N	VEHICLE	3
PEP005-014-68023	MYOCARDIAL INFARCTION	N	INGENOL MEBUTATE	4

			0.05%	
PEP005-028-74-002	RENAL FAILURE ACUTE	N	INGENOL MEBUTATE 0.05%	34
PEP005-028-79-014	CORONARY ARTERY DISEASE	N	VEHICLE	49
PEP005-028-82-011	CHEST PAIN	N	INGENOL MEBUTATE 0.05%	13

2. Clarify the apparent discrepancy. On page 70/192 of the Integrated Summary of Safety (ISS) it is stated that Patient 07/0102, of Study PEP005-008 discontinued from the study. However, on page 9/608 of the legacy clinical study report of the study, it is stated that all 25 subjects completed the study. Provide clinical narrative for the surrounding events for Subject 07/0102, who discontinued from Study 008 due to severe diarrhea.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, M.D.
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/

JILL A LINDSTROM
08/02/2011



NDA 202833

INFORMATION REQUEST

LEO Pharma A/S
Attention: Cheri Jones, M.S., RAC, FRAPS
U.S. Agent
481 Haven Point Drive
Treasure Island, Florida 33706

Dear Cheri Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Picato (ingenol mebutate) Gel, 0.015% and 0.05%.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response by August 3, 2011 in order to continue our evaluation of your pending NDA.

1. Submit clinical narratives regarding eye AEs on subjects who had the following eye disorders AEs: eye hemorrhage, scleral discoloration, diplopia, visual disturbance, and blurry vision. Include information on final follow up.
2. The ISS stated (page 58 of 172) that there were 5 severe AEs involving eye disorders; periorbital edema, eyelid edema, eye edema, eye pain, and eyelid ptosis. Our tabulation of severe AEs in the ADAE dataset did not find eye pain to be among the listed as 'severe.' Provide a clarification for this apparent discrepancy.
3. Submit information for SAEs for Phase 2 and 3 trials (AK field treatment) in a table format similar to the following, as a WORD document and as a JMP dataset. Provide this listing in two forms: sorting by subject, and sorting by adverse event. Segregate SAEs by PEP005 Gel treated subjects (head vs. non head locations) vs. vehicle subjects. The following variables should be included in the listing:
 - Trial number
 - Center number
 - Subject number (a unique number that identifies this subject in the NDA database)
 - Preferred term for event
 - Adverse event as reported by investigator and/or subject
 - Body system category for event (SOC)
 - Age
 - Sex

- BMI
- Treatment assignment (dose and dosing regimen)
- Study day of onset of AE
- Study day of end of AE
- Severity
- An indication of whether or not the event led to withdrawal of study drug and/or study participation
- Serious adverse event type (e.g., fatal, life-threatening)
- Location (inside of treatment area?)

Table 7 Serious Adverse Event Listing New Drug Clinical Trials Source: Phase 2-3 Trials Sorting A: Randomized Treatment, Trial #, Investigator/Center #, Subject #¹ Treatment = New Drug² Cutoff Date: xx,xx,xx³										
Trial	Center	Subject	Age (yrs) ⁴	Sex	Dose (mg) ⁴	Time (days) ⁵	Body System	Preferred Term	Adverse Event ⁶	W/D ⁷

¹ It is essential to provide this listing in two different forms (i.e., sorting A (by subject) and sorting B (by adverse event)). This listing is for sorting A (by subject) and permits the reviewer to explore all the serious adverse events reported for each individual subject. Sorting B (by adverse event) should be as follows: Randomized Treatment, Body System, Preferred Term, Adverse Event, Trial, Center, Subject #, Age, Sex, Dose, Time, W/D. Sorting B permits the reviewer to explore all the reported serious adverse events of a similar type.

² This sample listing is for all new drug subjects across all clinical trials in the phase 2 to 3 development program. Similar listings should be provided for active-controlled and placebo subjects.

³ This is the data lock date for entering data into this table (i.e., the date beyond which additional exposed subjects were not available for entry). Generally, this date should be no more than several months before the submission date for an NDA. This date, as well as this table, will likely need to be updated during the course of NDA review as more data become available.

⁴ This column should include the dose being administered (in mg/day) at the time the event occurred.

⁵ This column should include the time (i.e., duration of exposure (in days)) that the event occurred. If the event occurred after discontinuation of drug, a footnote should note how long after discontinuation.

⁶ This column should include the adverse event in the language reported by the investigator and/or subject (i.e., before coding).

⁷ This column should include an indication of whether or not the adverse event led to discontinuation of the assigned treatment.

4. Provide adverse event dropout listing for all trials/studies in the clinical development program, in a table format, similar to the following, as a WORD document and as a JMP dataset. This table is a line listing of all reported adverse events (in all trials in the clinical development program) identified as leading to discontinuation of the study drug treatment or study participation, regardless of whether or not they were considered drug-related, for all subjects participating in trials identified as sources for this listing. Thus, all events categorized as intercurrent illness leading to discontinuation would, nevertheless, be included in this listing, and any judgments about attribution can be included in the narrative summary. Segregate the AEs by PEP005 Gel treated group (head vs. non head locations) and vehicle group. The following variables should be included in this listing:

- Trial number
- Center number
- Subject number (a unique number that identifies this subject in the NDA database)
- Age
- Sex
- Treatment assignment and dose/regimen
- Time (study day of the onset of AE onset, study day of end of AE)
- Body system category for event (SOC)
- Preferred term for event
- Adverse event as reported by investigator and/or subject
- SOC
- Outcome (discontinued study, discontinued study drug)
- Severity
- Serious Adverse Event?
- Location (inside the treatment area?)

<p style="text-align: center;"> Table 9 Adverse Event Dropout Listing New Drug Clinical Trials Source: Phase 2-3 Database Sorting A: Randomized Treatment, Trial #, Investigator/Center #, Subject #¹ Treatment = New Drug² Cutoff Date: xx,xx,xx³ </p>											
Trial	Center	Subject	Age (yrs)	Sex	Dose (mg) ⁴	Time (days) ⁵	Body System	Preferred Term	Adverse Event ⁶	Serious ⁷	Outcome ⁸

¹ It is essential to provide this listing in two different forms (i.e., sorting A (by subject) and sorting B (by adverse event)). This listing is for sorting A (by subject) and permits the reviewer to explore all the adverse events reported as leading to discontinuation for each individual subject. Sorting B (by adverse event) should be as follows: Randomized Treatment, Body System, Preferred Term, Adverse Event, Trial, Center, Subject #, Age, Sex, Dose, Time, Serious. Sorting B permits the reviewer to explore all the adverse events of a similar type reported as leading to discontinuation.

² This sample listing is for all new drug subjects across all clinical trials in the phase 2 to 3 development program. Similar listings should be provided for active-controlled and placebo subjects.

³ This is the data lock date for entering data into this table (i.e., the date beyond which additional exposed subjects were not available for entry). Generally, this date should be no more than several months before the submission date for an NDA. This date, as well as this table, will likely need to be updated during the course of NDA review as more data become available.

⁴ This column should include the dose being administered (in mg/day) at the time the event occurred.

⁵ This column should include the time (i.e., duration of exposure (in days)) that the event occurred.

⁶ This column should include the adverse event in the language reported by the investigator and/or subject (i.e., before coding).

⁷ This column should include an indication of whether or not the adverse event met the criteria for *serious* as defined for the development program overall.

⁸ This column should categorize the outcome upon follow-up evaluation for the adverse event leading to discontinuation, as follows:

- (R) Resolved
- (P) Persisting
- (U) Unknown

5. Clarify whether local skin reactions (LSRs) were actively assessed in the open label extension (OLE) studies (PEP005-030 and PEP005-032), using the graded scales that were used in the feeder Phase 3 trials. The protocols for the extension studies do not mention the use of active assessment or grading scale. Clarify how AEs and SAEs for the selected treatment area were elicited (e.g., by physical exam, passive questioning, etc.). Provide a rationale why different strategies were used for the Phase 3 trials and the open label extension studies on studying local skin reactions.
6. Construct a table (for Phase 3 trials) similar to Table 2 in the proposed labeling, except to include only
 - Incidence rate on maximum Grade 4 responses (i.e., do not include Grade 1, 2, 3);
 - Incidence rate on subject with maximum response of any Grade >0 (see Table 32 and Table 33, ISS); and,
 - Incidence rate subject with maximum grade response that was greater than present at Baseline (see Table 32, ISS).
7. Construct a table (for Phase 3 trials) with final LSRs scores for each of the responses (erythema, flaking/scaling, etc.), by number and percent subjects, at Day 57. And if LSRs were actively assessed using the same grading system for the OLE studies, provide this information for data collected at 3, 6, 9, and 12 Month.

8. Clarify whether pigmentation and scarring were actively assessed in the OLE studies (Study 030, 032).

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, 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/

JILL A LINDSTROM
07/22/2011



NDA 202833

**REQUEST FOR METHODS
VALIDATION MATERIALS**

LEO Pharma A/S
Attention: Cheri Jones, M.S., RAC, FRAPS
U.S. Agent
481 Haven Point Drive
Treasure Island, Florida 33706

Dear Cheri Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Picato (ingenol mebutate) gel, 0.015% and 0.05%.

We will be performing methods validation studies on Picato (ingenol mebutate) gel, 0.015%, as described in NDA 202833.

In order to perform the necessary testing, we request the following sample materials and equipments:

- 100 mg- Ingenol Mebutate Reference Standard
- 50 mg- Ingenol Mebutate containing (b) (4) for system suitability
- 100 mg Ingenol Mebutate Drug Substance
- 10 g- PEP005 Gel Placebo
- 10 g- Picato (Ingenol Mebutate) gel 0.015%
- 1- Acquity UPLC BEH C18, 1.7 μ m. 2.1 x 100mm

Include the Certificate of Analysis and MSDS for the materials sent. Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
07/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Dr. Nina Ni, CMC Reviewer
Dr. Shulin Ding, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Nina.Ni@fda.hhs.gov
Phone: (301)-796-5296
Fax.: (301)-796-9749

Through: Dr. Moo-Jhong Rhee, Branch Chief, Branch IV, ONDQA
Phone: (301)-796-1440

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 202-833

Name of Product: Picato (ingenol mebutate) gel, 0.015% and 0.05%

Applicant: Leo Pharma A/S

Applicant's Contact Person: U.S. Agent: Cheri Jones, M.S., RAC, FRAPS

Address: 481 Haven Point Drive, Treasure Island, Florida 33706

Telephone: 727-940-4535 Fax: cherijonesrac@gmail.com (email) / 970-232-8150 (mobile)

Date NDA Received by CDER: **3/25/2011**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP:

Special Handling Required: No

DATE of Request: **July 8, 2011**

DEA Class: N/A

Requested Completion Date:

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **1/17/2012**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 202-833
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5
Supporting Data for Accuracy, Specificity, etc.				3.2.S.4.3 and 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.S.5.4 Batch analysis 3.2.S.7.3 Stability data 3.2.P.5.4 Batch analysis 3.2.P.8.3 Stability data
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
AP 000459	Ingenol mebutate: Identification, assay and determination of organic impurities by HPLC	3.2.S.4.2	8	
AP 000449	PEP005 (ingenol mebutate) gel: Identification, assay and determination of organic impurities of ingenol mebutate by UPLC	3.2.P.5.2	8	
Additional Comments:				

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

NINA NI
07/08/2011

MOO JHONG RHEE
07/08/2011
Chief, Branch IV

JEANNIE C DAVID
07/08/2011
ONDQA Methods Validation Project Manager



NDA 202833

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Leo Pharma A/S
c/o Jones Regulatory Consulting, LLC
481 Haven Point Drive
Treasure Island, FL 33706

ATTENTION: Cheri Jones, M.S., RAC, FRAPS
Regulatory Consultant, U.S. Agent

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) dated March 25, 2011, received March 25, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ingenol Mebutate Topical Gel, 0.015% and 0.05%.

We acknowledge receipt of your May 30, 2011 correspondence, on May 31, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name [REDACTED] (b) (4). This proposed proprietary name request is considered withdrawn as of May 31, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call 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 the Office of New Drugs (OND) Regulatory Project Manager, Paul Phillips at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

CAROL A HOLQUIST
06/21/2011



NDA 202833

FILING COMMUNICATION

Leo Pharma A/S
c/o Jones Regulatory Consulting
Attention: Sheri Jones, M.S., RAC
Regulatory Consultant, U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) dated March 31, 2011, received March 25, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (ingenol mebutate) Gel, 0.015% and 0.05%.

We also refer to your submissions dated April 5, 28, 29, and May 4, 2011.

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 25, 2012.

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, midcycle, 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 December 7, 2011.

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 also request that you submit the following information:

Clinical

1. Datasets for non-melanoma skin cancer studies (4 studies), topical safety studies (3 studies), and AK lesion-specific studies (2 studies) have not been submitted. Only legacy reports were submitted for these studies. Please submit individual subject data listing (including data tabulation, analysis datasets, and annotated CRFs) for all clinical studies used to support the application.
2. Clarify your procedures for coding and counting serious adverse events (SAEs), i.e., why certain AEs (e.g., melanoma, hip fracture) that are typically coded as serious (SAEs) were not coded as such in the AE datasets. For example, Subject PEP-005-06-016 experienced hip fracture, loss of consciousness, pneumothorax, etc. but these AEs were not coded as SAEs

CMC

3. Provide drug product samples with lower viscosity for dosage form evaluation. The viscosity of the samples should be near the lower limit of the proposed viscosity acceptance criterion. The samples should be accompanied with their certificates of analysis.

Clinical Pharmacology

4. Provide a rationale for not assessing the PK of your drug product under maximal use conditions following application to the head and scalp.

Labeling

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

5. The required highlights limitation statement (i.e. “These highlights do not include...”) is duplicated at the beginning of the Highlights section. One of the occurrences should be deleted.
6. The required adverse reactions reporting statement (i.e. “To report SUSPECTED ADVERSE REACTIONS...”) is duplicated at the end of the Highlights section. One of the occurrences should be deleted.
7. Capitalize “Full Prescribing Information” in the asterisk statement at the end of the Contents.
8. Remove the subsection 17.4 (FDA approved patient labeling) from section 17 (Patient Counseling Information) in the Contents. The patient labeling is appended to label as separate document, and is not a subsection of section 17 (see labeling comment #8 below).

9. Add an “s” to the title of section 1 “INDICATIONS AND USAGE” where it appears in both the Contents and the Full Prescribing Information (FPI).
10. Under section 6 (Adverse Reactions) of the FPI, revise the standard disclaimer statement to read verbatim as follows:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
11. Under section 17 (Patient Counseling Information) on the line immediately following the section header, revise the reference to patient approved labeling to read as follows:

“See FDA-approved patient labeling (Patient Information)”
12. Remove the subsection number 17.4 from the header for patient labeling (currently under section 17) and start patient labeling on a new page. This information is not included as a subsection to section 17, but rather is a stand alone piece of labeling that is appended to the package insert.

We request that you submit your responses by June 21, 2011.

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.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

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

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/s/

SUSAN J WALKER
06/03/2011



NDA 202833

INFORMATION REQUEST

Leo Pharma A/S
c/o Jones Regulatory Consulting
Attention: Sheri Jones, M.S., RAC
Regulatory Consultant, U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

We are reviewing the Combined Cardiac ECG Safety Report provided in your original NDA submission. We have identified a need for additional information in order to continue our evaluation.

Please complete the attached Highlights of Clinical Pharmacology sheet and submit the information to your NDA by close of business on May 27, 2011.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

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

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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/s/

JILL A LINDSTROM
05/23/2011

REQUEST FOR CONSULTATION

TO (Office/Division): DCRP
c/o Devi Kozeli, RPM

FROM (Name, Office/Division, and Phone Number of Requestor):
Joanna Ku, MD/DDDP, x6-2103
c/o J. Paul Phillips/DDDP, x6-3935

DATE
05/13/2011

IND NO.

NDA NO.
202833

TYPE OF DOCUMENT

DATE OF DOCUMENT
03/31/2011

NAME OF DRUG
Picato (ingenol mebutate)
Gel, 0.015% and 0.05%

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
08/05/2011

NAME OF FIRM: Leo Pharma

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Background

The proposed drug is a new molecular entity (NME) topical product applied 2-3 days during a treatment cycle, with an indication of treating actinic keratosis (AK), which is a benign skin condition that has the potential to evolve into squamous cell carcinoma. AKs occur most frequently in the elderly, especially elderly men, who are also at highest risk for cardiac morbidities. Since AKs can recur, patients may need retreatment but it is unclear at what frequency, or for what total duration. AK is considered to be a chronic indication both clinically and for regulatory proposes.

The Sponsor has not conducted a "Thorough QT/QTc Study." In lieu, they performed EKG analysis throughout Phase 2-3, and submitted a "Combined Cardiac ECG Safety Report" (Section 5.3.5.3.28). Plasma concentration appears in the subnanomolar range, which typically waives the requirement for a TQT study. Preclinical cardiac safety, both in vitro and in vivo data, also appear to support waiver of a TQT study; however, based on a preliminary review of the clinical data, it appears that there are some non-specific EKG morphology (e.g., new myocardial infarction patterns seen in one more drug treated patient vs. vehicle, new ST depression, T-wave changes etc.)

Per the ICH E14 QT/QTc Guidance (October 2005), TQT discussion is generally applicable to new drugs having systemic bioavailability -- which this drug does not. The purpose of the TQT Study is typically carried out, in healthy volunteers early in clinical development, not to

identify drugs as being pro-arrhythmic, but as a way to determine the effect of a drug on the QT/QTc interval in target patient population should be studied intensively during later stages of drug development. At the end-of-Phase 2 meeting, the Division did not specifically request a TQT Study, but referred the Sponsor to the Guidance.

This submission is electronic and can be accessed in the CDER EDR at the following link:

<\\CDSESUB1\EVSPROD\NDA202833\202833.enx>

Questions

1. Do you agree that a TQT Study is not needed?
2. Do you have further recommendations regarding cardiac safety monitoring, including long term post-marketing cardiac surveillance with regards to proarrhythmic potential for QT interval prolongation?

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

J P PHILLIPS
05/13/2011

REQUEST FOR CONSULTATION

TO (Office/Division): Raanan (Ron) Bloom, OPS/PARS, 301-796-2185

FROM (Name, Office/Division, and Phone Number of Requestor):
Nina Ni, CMC reviewer 301-796-5296
Shulin Ding, CMC lead 301-796-1349
Jeannie David, RPM 301-796-4247
Office of New Drug Quality Assessment

DATE
May 13, 2011

IND NO.

NDA NO.
202-833

TYPE OF DOCUMENT
NDA original submission

DATE OF DOCUMENT
March 25, 2011

NAME OF DRUG
ingenol mebutate gel,
0.015% and 0.05%

PRIORITY CONSIDERATION
Standard review

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
August 25, 2011 (midcycle)

NAME OF FIRM: LEO Pharma AS

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This is an NME botanical NDA. Please review the environmental assessment sections of this NDA. The NDA is electronically available in EDR and GSReview. Thank you.

SIGNATURE OF REQUESTOR
{electronic signature attached}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

JEANNIE C DAVID
05/13/2011



NDA 202833

INFORMATION REQUEST

Leo Pharma A/S
c/o Jones Regulatory Consulting
Attention: Sheri Jones, M.S., RAC
Regulatory Consultant, U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

During our preliminary review of your application, we noted that the Debarment Certification statement document is incomplete.

As stated in the FDA Guidance for Industry *Submitting Debarment Certification Statements*, found online at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080584.pdf>

“Domestic agents should countersign the certification for foreign applicants they represent under 21 CFR 314.50(a)(5).”

We have the following information request:

Submit a Debarment Certification statement signed by the foreign applicant and countersigned by the U.S. Agent.

You should submit the above requested information by the close of business on May 4, 2011.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, M.D.
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/

JILL A LINDSTROM
05/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE/DRISK		FROM: DDDP J. Paul Phillips/RPM, ODE III/DDDP/x6-3935		
DATE 05/02/2011	IND NO.	NDA NO. 202833	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 03/25/2011
NAME OF DRUG (ingenol mebutate) Gel, 0.015% and 0.05%		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 4022510	DESIRED COMPLETION DATE 09/23/2011
NAME OF FIRM: LEO Pharma				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Background: The sponsor of NDA 202833 (ingenol mebutate) sent in their new NDA on 3/25/2011. The NDA contains proposed carton/container labeling along with a proposed package insert and a proposed patient package insert (currently section 17.4). EDR LINK: \\CDSESUB1\EVSPROD\NDA202833\202833.enx *Select entry dated 3/31/2011 (Original Application)				
Consult Request: Please review the proposed patient package insert (currently section 17.4) for any feedback that may need to be provided to the sponsor.				
Thank you.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

J P PHILLIPS
05/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE/DMEPA		FROM: DDDP J. Paul Phillips/RPM, ODE III/DDDP/x6-3935		
DATE 05/02/2011	IND NO.	NDA NO. 202833	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 03/25/2011
NAME OF DRUG (ingenol mebutate) Gel, 0.015% and 0.05%		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 4022510	DESIRED COMPLETION DATE 09/26/2011
NAME OF FIRM: LEO Pharma				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Background: The sponsor of NDA 202833 (ingenol mebutate) sent in their new NDA on 3/25/2011. The NDA contains proposed carton/container labeling along with a proposed package insert and a proposed patient package insert. EDR LINK: \\CDSESUB1\EVSPROD\NDA202833\202833.enx *Select entry dated 3/31/2011 (Original Application)				
Consult Request: Please review the proposed carton/container labeling for any feedback that may need to be provided to the sponsor.				
Thank you.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

J P PHILLIPS
05/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) J. Paul Phillips/RPM, ODE III/DDDP/x6-3935	
REQUEST DATE 05/02/2011	IND NO.	NDA NO. 202833	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG (ingenol mebutate) Gel, 0.015% and 0.05%	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 4022510	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 11/07/2011
NAME OF FIRM: Leo Pharma		PDUFA Date: 01/25/2012	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
EDR link to submission:			
EDR Location: \\CDSESUB1\EVSPROD\NDA202833\202833.enx *Select entry dated 3/31/2011 (Original Application)			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: 09/06/2011 Labeling Meetings: 09/26/2011; 10/04/2011; 10/18/2011; 10/25/2011 Wrap-Up Meeting: 11/14/2011			
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND	

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/s/

J P PHILLIPS
05/02/2011



NDA 202833

INFORMATION REQUEST

Leo Pharma A/S
c/o Jones Regulatory Consulting
Attention: Sheri Jones, M.S., RAC
Regulatory Consultant, U.S. Agent
481 Haven Point Drive
Treasure Island, FL 33706

Dear Ms. Jones:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ingenol mebutate) Gel, 0.015% and 0.05%.

Please provide the following information by 12:00 p.m. (EDT) on Friday, April 29, 2011:

Provide Master Batch Records, one for each proposed manufacturing site (i.e. DPT in Texas and Leo Laboratories in Ireland) for the drug product (ingenol mebutate) Gel, 0.015% and 0.05%.

If you have questions, call Paul Phillips, Regulatory Health Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, M.D.
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/

JILL A LINDSTROM
04/27/2011

DSI CONSULT: Request for Clinical Inspections

Date: April 19, 2011

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Roy Blay, Ph.D., Reviewer, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Joanna Ku, M.D., Clinical Reviewer, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Susan J. Walker, M.D., F.A.A.D., Director, DDDP

From: J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 202833

Applicant/ Applicant contact information (to include phone/email):

Leo Pharma A/S
c/o Jones Regulatory Consulting, LLC
Attention: Cheri Jones, U.S. Agent
481 Haven Point Dr.
Treasure Island, FL 33706
(727) 940-4535
cheri@cjonesreg.com

Drug Proprietary Name: TRADENAME (ingenol mebutate) Gel, 0.015% and 0.05%

NME (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

- Topical treatment of actinic keratosis on the face and scalp
- Topical treatment of actinic keratosis on the trunk and extremities

PDUFA: 01/25/2012

Action Goal Date: 01/17/2012

DSI Consult

Version: 5/08/2008

Inspection Summary Goal Date: 09/01/2011

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 06: Karl G. Heine, MD Solutions...A Clinical Trials Company, LLC 880 Seven Hills Drive, Suite 150 Henderson, NV 89052-4380 Phone: (702) 285-6081 Fax: (7002) 456-0088	PEP005-025	N=16	Topical treatment of actinic keratosis on the face and scalp (Head)
Site 62: Suzanne Bruce, MD Suzanne Bruce and Associates, PA The Center for Skin Research 1900 St. James Place, Suite 650 Houston, TX 77056 Phone: (713) 985-0210	PEP005-028	N=16	Topical treatment of actinic keratosis on the trunk and extremities (non-Head)

III. Site Selection/Rationale

The product is an NME, and is indicated for treating actinic keratosis in the head and non head regions. We have chosen two DSI inspection sites from the pivotal studies, one of each from the head studies and the non head studies. These centers were chosen for large enrollment and high treatment effect. These sites have not been inspected by DSI.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): NME

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/s/

J P PHILLIPS
04/20/2011

JILL A LINDSTROM
04/20/2011



NDA 202833

NDA ACKNOWLEDGMENT

Leo Pharma A/S
c/o Jones Regulatory Consulting, LLC
Attention: Cheri Jones, U.S. Agent
481 Haven Point Dr.
Treasure Island, FL 33706

Dear Ms. Jones:

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

Name of Drug Product: TRADENAME (ingenol mebutate) Gel, 0.015% and 0.05%

Date of Application: March 31, 2011

Date of Receipt: March 25, 2011

Our Reference Number: NDA 202833

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 24, 2011, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 202833** submitted on March 25, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road

Beltsville, MD 20705-1266

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

If you have any questions, call me at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

J. Paul Phillips, M.S.
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

J P PHILLIPS
03/31/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070114

MEETING MINUTES

Peplin Operations USA, Inc.
Attention: Cheri Jones, M.S., RAC
Regulatory Consultant
6475 Christie Ave., Suite 300
Emeryville, CA 94608

Dear Ms. Jones:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PEP005 (ingenol mebutate) Gel, 0.015% and 0.05%.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2010. The purpose of the meeting was to discuss the requirements for submission of a New Drug Application (NDA) for PEP005 (ingenol mebutate) Gel.

A copy of the official minutes of the meeting is attached 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}

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

Enclosure
Official Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: December 15, 2010; 10:30 a.m. (EDT)
Meeting Location: W.O. 22, room 1311

Application Number: IND 070114
Product Name: PEP005 (ingenol mebutate) Gel, 0.015% and 0.05%
Indications: 0.015%: Topical treatment of actinic keratosis on the face and scalp
0.05%: Topical treatment of actinic keratosis on the trunk and extremities

Sponsor/Applicant Name: Peplin Operations USA, Inc.

Meeting Chair: Susan J. Walker, M.D.
Meeting Recorder: Paul Phillips

FDA ATTENDEES

Susan J. Walker, M.D., F.A.A.D., Director, DDDP
Tatiana Oussova, M.D., M.P.H., Deputy Director for Safety, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Brenda Carr, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jiaqin Yao, Ph.D., Pharmacology Reviewer, DDDP
Shulin Ding, Ph.D., CMC Lead, DNDQA II
Abimbola Adebowale, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Yuqing Tang, Ph.D., Biostatistician, DB III
Douglas Warfield, Regulatory Information Specialist, OBI/DRRS/eReDST
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Malene Kjær Müller, Head of Section, Regulatory Affairs
Thomas Nedergaard Jensen, Project Manager, LEO Project Management
Trine Thing Østerby, Regulatory Affairs Specialist, Regulatory Affairs
Gitte Marianne Schönwandt, Senior Regulatory Affairs Specialist, Regulatory Affairs
Christina Nymark Poulsen, Principal Scientist, Regulatory Affairs and Safety Support
Claus Bay, Head of Department, Biostatistics
Anita Melgaard, Senior R&D Scientist, Biostatistics
Kirsten Lykke Nørrelund, Senior Clinical Project Manager, Clinical Operations
Bjarke Naver, Principal Safety Scientist, Global Pharmacovigilance
Jørgen Schützsack, Senior Toxicologist, Preclinical Development
Cheri Jones, Regulatory Consultant, US Agent

Janice Drew, Senior Director, Clinical Development, Peplin Inc.
Mike White, Statistic Consultant, JM White Associates
Eugene A. Bauer, M.D., Consulting Chief Medical Officer, Peplin, Inc.

Regulatory Correspondence History

We have had the following meetings with you:

- 3/7/05: Guidance meeting
- 4/10/06: Guidance meeting
- 6/3/09: End-of-Phase 2 meeting
- 9/16/09: Guidance meeting
- 5/24/10: Responses for CMC guidance meeting (meeting cancelled following sponsor receipt of Agency comments)

We have sent the following correspondences:

- 8/3/04: Advice letter
- 8/17/04: Advice letter
- 10/27/04: Two advice letters
- 4/4/05: Meeting minutes for 3/7/05 guidance meeting
- 5/9/06: Meeting minutes for 4/10/06 guidance meeting
- 7/12/06: Executive Carcinogenicity Advisory Committee meeting minutes for nonclinical SPA
- 8/10/06: Additional comments regarding nonclinical SPA
- 12/20/06: Advice letter
- 3/24/08: Information request letter
- 6/2/08: Special Protocol Assessment letter
- 5/13/09: Revised Special Protocol Assessment letter
- 6/18/09: Advice letter
- 6/24/09: Meeting minutes for 6/3/09 End-of-Phase 2 meeting
- 9/21/09: Meeting minutes for 9/16/09 meeting

Chemistry, Manufacturing and Controls (CMC)

Question 1a:

Does the Agency agree that a single drug product section (3.2.P) can be submitted in the NDA?

Response:

Yes, we agree.

Question 1b:

In order to be able to present a complete overview of section 3.2.P the Sponsor suggests submitting only one Quality Overall Summary (2.3.P) for the drug product covering both strengths and manufacturing sites in the NDA. Does the Agency agree with this proposal?

Response:

Yes, we agree.

Question 2:

To support a shelf-life of 24 months the Sponsor wishes to submit 24 months' data for the 0.015% primary stability batches and updated stability data for the process validation batches from both manufacturing sites during NDA review, 6 months after submission of the NDA. Does the Agency concur with this stability submission schedule?

Response:

Yes, we concur if you can commit to a stability update no later than 24 weeks after submission of the NDA.

Question 3:

Does the Agency agree that five samples of each strength be submitted for decision of dosage form at the same time as the NDA and that further samples for drug substance and drug product testing can be submitted upon request from the Agency?

Response:

Yes, we agree. Please make sure that representative samples for which the viscosity is near the lower limit of the proposed viscosity acceptance criterion are included in the submission, and that each sample is accompanied with its certificate of analysis.

Additional Comments:

1. Please clarify whether batches manufactured by Leo Laboratories are used in any clinical studies.
2. Proper bridging studies may need to be conducted to demonstrate that batches made by DPT and Leo Laboratories are equivalent if a semisolid dosage form such as gel is granted as the dosage form for your proposed product. Examples for bridging different sites can be found in SUPAC-SS.
3. [REDACTED] (b) (4) Please address this safety concern for this compound, and provide justification to support your proposed limit for [REDACTED] (b) (4)

Meeting Discussion:

The sponsor stated that Leo's batches will not be used in any of the clinical studies supporting this NDA. The sponsor conducted IVRT to demonstrate the equivalence of the batches made between DPT and Leo laboratories.

The sponsor will send [REDACTED] (b) (4) of the final formulation for each concentration of the product to the project manager.

The sponsor stated they would submit nonclinical information to support potentially genotoxic impurities in the drug product with the NDA. The Agency responded that this information should be submitted to the IND. The sponsor agreed to submit this information to the IND.

Pharmacology/Toxicology

Question 4:

The Sponsor asks the Agency to reaffirm, at this time that the 2 to 3 day treatment regimen clinically tested and proposed for the market is supported by the nonclinical data package as presented for this NDA. Please refer to Section 4 of this briefing document.

Response:

It appears that the completed nonclinical studies are sufficient to support an NDA submission for the proposed clinical treatment regimen. However, whether additional nonclinical information is needed will be a review issue.

Provide information on test article analysis (including impurities) of batches/lots used in the nonclinical and clinical studies. Before the NDA submission, you should address the safety concern of any potentially genotoxic impurity in the IND (e.g. structure alert, proposed limit, daily exposure level, and nonclinical studies).

Clinical, Clinical Pharmacology, & Biostatistics

Question 5:

Does the Agency agree with the cut-off date of 30-Sep-2010 (approximately 6 months prior to the NDA submission) for inclusion of safety data from any ongoing studies?

Response:

Yes.

Question 6a:

Does that Agency agree with the Sponsors intention to submit full clinical study reports for the LTFU studies (12 month data) as part of Module 5 at the time of submission of the Day-120 safety update?

Response:

Yes.

Question 6b:

Does the Agency agree that at the time of the Day-120 safety update, a summary of the LTFU studies and comparative tables will be placed in Module 1.11.2 and no other modules (except providing full CSRs) will be updated?

Response:

Yes.

Questions 7:

Does the Agency agree with this proposal regarding submission of SDTs, annotated CRFs and data definition files?

Response:

Generally your proposal for the submission of the SDTs, annotated CRFs and data definition files appear to be acceptable. However, you need to provide an explanation for the meaning of "Trial Design Datasets". In addition, the following should be noted when you prepare the datasets:

1. You need to submit electronic analysis datasets in SAS transport format including efficacy and safety data as well as demographic and baseline data. Each dataset should include the assignment of the treatment.
2. The datasets for the pivotal studies should include both raw variables from the CRF and derived variables for conducting primary and secondary efficacy analysis.
3. The definition file should include the definitions of each variable in the dataset, indication for which variables are derived as well as the formulas for the derived variables, and the definition for each category for any factor variables.

For the maximal use PK study PEP005-017 together with the previous PK data from studies PEP005-004 and PEP005-013, this proposal also appears to be acceptable. Please include the bioanalytical reports and their corresponding method validation reports for the PK studies, in your NDA submission

Meeting Discussion:

The sponsor stated that they will not be submitting the plasma concentrations obtained in the PK studies as an electronic data set, because the concentrations were all below the lower limit of quantitation. The Agency requested that the sponsor submit all plasma concentrations as part of the bioanalytical reports.

Question 8:

Does the Agency agree with this proposal regarding analysis datasets?

Response:

No, the we do not agree. While the sponsor can submit the pooled analysis datasets for the integrated analyses of efficacy, the individual analysis dataset for each of the pivotal studies also need to be submitted.

Meeting Discussion:

The sponsor stated that they will submit demographic and efficacy data sets for the four pivotal trials. The efficacy data sets will include AK count at baseline as well as at day 57. The Agency requested that the sponsor submit AK counts which occurred during the course of the trial as well, as such data could be used to handle missing data and examine the subject response profile. The sponsor stated that for subjects who discontinued the trial they have their AK lesion count before they discontinued the trial which they used for imputing their missing data. The Agency encouraged the sponsor to submit all efficacy data which they have available.

The Agency encouraged the sponsor to submit a test data set to the eSUB group to ensure that all files are accessible.

Post Meeting Addendum:

To arrange a test submission, the sponsor may refer to the FDA website “Submit a Sample eCTD to the FDA”

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm> for guidance on sending a test submission. The sponsor may request dataset(s) analysis for CDISC specifications compliance as part of a test submission. Please note that the scope of test submissions is limited. The Agency will give priority to testing electronic submissions made in preparation for actual submission for review. If requested, the Agency will provide reports of the dataset(s) CDISC compliance analyses of the eCTD test submission processing to the submitter. The sponsor should notify the Agency if they want feedback for SDTM formatted datasets submitted by sending an email to esub@fda.hhs.gov or cder-edata@fda.hhs.gov.

Question 9:

Does the FDA agree with the proposed approach of not submitting patient profiles?

Response:

Yes

Question 10:

Based on the above, the Sponsor does not believe that the criteria for REMS are fulfilled and consequently does not believe that a REMS is needed for PEP005 Gel. Does the Agency agree?

Response:

This is a review issue. However, we are currently unaware of a safety signal that would necessitate a REMS.

Question 11:

The Sponsor will not include any requirements for the use of a finger cot in the proposed label and only stipulate hand washing following medication application for patients using PEP005 Gel for AK.

(b) (4)

Please refer to Appendix 1 Draft USPI.

Does the Agency agree?

Response:

You should provide the clinical data that support your proposal to use the product without the protective covering used in the clinical trials.

Additional Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. You are reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

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/s/

SUSAN J WALKER
01/13/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,114

Peplin Operations USA, Inc. (Peplin)
Attention: Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs
6475 Christie Avenue, Suite 300
Emeryville, CA 94608

Dear Ms. Jones:

Please refer to your Investigational New Drug Application (IND) file for PEP005 (ingenol mebutate) Gel for the treatment of actinic keratosis.

We also refer to the meeting between representatives of your firm and the FDA on June 3, 2009. The purpose of the meeting was to obtain the Agency's input and guidance for the development of the Phase 3 clinical trials.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: June 3, 2009 **Time:** 11:00AM
Location: Via Teleconference **Meeting ID:** 26046
Topic: PEP005 Gel, 0.015% for the treatment of actinic keratosis
Subject: End of Phase 2 (Type B) Meeting/ IND 70,114
Sponsor: Peplin Operations USA (Peplin)
Meeting Chair: Susan J. Walker, M.D.
Meeting Recorder: Catherine Carr, MSc.

FDA Attendees:

Susan Walker, M.D., Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Joanna Ku, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jiaqin Yao, Ph.D., Pharmacology Reviewer, DDDP
Catherine Carr, M.S., Regulatory Health Project Manager, DDDP
Mohamed Alesh, Ph.D., Biostatistics Team Leader, DB III
Mat Soukup, Ph.D., Biostatistics Reviewer, DB III
Dennis Bashaw, Pharm.D., Director, DCP III
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPMA II, Branch III

Sponsor Attendees: Peplin

Eugene A Bauer, M.D., Chief Medical Officer
Peter Welburn, Ph.D., Chief Scientific Officer
Gary Patou, M.D., Medical Consultant
Cheri Jones, M.S., RAC, FRAPS, Vice President Regulatory Affairs
Lynn Hansen, RAC, Director Regulatory Affairs
█^{(b) (4)}, Consulting Statistician
█^{(b) (4)} Nonclinical Consultant
Janice Drew, MPH, Senior Director of Clinical

Purpose:

The purpose of the meeting was to obtain the Agency's input and guidance for the development of the Phase 3 clinical trials to support the filing of an NDA for the indication of the treatment of actinic keratosis on the head (face and scalp) region.

Chemistry, Manufacturing and Controls:

Question 1:

Finished Product Nomenclature (From the Agency's 11/30/08 Letter):

Does the Agency agree that the gel nomenclature remains the designation for the unit-of-use product?

Response:

We cannot unequivocally agree with such a designation. The samples which you submitted for review for the end of Phase 2 meeting appear to be a borderline "gel" and to some extent resemble a thick solution. We are concerned that the viscosity and yield may be too low for a semi-solid dosage form such as gel. The final decision on dosage form for an NDA product will be made during the NDA review at which time you will need to submit again representative samples in the to-be-marketed container/closure system with rheological data (sheer stress vs. shear rate and viscosity vs. shear rate).

Question 2:

Pesticide Residue Testing (1/30/08 Agency Letter Follow up):

Does the Agency concur that, due to the below acceptable limit quantities hypothetically achievable in the finished product, the absence of detectable residue in the API batches tested, and the lack of detectable systemic absorption, testing for Mancozeb is unnecessary on API release?

Response:

Yes, we concur, provided that you will document and monitor the use of pesticide(s) for each batch of crop used in the manufacture of the proposed drug substance, and that each grower has a control system in place for the use of pesticides on his/her farm.

Additional CMC Comment:

1. Add Individual Unspecified to the test on Purity for drug substance.
2. Provide method information and test results in the IND for the Franz Cell Testing described on page 34 of the briefing package.

Pharmacology/Toxicology:

Question 3:

Based on the intended clinical therapeutic regimen in which the maximum duration of exposure will not exceed three consecutive days, and under current clinical management strategies for patients with actinic keratosis, the anticipated total duration of exposure even with retreatment

will be relatively short, the Sponsor believes that the clinical treatment course is an acute treatment.

Does the Agency concur?

Response:

Actinic keratosis is considered to be a chronic indication both clinically and for regulatory purposes, because it is anticipated that the patients will likely receive repeat treatment. The Agency agrees that the intended clinical treatment course, topical application of 0.05% PEP005 Gel for 2 consecutive days to non-head locations (trunk and extremities) and 0.015% PEP Gel for 3 consecutive days to head locations (face and scalp), is a short term treatment.

Question 4:

Based on this intended acute clinical therapy of PEP005 (ingenol mebutate) Gel, and the Agencies response of August 10, 2006, the Sponsor believes that non-clinical evaluation of carcinogenicity is not required.

Does the Agency concur?

Response:

The need for nonclinical evaluation of carcinogenicity may not be necessary at this time to support this short term (3-day) topical treatment regimen. However, the need for carcinogenicity studies may change in the future if the clinical use changes.

Question 5:

Does the Agency agree that in consideration of the results of completed reproductive toxicity studies per ICH Stages C/D of the reproductive process, if clinical pharmacokinetic data demonstrate that systemic exposure to PEP005 (ingenol mebutate) and metabolites under conditions of maximum exposure are below the limit of quantitation (0.1 ng/mL using a validated highly sensitive and specific LC MS/MS whole blood assay), that a waiver of the requirement for reproductive toxicity evaluations per ICH Stages A/B (fertility and early development), and E/F (peri-and postnatal development) will be granted?

Response:

It appears that the completed reproductive toxicology studies in pregnant rats and rabbits by intravenous administration of PEP005 have assessed the potential effects on embryo-fetal development of PEP005. If systemic exposure to the drug substance and metabolites during clinical use under conditions of maximum exposure does not occur at a measurable level, the fertility and early embryonic development toxicity study and the prenatal and postnatal development toxicity study may not be recommended.

Question 6:

The Sponsor believes that with the exception of potential requirement for conduct of reproductive toxicity studies per ICH Stages A/B and E/F, the completed nonclinical studies are sufficient to support submission of a New Drug Application for PEP005 (ingenol mebutate) Gel for the indication of treatment of Actinic Keratosis.

Does the Agency concur?

Response:

It appears that the completed nonclinical studies are sufficient to support an NDA for the proposed short term (3-day) topical treatment regimen. However, additional nonclinical studies may be needed if other toxic effects are noted in the patients following topical treatment of PEP005 Gel.

Clinical Pharmacology:

Question 7:

Does the Agency agree that the pharmacokinetic data provided from the maximal use study PEP005-017, together with the previous PK data from studies PEP005-004 and PEP005-013, are sufficient to address the lack of systemic absorption of PEP005 and fulfill the pharmacokinetic requirements to file the NDA?

Response:

These are ultimately review issues. However, the information you have outlined in your package appears to be sufficient to allow for us to evaluate the systemic exposure potential for your product.

Clinical:

Question 8:

Does the Agency agree that the design of the Phase 3 protocols, PEP005-016 and PEP005-025 (PEP005 Gel, 0.015% for 3 consecutive days), modeled upon the previous SPA-reviewed Phase 3 non-head (trunk and extremities) protocol, are acceptable to confirm the safety and efficacy of PEP005 Gel for AK lesions located in the head (face and scalp)?

Response:

You received special protocol assessment (SPA) comments for a Phase 3 clinical trial (PEP005-014) that was conducted in 255 patients in the non-head (trunk and extremities) region, using PEP005 Gel, 0.05%, applied daily for 2 consecutive days to a contiguous area of skin (25 cm²) containing 4-8 AK lesions. The primary efficacy endpoint was complete clearance rate of AK lesions, defined as the proportion of patients at the Day 57 visit, with no clinically visible AK lesions in the selected treatment area. The secondary efficacy endpoint was partial clearance rate

of AK lesions, defined as the proportion of patients at the Day 57 visit with a 75% or greater reduction in the number of AK lesions identified at Baseline in the selected treatment area. The study has been completed.

Now you propose to conduct two Phase 3 clinical trials (PEP005-016 and PEP005-025) to support the safety and efficacy for using PEP005 for the treatment of AK lesions located in the head (face and scalp) region. You state that the designs these two head studies are to model after that of the non-head study, which incorporated all of the Agency's SPA comments. These are multi-center, randomized, parallel-group, double-blind, and vehicle- controlled studies. Approximately 250 patients (125 patients per treatment arm) will be enrolled into each of these Phase 3 studies. The primary objective will be to evaluate the efficacy and safety of PEP005 Gel, 0.015% compared to vehicle gel when administered once daily for 3 consecutive days, to a 25 cm² contiguous area of skin located on the head (face or scalp). The dose selection is based on Study PEP005-015, which is a Phase 2b dosing study conducted in the head region. The primary efficacy endpoint will be complete clearance rate of AK, defined as the proportion of patients at Day 57 visit with no clinically visible AK lesions in the selected treatment area. The secondary efficacy endpoint will be partial clearance rate of AK lesions, defined as the proportion of patients at the Day 57 visit with a 75% or greater reduction in the number of AK lesions identified at Baseline, in the selected treatment area.

We agree that complete clearance of AK would be a meaningful endpoint for labeling. However, it is not clear that partial clearing (e.g., 75%) is clinically meaningful. For example, a 75% or greater reduction in the number of AK lesions could still leave the largest AK lesion in the treatment area unaffected, and the lesion could progress into a squamous cell carcinoma.

Given that AK lesions can spontaneously regress but recur, it will be important to follow longer term outcome following treatment (e.g., 6 months and a year out). Lesions that appear, or lesions that remain refractory to treatment should be fully evaluated, including biopsy and measurement for size and thickness.

Additional Comments Pertaining to the Statistical Analysis:

The following comments pertain to the statistical analysis of the primary endpoint, complete clearance rate.

- Randomization is stratified on BOTH investigative center as well as location of the treatment area (face or scalp). The Division is in agreement with the proposed method of Cochran-Mantel-Haenszal (CMH) stratified by analysis center as the primary analysis method. However, as a supportive analysis the protocol should also specify a testing approach that also takes into account the randomization factor of location (face or scalp) which is in line with recommendations of the *Guidance for Industry: E9 Statistical Principles for Clinical Trials*.
- The protocol states that if the Breslow-Day test is significant then an exploratory analysis will be conducted to assess the impact of site-by-treatment interactions on the study results. Such an analysis should be pre-specified in the protocol. The sponsor might consider deleting the most extreme center(s) and applying CMH stratified by the remaining centers to assess the robustness of efficacy conclusions.
- The proposed sensitivity analysis of handling missing data and out-of-window observations is to impute these observations as treatment failures. It should be noted that

subjects who miss the Day 57 visit are essentially imputed as treatment failures using the primary method of data imputation, LOCF, as the Baseline and Day 57 visit are the only visits where efficacy is assessed. Thus, it is expected that the sensitivity analysis of the method of data imputation and the primary method of data imputation will yield similar results. The protocol should propose an alternate method of data imputation as a sensitivity analysis of the primary method of data imputation to ensure efficacy results are not driven by the method of data imputation.

Question 9:

The clinical development plan for PEP005 Gel includes two, 250 patient confirmatory studies for AK of the face and scalp and one confirmatory study (study PEP005-014) for AK lesions on non-head areas (trunk and extremities) in addition to the supportive information in the dose ranging trials. Based on the clinical development plan and the compelling evidence of efficacy from study PEP005-014, does the Agency agree that the one study (Study PEP005-014) would be sufficient for approval of the indication for AK lesions on non-head areas?

Response:

The Division cannot make a formal agreement on the sufficiency of a single Phase 3 trial submission at this stage for the treatment of non-head regions as this will depend on the actual review of the data submitted to the NDA. The sponsor is referred to the previous comment made in the SPA review of Protocol PEP005-014. “Typically for an efficacy claim, the Division recommends at least two well-controlled trials as this provides independent substantiation of the efficacy result. The sponsor is referred to *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* which should be used to guide the sponsor in developing their drug product in one or more clinical trials.” In general, for efficacy claims based on a single study submission, the efficacy results need to meet certain criteria related to persuasive study findings as well as consistency of findings across subgroups.

Question 10:

Peplin believes that the data from the two formal dose-ranging trials along with the three Phase 3, adequate and well controlled studies, PEP005-014 (PEP005 Gel, 0.05% for 2 consecutive days), PEP005-016 and PEP005-025 (PEP005 Gel, 0.015% for 3 consecutive days), will provide the evidence of efficacy and safety for the development of PEP005 Gel for the treatment of actinic keratosis. Does the Agency agree that no further adequate and well controlled trials are required for NDA filing?

Response:

It appears that your proposal would be adequate for NDA filing. The adequacy of findings for head and non-head regions should stand on their own. Therefore it is difficult to offer specific comment on whether or not the clinical trials will be sufficient at this time. Whether a single study could support the approval for the non-head indication will be a review issue (see response to Question 9).

Question 11:

Peplin believes that the safety data provided from the 1508 patients and healthy subjects at the time of NDA filing will provide an adequate safety profile for PEP005 Gel when used to treat actinic keratosis. Does the Agency concur?

Response:

The adequacy of the safety database will be a review issue and will depend on the adequacy of data based on the concentration of the drug used, location of where the drug was applied, duration of treatment, and the adverse reactions profile. Additional safety follow-up for at least a year after treatment should be collected. New, recurrent, and unresolved lesions should be characterized.

Note that we consider PEP005 treatment for the indication of AK a chronic therapy, and as such it will need to meet safety requirements consistent with ICH E1A Guidelines (March 1995).

Question 12:

Due to the lack of systemic absorption of PEP005 and its acyl isomers, (b) (4), as demonstrated in the maximal use clinical study, PEP005-017, together with the negative results in the nonclinical cardiovascular safety studies, Peplin does not intend to conduct a formal QT/QTc interval study. Does the Agency agree with this decision?

Response:

Should no systemic absorption be detected in an adequate maximal use systemic exposure study using a sufficiently sensitive assay methodology, a formal QT study may not be needed. However, PEP 005 is a new molecular entity, and systemic absorption may occur at a level lower than that can be detected by assay sensitivity. Additionally, non-clinical studies cannot always predict the cardiovascular risks in human. Therefore we recommend that you follow the guidelines contained in Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

Question 13:

Does the Agency agree that the sponsor has conducted all needed clinical studies to support the filing of an NDA, provided data continue to demonstrate acceptable safety and efficacy results?

Response:

See responses to Questions 8-12.

Question 14:

Does the Agency have any additional comments related to the clinical or statistical portions of the NDA?

Response:

The duration of safety follow up in the head studies should also take into consideration the time frame of the occurrence of adverse events observed in the completed studies, including in the non-head study (PEP005-014). For example, in that study, one patient was observed to have “abnormal proliferation, commencing at Day 29 of study which required additional post study follow up visits beyond Day 57. The area was biopsied and identified as being chronic eczematous dermatitis associated with focal actinic keratosis.” Safety follow up in the to-be-conducted head studies needs to be long enough, based on previous clinical experience, to ensure that adverse events are followed up until satisfactory resolution of the event and/or a diagnosis has been obtained.

Clarify whether the product is intended to treat different areas simultaneously in clinical use, and whether there would be a maximum-use guideline, i.e., in terms of how often the patient may be treated in a given period of time, and what is the total maximum surface area that can be treated at any given time. Clarify how you will provide data to support labeling to address these issues.

For Studies PEP-005-016 and PEP005-025, SAEs must also be reported to the FDA according to regulatory requirements. Laboratory abnormalities (as listed Appendix I) should include both upper and lower limits of normal for potassium, hemoglobin, platelets, and neutrophil count.

Meeting Discussion:

Two main points emerged during the meeting discussion:

1. *Recurrence of AK and safety data obtained from long-term follow up is needed for this new molecular entity (NME).*

The Division re-iterated that all patients, regardless of AE status, should be followed for at least one year after the primary efficacy time point, to obtain recurrence and safety data. The Division deems this information clinically important, and necessary for the public health.

The Division is open to further discussions with the sponsor regarding fulfillment of this requirement.

2. *Treatment of AK in the head region should be considered a separate indication from treatment of AK in the trunk and extremities (non-head region).*

In the meeting package provided by the sponsor, the clinical development program appears to be pursuing two separate indications, based on the two different dosing regimens, two different dosage strengths, two different anatomical treatment locations, and two separate pivotal study pathways to study the head, and non head regions. Furthermore, the head region may respond differently to treatment, and requires additional clinical considerations (e.g., for cosmetic implications) from the non-head regions. For all of these reasons, the Division considers these to be two separate indications.

The sponsor will discuss internally the regulatory and developmental approach that they would like to take for seeking two indications under one NDA. The Sponsor will follow up with the Agency if further discussions are necessary.

The Division also clarified that special protocol assessment (SPA) comments are specifically relevant to the protocol submitted for the SPA. Therefore, the Division's comments provided for the SPA for Study PEP005-014 pertain only to that study, and do not imply agreement on other issues relating to the clinical development program.

Project Management:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. 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) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
5. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.
6. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
7. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
8. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 70114

PEPLIN OPERATIONS
USA INC

AGN 204332 GEL 0.01%

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

/s/

SUSAN J WALKER

06/24/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 70,114

PRELIMINARY COMMENTS

Peplin Operations USA, Inc.
Attention: Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs
6475 Christie Avenue, Suite 300
Emeryville, CA 94608

Dear Ms. Jones:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PEP005 (ingenol mebutate) Gel.

We also refer to your March 30, 2010, correspondence requesting a Chemistry, Manufacturing and Controls (CMC) Type C (Guidance) meeting to discuss API and Finished Product questions pertaining to ingenol mebutate, a New Chemical Entity (NCE).

Please see the attached preliminary responses to your questions, in preparation for the meeting granted and scheduled for June 8, 2010, 1:00 PM – 2:00 PM, at the FDA White Oak Campus, Silver Spring, MD 20993.

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Peplin Operations USA, Inc.
Application Number:	IND 70,114
Product Name:	PEP005 (ingenol mebutate) Gel
Meeting Type:	Type C Guidance Meeting
Meeting Category:	Chemistry, Manufacturing and Controls (CMC)
Meeting Date and Time:	Tuesday, June 8, 2010, 1:00 PM – 2:00 PM EST
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	May 7, 2010

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a **face-to-face meeting** on **Tuesday, June 8, 2010, between 1:00 PM – 2:00 PM EST** between **Peplin Operations USA, Inc.** and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Jeannie David, M.S., Regulatory Project Manager, 301-796-4247). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

BACKGROUND

Peplin Operations USA, Inc. (Peplin) requested a Type C Chemistry, Manufacturing, and Controls (CMC) meeting, letter dated March 30, 2010, to discuss CMC topics related to PEP005 (ingenol mebutate) Gel for intended for the treatment of actinic keratosis (IND 70,114). A Type C Guidance meeting between Peplin and the FDA was held on September 16, 2009 (FDA Meeting Minutes dated September 21, 2009). FDA's initial responses to Peplin's questions in the CMC briefing package received May 7, 2010, are listed below.

Sponsor Questions and FDA Response:

Active Pharmaceutical Ingredient (API, drug substance):

Question 1 (Section 4.2): Starting Material

Does the Agency concur with the designation of (b) (4) as the starting material for the manufacturing process of the ingenol mebutate API?

FDA Response:

Yes, we concur.

Question 2 (Section 4.3): Batch Record

The sponsor plans to provide a flow diagram and a description of the manufacturing process for the API in Module 3.2.S.2.2. The sponsor does not plan to submit a master or executed manufacturing batch record for ingenol mebutate drug substance in the NDA. These documents will be available at the manufacturing site.

Does the Agency concur?

FDA Response:

This is a review issue. We will be open to your proposal if adequate information is provided in the NDA regarding manufacturing process, quality and control of starting material/reagents/solvents/intermediates/resins, controls on critical steps and process variables, hold times, etc. We will also review lot-to-lot manufacturing consistency, batch analysis, and stability.

Question 3 (Section 4.4): Drug Substance Tests

Does the Agency agree with the proposed tests in the specification for the ingenol mebutate API?

FDA Response:

We have not identified any major missing test. However, the adequacy of drug substance specification for NDA approval is a review issue.

Drug Product:

Question 1 (Section 4.6): Stability Data Collection Plan

Does the Agency agree that the stability data collection plan will be acceptable for establishing the expiration dating for both strengths of the drug product?

FDA Response:

The stability data collection plan appears to be reasonable. However, this is a review issue. We will need to review method validation package for the UHPLC method, and the results of the bridging study which involves side-by-side testing by both methods. Please also provide batch release and stability data for any new drug product lots which are released using the proposed regulatory method.

Question 2 (Section 4.7): Drug Product Tests

Does the Agency agree with the proposed tests in the specification for the drug product?

FDA Response:

This is a review issue. We notice that the proposed tests do not include weight loss and USP<51> Antimicrobial effectiveness testing. You will need to provide justification in the NDA to support their exclusion from the specification.

ISSUES REQUIRING FURTHER DISCUSSION

- 1. Drug product registration stability data should be generated for weight loss and USP<51>. You will also need to show in a development study that the proposed product can meet USP<51> requirements at the lower limit of benzyl alcohol acceptance criterion.*
- 2. Please clarify if the manufacturing site for Phase 3 supplies will also be the commercial site. If it is not the same site, a bridging study may be necessary. SUPAC-SS contains examples for bridging different sites.*
- 3. The proposed product contains a significant amount of alcohol. Therefore, please evaluate the flammability of the product in accordance with 16CFR 1500.43. If necessary, an appropriate flammability warning must be included in the product labeling.*

CONCURRENCE:

{See appended electronic signature page}

Jeannie David, M.S.
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-70114

GI-1

PEPLIN LTD

PEP005 GEL

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

/s/

JEANNIE C DAVID
05/24/2010

MOO JHONG RHEE
05/24/2010
Chief, Branch IV

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 202833	NDA Supplement # 0	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Picato Established/Proper Name: ingenol mebutate Dosage Form: Gel		Applicant: Leo Pharma Agent for Applicant (if applicable): Cheri Jones
RPM: J. Paul Phillips		Division: Dermatology and Dental Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>01/25/2012</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> 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		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>Comments:</p>	
<p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> REMS not required</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p> <input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other </p>

² 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

<p>Exclusivity</p>	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
<p>❖ Patent Information (NDAs only)</p>	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ³	<input checked="" type="checkbox"/> Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	<input checked="" type="checkbox"/> Included
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	01/16/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	03/25/2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	07/15/2011 (Zyclara S-003)

³ Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	01/16/2012
<ul style="list-style-type: none"> Original applicant-proposed labeling 	11/07/2011
<ul style="list-style-type: none"> Example of class labeling, if applicable 	07/15/2011 (Zyclara S-003)
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	01/12/2012
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	08/10/2011 (Letter) 08/08/2011; 11/10/2011 (Reviews)
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 05/26/2011 <input checked="" type="checkbox"/> DMEPA 05/16/2011 <input checked="" type="checkbox"/> DMPP 11/22/2011 <input checked="" type="checkbox"/> OPDP 11/23/2011 <input checked="" type="checkbox"/> SEALD 01/11/2012 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	CMC- 05/13/2011 P/T- 05/17/2011 ClinPharm- 05/17/2011 Biostat- 05/24/2011 Clinical- 05/31/2011 RPM- 05/31/2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC 08/17/2011 If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	<input checked="" type="checkbox"/> Included
❖ Internal memoranda, telecons, etc.	Memo of CMC tcon (12/23/2011) Memo of tcon (01/12/2012)
❖ Minutes of Meetings <ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) EOP2 meeting (<i>indicate date of mtg</i>) Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A or no mtg 12/15/2010 06/03/2009 05/24/2010 (CMC mtg)
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 01/23/2012
Division Director Summary Review (<i>indicate date for each review</i>)	12/30/2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	12/16/2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews <ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) Clinical review(s) (<i>indicate date for each review</i>) Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	(See CDTL review) 12/06/2011 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review, pg. 19/ 12/06/2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	08/08/2011 (DCRP)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A <input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	12/12/2011 (letter) 10/03/2011 (review summary) 09/26/2011 (2 letters)
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	11/18/2011 (2 reviews)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	11/18/2011
DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	11/01/2011
• Supervisory Review(s) (<i>indicate date for each review</i>)	11/01/2011
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	11/01/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	07/12/2006
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 01/23/2012
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	01/23/2012 (CMC amendment); 11/18/2011 (CMC); 11/11/2011 (Biopharm)
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	09/16/2011
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: 01/20/2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

6. i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.