*If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐

If yes, explain:

Applicant states the following: Connetics claims a three year marketing exclusivity period for Emulsion Formulation Clobetasol Propionate Foal, 0.05% (EF Clobetasol Foam) under the provision of 21 CFR 314.50(j) and 21 CFR 314.108(b)(4), based on the rationale listed:

(1) The application is submitted under section 505(b) of the Act;

(2) The approval date of this application will be after 24 Sept. 1984;

(3) Clobetasol Foam contains an active moiety, clobetasol propionate, that has been previously approved in other application under section 505(b) of the Act as listed in Table 1 (e.g. Temovate Cream, Ointment and Solution, 0.05%.

(4)The application contains report of new clinical investigations (other than bioavailability studies) conducted and sponsored by Connetics under IND 67,818 that are essential to the approval of the application.;

(5) Connetics certifies that a thorough search of the scientific literature has been performed and to the best of Connetics knowledge at the time of NDA submission, there are no published studies publicly available reports of clinical investigations with EF Clobetasol Foam for topical application in the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Therefore, it is Connetics' opinion that there are not publicly available reports that provide a sufficient basis for approval of EF Clobetasol Foam for the treatment of corticosteroid-responsive dermatoses without reference to the new clinical investigation report contained in the application

(6) Each study listed in Table 2 was submitted to Conntics' IND 67,818 and Connectics was the sponsor identified on the FDA Forms 1571 submitted in the IND.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain: This is an eCTD. No TOC provided in the hard copy archival volume. However, a TOC is provided electronically in Module 1.

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  **If an electronic NDA, all forms and certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments: The entire application is submitted in electronic format. All forms and certifications requiring a signature were provided in paper.

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

***NOTE:*** *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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 application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
**(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**
**NOTE:** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 67,818

- End-of-Phase 2 Meeting(s)? Date(s) 11/29/04 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 12/14/05 NO ☐
If yes, distribute minutes before filing meeting.

## Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☒ NO ☐
- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A ☒ YES ☐ NO ☐

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

## Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review**
**Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

   *If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Temovate Ointment, 0.05%, NDA 19-323

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "No," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "Yes," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "No," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).) **SEE ATTACHMENT #1 for list of other pharmaceutical alternatives.**

*NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☒

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **This application provides for a change in dosage form of the reference listed drug, Temovate ointment, 0.05%, NDA 19-323.**

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s): 3,721,687 and 4,370,322 **(SEE ATTAHCMENT #2 for paragraph certification statement)**

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A ☐ YES ☒ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A ☒ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES ☒ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES ☒ NO ☐

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 67,818 NO ☐

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☒ NO ☐

NDA Regulatory Filing Review
NDA 22-013 Primolux (clobetasol propionate) Foam, 0.05%

## ATTACHMENT 1

List of other pharmaceutical alternatives for Primolux (clobetasol propionate) Foam, 0.05% (not including the reference listed drug, Temovate Cream, 0.05%, NDA 19-322)

| | |
|---|---|
| Olux (clobetasol propionate) Foam, 0.05% | NDA 21-142 |
| Temovate E (clobetasol propionate) Cream, 0.05% | NDA 20-340 |
| Temovate (clobetasol propionate) Gel, 0.05% | NDA 20-337 |
| Clobex (clobetasol propionate) Lotion, 0.05% | NDA 21-535 |
| Temovate (clobetasol propionate) Ointment, 0.05% | NDA 19-323 |
| Clobex (clobetasol propionate) Shampoo, 0.05% | NDA 21-644 |
| Temovate (clobetasol propionate) Solution, 0.05% | NDA 19-966 |
| Clobex (clobetasol propionate) Spray, 0.05% | NDA 21-835 |

**ATTACHMENT 2**

(Applicant's Patent Certification Statement – Paragraph II)

1.3.5.2 PATENT CERTIFICATION

Paragraph II Certification

Pursuant to 21 USC §355(b)(2)(A)(ii) and 21 CFR §314.50(i), Connetics Corporation certifies to the best of its knowledge that U.S. Patent Nos. 3,721,687 and 4,370,322, which claim clobetasol propionate drug substance, drug product, and method of use, owned by Glaxo Group Limited, expired on March 20, 1992 and October 5, 2001, respectively.

20 Feb 2006

Kathina J. Church
Executive Vice-President
Legal Affairs and General Counsel

Date

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On Original

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

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/s/

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Margo Owens
5/24/2006 01:25:51 PM
CSO

Mary Jean Kozma Fornaro
5/24/2006 01:29:50 PM
CSO

Appears This Way
On Original

**Division of Dermatologic and Dental Drug Products (HFD-540)**
**Pharmacology/Toxicology Checklist for NDA Filing Meeting**

**Date**: 5/1/06
**Reviewer:** Carmen Booker, Ph.D.
**NDA Number:** 22-013
**Drug Name:** Primolux™, Emulsion Formulation Clobetasol Propionate Foam, 0.05%
**CAS Number:** 25122-46-7
**Drug Class:** corticosteroid
**Indication:** Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses
**Route of Administration:** topical to the skin
**Date CDER Received:** March 16, 2006
**User Fee Date:** January 16, 2007
**Date of Draft Review:** October 13, 2006
**Sponsor:** Connetics Corporation

**Fileability:**
On initial overview of the NDA application:

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed?
Yes

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review?
Yes

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed?
Yes

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?
No. In addition to several new studies submitted to this NDA, the sponsor is relying on the Agency's previous findings of nonclinical safety for Temovate Ointment for single-dose toxicity, repeat-dose toxicity, genotoxicity, and reproductive toxicity data on clobetasol propionate. The sponsor commits to conduct a dermal carcinogenicity study in a single species and a photocarcinogenicity study, also in a single species, with EF Clobetasol Foam as a post-marketing commitment. Nonclinical studies were previously submitted and reviewed for IND 67,818 and NDA 19-323 (Temovate Ointment).

(5) If the formulation to be marketed is different from the formulation used in the toxicology

studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required?

Yes. Nonclinical studies were conducted using clobetasol propionate.

(6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either $mg/m^2$ or comparative serum/plasma levels) and in accordance with 201.57?

Yes

(7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?

Yes

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route?

Yes

(9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?

Yes

(10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?

The sponsor has committed to conducting a nonclinical carcinogenicity study and a nonclinical photocarcinogenicity study upon approval of the NDA. The sponsor states that the dose-ranging studies will be initiated within 1 year of the product launch in the US, and the protocols for the definitive studies will be submitted to the CAC within 1 year after completion of the dose-ranging studies.

(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.

Yes

(13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify:

No

(14) Issues that should not be conveyed to the Sponsor:

None at this time.

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/s/
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Carmen Booker
5/8/2006 11:33:11 AM
PHARMACOLOGIST

Paul Brown
5/10/2006 05:28:43 PM
PHARMACOLOGIST

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# Initial Quality Assessment
# Branch III
# Pre-Marketing Assessment Division II

| | |
|---|---|
| **OND Division:** | Division of Dermatology and Dental Products |
| **NDA:** | 22-013 |
| **Applicant:** | Connetics Corporation |
| **Stamp Date:** | March 16, 2006 |
| **PDUFA Date** | Jan. 16, 2007 |
| **Trademark:** | EF Clobetasol Foam 0.05% |
| **Established Name:** | Clobetasol Propionate |
| **Dosage Form:** | Foam |
| **Route of Administration:** | Topical |
| **Indication:** | Inflammatory and pruritic manifestation of corticosteroid-responsive dermatoses |
| **PAL:** | Shulin Ding |

| | YES | NO |
|---|---|---|
| **ONDQA Fileability:** | ☒ | ☐ |
| **Comments for 74-Day Letter** | ☐ | ☒ |

**Summary and Critical Issues:**

A. Summary

The drug substance, clobetasol propionate USP, is the subject of DMF [redacted]. DMF [redacted] has been reviewed multiple times, most recently in January 2005, and found adequate.

The drug product, EF Clobetasol Foam 0.05%, is packaged in an aluminum can at a fill size of 100 g. The formulation contains the following excipients: Propylene Glycol, USP; Phenoxyethanol, NF; White Petrolatum, USP; Light Mineral Oil, NF; Isopropyl Myristate, NF; Sorbitan Monolaurate, NF; Cetyl Alcohol, NF; Cyclomethicone, NF; Purified Water, USP; Anhydrous Citric Acid, USP; Potassium Citrate (Monohydrate), USP; and Polyoxyl 20 Cetostearyl Ether, NF. Non-compendial excipients are the components of the propellant which is [redacted] propane. [redacted] It is noted that the vehicle of the proposed drug product is almost identical to that of [redacted] under review).

The formulation is packaged in an aluminum aerosol containers lined with [redacted] which is fitted with an [redacted] valve, an actuator, and a non-product contacting cap. The [redacted], the subject of DMF [redacted] has been reviewed previously and found adequate. The valve and the actuator are not referenced to a DMF but the entire [redacted] has been used in [redacted] under review) and in approved foam products such as [redacted]

The to-be-marketed formulation is the same formulation used in all clinical trials and registration stability batches. Stability data provided in the initial submission to support an expiry period of [redacted] months at a controlled room temperature of 68-77°F (20-25°C) include long term (25°C/60%

2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

[redacted]stability in the can[redacted], and the comparability protocol for an alternate site.

Shulin Ding
Pharmaceutical Assessment Lead

Moo Jhong Rhee
Chief, Branch III

# Filing Checklists

## A. Administrative Checklists

| YES | NO | | Comments |
|---|---|---|---|
| x | | On its face, is the section organized adequately? | |
| x | | Is the section indexed and paginated adequately? | |
| x | | On its face, is the section legible? | |
| x | | Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs? | |
| x | | Has an environmental assessment report or categorical exclusion been provided? | |

## B. Technical Checklists

### 1. Drug Substance Referenced to DMF [redacted]

| | | | |
|---|---|---|---|
| | | Does the section contain synthetic scheme with in-process parameters? | Not applicable. |
| | | Does the section contain structural elucidation data? | Not applicable. |
| | | Does the section contain specifications? | Not applicable. |
| | | Does the section contain information on impurities? | Not applicable. |
| | | Does the section contain validation data for analytical methods? | Not applicable. |
| | | Does the section contain container and closure information? | Not applicable. |
| | | Does the section contain stability data? | Not applicable. |

### 2. Drug Product

| | | | |
|---|---|---|---|
| x | | Does the section contain manufacturing process with in-process controls? | |
| x | | Does the section contain quality controls of excipients? | |
| x | | Does the section contain information on composition? | |
| x | | Does the section contain specifications? | |
| x | | Does the section contain information on degradation products? | |
| x | | Does the section contain validation data for analytical methods? | |
| x | | Does the section contain information on container and closure systems? | |
| x | | Does the section contain stability data with a proposed expiration date? | |
| x | | Does the section contain information on labels of container and cartons? | |
| x | | Does the section contain tradename and established name? | |

## C. Review Issues

| | | | |
|---|---|---|---|
| | x | Has all information requested during the IND phases, and at the pre-NDA meetings been included? | Issues addressed. Unsure adequacy. |
| | x | Is a team review recommended? | |
| x | | Are DMFs adequately referenced? | |

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

/s/
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Shulin Ding
5/5/2006 04:40:14 PM
CHEMIST

Moo-Jhong Rhee
5/5/2006 04:56:49 PM
CHEMIST
Chief, Branch III

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IND 67,81[illegible] 12/14/05 meeting

**Sponsor's CMC Question 3:**

[redacted]

**Agency's Response:**

[redacted]

**Additional Comments:**

1. The following data should be generated for DP characterization:

[redacted]

IND 67,818 12/14/05 meeting

**Discussion during the meeting:**

**Pharmacology/Toxicology:**

**Sponsor's Nonclinical Question 1:**

Connetics plans to submit a 505(b)(2) marketing application as summarized in the Agency's 02 March 2005 Special Protocol Assessment Meeting minutes (Appendix 1). Connetics intends to rely on the Agency's finding of nonclinical safety for the RLD, Temovate Ointment, for single-dose toxicity, repeat-dose toxicity, genotoxicity, and reproductive toxicity data on clobetasol propionate. In addition, Connetics has conducted eight new nonclinical studies to support the NDA for EF Clobetasol Foam: acute dermal irritation and acute eye irritation with EF Clobetasol Foam; ICH battery of genotoxicity studies (Ames assay, mouse lymphoma assay, mouse micronucleus assay) for clobetasol propionate; and ICH battery of genotoxicity studies for sorbitan monolaurate, an excipient in the foam formulation. Carcinogenicity and photocarcinogenicity studies with EF Clobetasol Foam will be conducted as post-marketing commitments, as agreed with the Agency during the 02 March 2005 Special Protocol Assessment meeting. A timeline for the conduct of both post-marketing commitments will be included in the NDA.

Does the Agency agree that the proposed nonclinical development program is adequate to support the 505(b)(2) marketing application?

IND 67,818 12/14/05 meeting

**Agency's Response:**

The proposed nonclinical development program appears to be adequate to support submission of an NDA under section 505(b)(2), provided that an adequate clinical bridge to the listed drug has been established.

**Sponsor's Nonclinical Question 2:**

Connetics conducted the ICH battery of genotoxicity studies (Ames assay, mouse lymphoma assay, mouse micronucleus assay) for clobetasol propionate. Clobetasol propionate was not mutagenic in the Ames assay or the mouse lymphoma assay. In the mouse micronucleus assay, there was an increase in the number of micro nucleated polychromatic erythrocytes (MN-PCEs) in the highest dose group (2000 mg/kg) at the 24-hour timepoint, but not at the 48-hour timepoint, as compared to the negative control group. There were no statistically significant increases in the number of MN-PCEs in the 800 mg/kg or 1400 mg/kg groups. Clobetasol propionate has been tested in multiple genotoxicity assays, and was repeatedly shown to be non-genotoxic, including in another mouse micronucleus assay

Based on the weight-of-evidence approach in the draft *Guidance For Industry: Recommended Approaches to Integration of Genetic Toxicology Study Results (November 2004)*, we conclude that clobetasol propionate is not genotoxic. The test results from Connetics' ICH battery of genotoxicity studies will be reflected in the product package insert. Connetics believes that no additional studies are necessary to further characterize the genotoxicity profile of clobetasol propionate. Does the Agency agree?

**Agency's Response:**

The Agency agrees that no additional genotoxicity studies are necessary to support submission of the NDA for ethanol-free clobetasol propionate foam. As stated by the sponsor, the results of the genotoxicity studies will be reflected in the product package insert.

**Clinical Pharmacology and Biopharmaceutics:**

No Biopharm questions were identified in the briefing document.

**Clinical**

**Sponsor's Clinical Question 1:**

Does the Division continue to agree that the clinical development program is adequate to support filing of a 505(b)(2) marketing application for the proposed indication?

**Agency's Response:**

Based on the information contained in the briefing document, the development program appears adequate to support filing of the NDA.

IND 67,818 12/14/05 meeting

**Sponsor's Clinical Question 2:**

Connetics believes that this provides an adequate safety database to inform necessary pediatric age groups and support a label for patients 12 years of age and older. Does the Agency agree?

**Agency's Response:**

The sponsor contends that patients 12 to 17 years of age with moderate to severe AD represent approximately 3% of patients in the overall AD population. The sponsor is requested to provide the proportion of patients aged 12 to 17 in the AD population aged 12 and greater (i.e., excluding patients 0 to 11 years), which may be more relevant for discussion of the sponsor's question.

At the Agency's request, the sponsor briefly reviewed the results of the HPA axis suppression study by cohort. The sponsor provided the requested information, and will include this information as well as justification for the sufficiency of the pediatric safety database in the NDA submission.

**Sponsor's Clinical Question 3:**

If these studies demonstrate that EF Clobetasol Foam was not superior to the RLD for efficacy (in a three-arm psoriasis trial), did not have a worse overall safety profile than the RLD, and did not demonstrate greater systemic bioavailability as demonstrated in an analytically robust PK study, does the Agency concur that a sufficient clinical bridge has been established and that the safety data requirements as described in ICHE1A have been met?

**Agency's Response:**

The adequacy of the clinical bridge and the sufficiency of the safety data will be based on review of the data submitted. The sponsor was asked to address the comparative safety of their product in atopic dermatitis.

**Sponsor's Question 4:**

Connetics believes that if a clinical bridge is established to the RLD, and the observed safety profile for EF Clobetasol Foam is what would be expected for a clobetasol propionate product, then a long term safety study is not needed for EF Clobetasol Foam. Does the Division agree? If not, does the Division agree that this requirement can be satisfied as a post-marketing commitment?

**Agency's Response:**

The adequacy of the clinical bridge will be a review issue. The sponsor needs to provide sufficient evidence of the safety of their product, as addressed in the ICH E1A Guideline, in their NDA submission, whether through a clinical bridge, clinical studies, or other means. It *may* be possible to address unanticipated safety data needs as a post-marketing commitment.

The sponsor was asked to clarify the role of propylene glycol in their formulation; the sponsor stated that the function of propylene glycol [redacted], but it can be considered a [redacted] at the concentration at which it is present. The Agency requested that the sponsor's NDA submission identify the intended function of each excipient. The sponsor was informed that if they intend the

propylene glycol to function as a [redacted] the NDA submission will need to demonstrate the contribution of each active component to the efficacy of their product. Alternatively, if the sponsor does not intend the propylene glycol to function as a [redacted], this should be stated in the NDA submission; the sponsor was informed that they would not be able to make efficacy or safety claims for such an excipient.

**Biostatistics:**

**Sponsor's Biostatistics Question 1:**

Are the types of analyses planned for the primary and principle secondary efficacy endpoints in pivotal Phase 3 studies CPE.C.301 and CPE.C.302 acceptable?

**Agency's Response:**

The submitted details of the statistical analysis plan appear to be consistent with the analysis plans submitted in drafts of the Phase 3 protocols. The Division was in agreement with such analysis plans, so these should be acceptable for the NDA submission.

**Additional Comments:**

1. The NDA submission should include the following items:
   a. Study protocols, protocol amendments, statistical analysis plans and a copy of the Case Report Form.
   b. The randomization lists and the actual treatment allocations (with date of randomization) from the trials.
   c. Subgroup analyses by race, gender, age and baseline severity.

2. The following are some comments about the electronic data sets to be submitted to the NDA.
   a. The Agency requires submission of electronic data sets for the Phase 3 trials in SAS transport format. For additional details about the format of electronic data sets, refer to the guidance documents "Regulatory Submissions in Electronic Format-General Considerations" and "Regulatory Submissions in Electronic Format: New Drug Application" (http://www.fda.gov/cder/guidances/index.htm).
   b. The database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses (such as Investigator Global Assessment Success and indicators for Full Analysis, amended Full Analysis and Per Protocol status, etc.).
   c. The data sets should include variables where missing data has been imputed for the primary and secondary endpoints according to the protocol.
   d. Each data set should include the treatment assignments.
   e. The submission should include adequate documentation for the data sets including the definitions, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation.

IND 67,818 12/14/05 meeting

**Regulatory**

**Sponsor's Regulatory Question 1:**

Connetics plans to electronically submit the planned NDA in the CTD format in accordance with *Guidance for Industry – Providing Submission in Electronic Format – NDAs (January 1999).* The NDA will consist of files and comprehensive Tables of Content in the Adobe® PDF format. A draft Table of Contents and screen shot of the proposed CTD file structure is provided in Appendix 3 and 4 respectively. Does the Division concur that the submission format described above is acceptable for filing?

**Agency's Response:**

The draft Table of Contents and folder structure appears acceptable for filing with the exception of the SPL folder. SPL is properly placed within the labeling folder and not as a stand-alone folder. It should be under 1.14.1 Draft Labeling.

**Sponsor's Regulatory Question 2:**

Connetics plans to submit the draft labeling for EF Clobetasol Foam in the SPL electronic format described in *Guidance for Industry – Providing Submission in Electronic Format – Content of Labeling (April 2005),* Section II, Part B, "New Technology for Processing Labeling and Labeling Changes." Connetics proposes to place the SPL folder in the US folder of Module 1 as shown in Appendix 4. Does the Division find this acceptable?

**Agency's Response:**

See answer to Question 1.

**Sponsor's Regulatory Question 3:**

EF Clobetasol Foam uses the same drug substance and has the same indication as the RLD, Temovate Ointment. The clinical program will establish the safety and efficacy of the new emulsion aerosol foam formulation and establish a bridge to the RLD for safety. The NDA for EF Clobetasol Foam will be submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the same indication as the RLD; therefore Connetics does not plan to submit a User Fee. Does the Agency concur that an Application User Fee is not required?

**Agency's Response:**

Please contact Mike Jones to discuss User Fee issues.

**Administrative Comments**

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

2. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

3. All manufacturing facilities named in your application should be ready for inspection when the application is submitted. We recommend that this information be provided in the application in the form of a table or spread sheet so that these sites can be properly identified early in the review process.

Minutes Preparer: _____
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDP, HFD-540

Chair Concurrence: _____
Stanka Kukich, M.D./Acting Division Director, DDDP, HFD-540

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IND 67,818 3/2/04 meeting

MEMORANDUM OF MEETING MINUTES

| | | |
|---|---|---|
| **Meeting Date:** | March 2, 2005 | **Time:** 1:00 P.M. |
| **Location:** | N225 | **Meeting ID:** 14947 |
| **Topic:** | IND 67,818, Ethanol Free Clobetasol Propionate Foam, 0.05% for Corticosteroid-Responsive Dermatoses | |
| **Subject:** | Special Protocol Assessment meeting | |
| **Sponsor:** | Connetics Corporation | |
| **Meeting Chair:** | Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540 | |
| **Meeting Recorder:** | Melinda Harris, M.S./Regulatory Project Manager, DDDDP, HFD-540 | |

FDA Attendees:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Stanka Kukich, M.D./Deputy Division Director, DDDDP, HFD-540
Jill Lindstrom, M.D./Team Leader, Clinical, DDDDP, HFD-540
Paul Brown, Ph.D./Acting Supervisor, Pharmacology, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Mat Soukup, Ph.D./Biostatistician, DBIII, HFD-725
Raman Baweja, Ph.D., R.ph/Team Leader, Pharmacokinetics, DPEIII, HFD-880
Chandra Chaurasia, Ph.D./Pharmacokinetics Reviewer, DPEIII, HFD-880
Donald Hare, Ph.D./Special Assistant to the Director, OGD, HFD-604
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDDP, HFD-540

Sponsor Attendees:

**Connetics Corporation**

Gretchen Arnold/Coordinator, Contract Toxicology
Diana Chen, M.D./Vice President, Medical Affairs
Wendy Chern/Vice President, Research and Preclinical Development
Mark Davis/Senior Director, Clinical Operations
Kathy Dumas/Regulatory Consultant
Sharon Hall/Regulatory Consultant
Teri Koller/Senior Director, Project Management
Lincoln Krochmal, M.D./Executive Vice President, Research and Product Development
Katy Morton/Director, Regulatory Affairs/CMC
Zane Rogers/Senior Associate, Regulatory Affairs
Greg Vontz/President



 

IND 67,818 3/2/04 meeting

Melody Wyrns/Director, Clinical Operations
Alex Yaroshinsky/Vice President, Clinical Operations and Biostatistics
Beth Zib/Team Leader

Purpose:

To provide general guidance on the content and format of the Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted February 15, 2005) requests clarification from the Agency on the Special Protocol Assessment responses.

Chemistry, Manufacturing and Controls:

No CMC questions were identified in the briefing document.

Pharmacology/Toxicology:

No Pharm/Tox questions were identified in the briefing document. The Agency has the following comments:

An NDA should be fully supported with an adequate finding of nonclinical safety. This finding of safety can be derived from studies conducted by or for the sponsor or for which the sponsor has right to refer. An NDA submitted under section 505(b)(2) of the FD&C Act must still have an adequate finding of safety as per section 505(b)(1) but it may refer to information for which the sponsor does not have the right to the underlying data. An adequate clinical bridge to an approved product may permit the sponsor to refer to the Agency's finding of safety for that product. Any new safety concerns unique to the new product should be addressed by adequate studies. It does not appear that the proposed nonclinical plan would be adequate to support an NDA without referring to the Agency's finding of safety for another approved product. Without a clinical bridge to an approved product permitting reference to the Agency's finding of safety, an NDA should have complete nonclinical information addressing all aspects of nonclinical safety. This includes genotoxicity, reproductive toxicity, repeat dose toxicity, carcinogenicity, and photocarcinogenicity. If any of this information is from literature, then the application would fall under section 505(b)(2), since it is considered necessary for approval.

An initial NDA submission for clobetasol propionate foam should have nonclinical information to address genotoxicity, reproductive toxicity and repeat dose toxicity. It may be possible to address the photocarcinogenicity and carcinogenicity as phase 4 studies. This is consistent with other recent NDAs for similar products.

The sponsor's previous NDA for OLUX (NDA 21-142) established a clinical bridge to an approved product and was able to refer to the Agency's finding of safety for that product. NDA 21-142 did not independently contain sufficient nonclinical information to establish a finding of safety. If the NDA for the ethanol free foam clobetasol propionate formulation does not have a clinical bridge to an approved product, the Agency cannot refer to a previous finding of safety. The information in approved NDAs is not considered general scientific knowledge.

IND 67,818 3/2/04 meeting

*The sponsor indicated that they would address carcinogenicity and photocarcinogenicity in phase 4 studies.*

**Clinical Pharmacology and Biopharmaceutics:**

**Sponsor's Question 3:**

Connetics believes the requirement for demonstrating bioavailability of clobetasol propionate has been met with the completed vasoconstrictor assay study (Study CPE.C.101) the ongoing HPA axis suppression study (Study CPE.C.201), and the two Phase 3 studies (CPE.C.301 and CPE.C.302) planned for this program. Does the Agency concur?

**Agency's Response:**

The Agency does not concur. While it is true that the proposed drug product is not intended to be absorbed into the bloodstream for systemic distribution, an assessment of any systemic absorption of the drug is critical in terms of establishing its safety.

The vasoconstrictor study CPE.C.101 is designed to establish the relative potency of test product in comparison to low and high potent topical corticosteroids. It does not demonstrate systemic bioavailability of the test product following topical administration.
The study CPE.C.201 is designed to evaluate pharmacologic effect (HPA suppression). While any HPA suppression is a reflection of systemic absorption of the topical corticosteroid, it is not a direct measure of bioavailability of the product administered topically. It is further noted that sections 21 CFR 320.24(b)(3) and 320.24 (b)(4) may be considered acceptable for determining the bioavailability only when appropriate methods are not available for measurement of the concentration of the moiety in biological fluids.

*The Sponsor agreed to do a relative bioavailability study comparing the test product with the reference product, and plans to submit a protocol for review. The Agency recommended that the study should have at least 15 evaluable patients in the relative BA study. In addition, the study design should be under maximal use conditions in the patient population.*

**Clinical:**

**Sponsor's Question 1:**

Connetics believes that adequate information on the efficacy and safety of EF Clobetasol Foam will be presented in the marketing application such that a bridge to a listed drug is not necessary. Please explain the regulatory rationale for the recommendation to include a clinical bridge to a listed product.

**Agency's Response:**

If the sponsor does not intend to rely on the Agency's finding of safety and effectiveness for an approved clobetasol propionate product, and if sufficient non-clinical data is available from the literature and/or data owned by the sponsor or to which the sponsor has right of reference, then the proposed approach (two adequate and well-controlled studies against vehicle, without a bridge to a

IND 67,818 3/2/04 meeting

RLD) may be acceptable. However, if a clinical bridge is not established, the sponsor may not rely on the Agency's prior findings of safety to fulfill any of the non-clinical data needs. Please see additional comments from Pharmacology/Toxicology.

Should the sponsor not establish a bridge to a RLD, the sponsor will need to establish the clinical safety and efficacy of their product through clinical studies. Because both atopic dermatitis and psoriasis are chronic, non-life-threatening disorders, the safety data needs of ICH E1A, with regard to both number of subjects exposed and duration of chronic intermittent use.

*The sponsor stated that they intend to establish a clinical bridge to Temovate E cream and rely on the Agency's finding of safety for the RLD in order to meet the safety data needs described in ICH E1A as well as non-clinical data needs. The Agency responded that establishment of such a bridge would rest on demonstration that the sponsor's product was not superior to the RLD for efficacy (in a three-arm psoriasis trial), did not have a worse safety profile than the RLD, and did not demonstrate greater systemic bioavailability as demonstrated in a comparative HPA axis suppression study or very robust PK study.*

*The sponsor informed the agency that the adolescent (12 to 17 years) cohort in the HPA axis suppression study has been completed and none of the subjects suppressed. Additionally, 4 subjects in the 6-12 year old cohort have demonstrated suppression, but this cohort has not concluded. The sponsor agreed to submit the data from these three cohorts (adult, 12 to 17 years, 6 to 12 years) to the Agency for review.*

**Sponsor's Question 2:**

Does the Agency agree with Connetics's responses to the Special Protocol Assessment for Studies CPE.C.301 and CPE.C.302 and as incorporated into the revised, amended draft protocols?

**Agency's Response:**

Please submit the revised protocols to the IND for full review and comment. The following comments are provided for general guidance.
Comments on CPE.C.302

1. The approach is generally acceptable for a 505(b)(1) application. For a 505(b)(2) in which the sponsor relies on the Agency's finding of safety and efficacy for a reference listed product, the sponsor needs to establish a clinical bridge to that product. This may be accomplished by including a comparator arm for a reference listed product. The ages for inclusion would then be 12 and older. Please see the Addendum to the Clinical section of the meeting minutes from the End-of-Phase 2 meeting, November 29, 2004, as well as comments above.

2. The category descriptors in the striae assessment scale do not correspond to recognized gradations of mild, moderate and severe. For example, two wide, long, dark red striae may be more clinically significant than four narrow, short, white striae, but this would not be reflected in the grade assigned based on the proposed scale. If the sponsor is unable to craft clinically meaningful category descriptors, the sponsor may wish to assess for the presence or absence of striae.

IND 67,818 3/3/04 meeting

3. Pruritus is not a universal symptom in psoriasis, and complaint of pruritus was not an inclusion criterion. Therefore the secondary endpoint, proportion of subjects with a pruritus score of 0 at week 2, may not have regulatory utility.

4. The Additional Evaluations will not have regulatory utility.

5. Please propose study drug use limits in grams/week that will be appropriate for younger (and smaller) subjects who may be enrolled after completion of the younger cohorts in the HPA-axis suppression study.

6. Photographs used for education or marketing purposes need to be representative of typical response. The Division would like to have input in the selection of the photographs.

Comments on CPE.C.301

1. For a 505(b)(2) application which relies on the Agency's findings for a reference listed product, there must be a bridge to that product. Should the sponsor pursue the indication of atopic dermatitis alone, the bridge may be achieved by a three-arm (sponsor's product, sponsor's vehicle, listed product) efficacy study in atopic dermatitis subjects 12 years of age and older, and safety needs may be achieved by augmentation with a large, open-label study in younger subjects. Should the sponsor choose to pursue the indication of corticosteroid-responsive dermatoses, a three-arm psoriasis trial (sponsor's product, sponsor's vehicle, listed product) in subjects 12 years of age and older and a two-arm atopic dermatitis trial (sponsor's product vs. vehicle) weighted toward the younger ages could together provide the requisite bridge and efficacy and safety data. Please see the Addendum to the Clinical section in the minutes from the End-of-Phase 2 meeting held on November 29, 2004, and comments above.

2. Since the indication is primarily pediatric, this application would not be fileable without a safety database adequate to inform all pediatric age groups.

3. It is not clear that the sponsor's plan to initiate their study in subjects 12 years of age and older and enroll younger subjects after completion of successive cohorts in the HPA axis suppression study will provide sufficient safety data in the younger age groups. An open-label safety study in younger pediatric subjects may be necessary to enrich the safety database for the lower age groups. Approval will rest on adequate demonstration of safety.

4. Please propose study drug use limits in grams/week that will be appropriate for younger (and smaller) subjects who may be enrolled after completion of the younger cohorts in the HPA-axis suppression study.

5. The Subject's Global Assessment addresses only erythema, so it would be more accurately entitled Subject's Assessment of Erythema. This parameter will not have regulatory utility.

6. The category descriptors for the striae assessment scale do not correspond to recognized gradations of mild, moderate and severe. For example, two wide, long, dark red striae may be more clinically significant than four narrow, short, white striae, but this would not be reflected in the grade assigned based on the proposed scale. If the sponsor is unable to craft clinically

IND 67,818 3/2/04 meeting

meaningful category descriptors, the sponsor may wish to assess for the presence or absence of striae.

7. The Additional Evaluations will not have regulatory utility.

8. Photographs used for education or marketing purposes need to be representative of typical response in the trial. The Division would like to have input in the selection of the photographs.

*The sponsor stated that they will assess for the presence or absence of striae rather than using a graded severity scale for this parameter. The sponsor acknowledged that their proposed secondary endpoint, the proportion of subjects with a pruritus score of 0 at week 2, would not have regulatory utility. The sponsor proposed a limit of 50 gm/week of study drug for subjects 12 years of age and older*

The sponsor should submit their Phase 3 protocols to the IND. These final protocols should be marked with HIGHLIGHT and STRIKEOUT to identify ANY CHANGES from the versions of the protocols submitted for review for today's meeting.

**Sponsor's Question 3:**

Connetics believes the requirement for demonstrating bioavailability of clobetasol propionate has been met with the completed vasoconstrictor assay study (Study CPE.C.101) the ongoing HPA axis suppression study (Study CPE.C.201), and the two Phase 3 studies CPE.C.301 and CPE.C.302) planned for this program. Does the Agency concur?

**Agency's Response:**

See comments by Dr. Chandra Chaurasia, Clinical Pharmacology and Biopharmaceutics reviewer.

**Biostatistics:**

No Biostatistics questions were identified in the briefing document. The Agency has the following comments:

1. The inclusion criteria in Protocol CPE.C.301 do not specify specific baseline scores for the secondary endpoints, pruritus, lichenification, erythema and induration/papulation. Yet, treatment success for these endpoints is defined as reaching a score of 0 or a score of 0 or 1. To interpret study findings, please include baseline scores for the secondary endpoints in the inclusion criteria as with Protocol CPE.C.302.

*The Division stated that success of the secondary endpoints requires a reduction of at least two units.*

2. The sponsor's submitted clarification of their proposed sequential generalized logistic models for imputing missing data are not sufficient to make judgments about the appropriateness of this approach in ensuring efficacy results are not driven by the imputation. The reviewer does not have access to the publication by Allison (2002) and could not find any further information

IND 67,818 3/2/04 meeting

about using sequential generalized logistic models to impute missing data. While the sponsor may include such an analysis as supportive, other possible sensitivity analysis might include

- imputing average response rate for subjects who remain in the trial receiving the same treatment.
- Imputing the response rate for subjects with similar baseline levels of disease severity (erythema, IGA, etc.) or subsequent levels of disease severity recorded after baseline who receive the same treatment.

3. The indication for Protocol CPE.C.301 was changed from mild to moderate atopic dermatitis to moderate to severe atopic dermatitis. In powering the Phase 3 study the sponsor used response rates to 20% and 7% for treatment and vehicle, respectively. However, no justification for estimates of these treatment effects was given. It should be noted that if treatment effects in the Phase 3 trial turn out less than the assumed response rate then the Phase 3 trial will be under powered.

Administrative Comments

1. 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).

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

3. The Sponsor is encouraged to request a Pre-NDA Meeting at the appropriate time.

Minutes Preparer: _____
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDDP, HFD-540

Chair Concurrence: _____
Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540

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Jonathan Wilkin
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IND 67,818 11/29/04 meeting

## MEMORANDUM OF MEETING MINUTES

| | | |
|---|---|---|
| **Meeting Date:** | November 29, 2004 | Time: 1:00 P.M. |
| **Location:** | S200 | Meeting ID: 14077 |
| **Topic:** | IND 67,818, Ethanol Free Clobetasol Propionate Foam for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses | |
| **Subject:** | End of Phase 2 meeting | |
| **Sponsor:** | Connetics Corporation | |
| **Meeting Chair:** | Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540 | |
| **Meeting Recorder:** | Melinda Harris, M.S./Regulatory Project Manager, DDDDP, HFD-540 | |

**FDA Attendees:**

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Stanka Kukich, M.D./Deputy Division Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDDP, HFD-540
Jill Lindstrom, M.D./Clinical Reviewer, DDDDP, HFD-540
Paul Brown, Ph.D./Acting Supervisor, Pharmacology, DDDDP, HFD-540
Ramesh Sood, Ph.D./Team Leader, Chemistry
Saleh Turujman, Ph.D./ Chemistry Reviewer, DNDCIII, HFD-830
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Steven Thomson, M.S./Biostatistician, DBIII, HFD-725
Chandra Chaurasia, Ph.D./Pharmacokinetics Reviewer, DPEIII, HFD-880
Donald Hare, Ph.D./Special Assistant to the Director, OGD, HFD-604
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDDP, HFD-540

**Sponsor Attendees:**

**Connetics**

Sharon Hall, Senior Director, Regulatory Affairs
Darlene O'Banion, Senior Manager, Regulatory Affairs
Gary Miller, Associate Director, Analytical Development
Lincoln Kiochmal, Executive Vice President, Research and Product Development
Wendy Chern/Vice President, Research and Preclinical Development
Gretchen Arnold/Coordinator, Contract Toxicology
Alex Yaroshinsky, Ph.D., Senior Director, Biostatistics

**Purpose:**

IND 67,818 11/29/04 meeting

To provide general guidance on the content and format of the proposed Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted October 28, 2004) provides background and questions (pp 8-9) for discussion. The sponsor requests that the Agency address the adequacy of the Phase 3 plan.

**Chemistry, Manufacturing and Controls:**

**Sponsor's CMC Question # 1:**

**Agency's Response:**

*Discussion during the meeting:*

**Sponsor's CMC Question # 2:**

Does the agency concur that the proposed commercial release and stability specification is acceptable for submission and sufficient to support a marketing application approval?

**Agency's Response:**

No.

1. The regulatory and stability specification should include an acceptance criterion for the spray rate. The acceptance criterion, as provided in the specification table,"report results", is not acceptable. It is noted that the spray rate is listed as "dispensing rate" in the regulatory specification table (page 38 of 151 in the briefing jacket) and is designated as a "Lot Release only".

*Discussion during the meeting:*

The sponsor consented, and stated that an acceptance criterion for the spray rate will be provided, based on data that will be collected and validated.

2. The acceptance criterion for total impurities, "Report results", as proposed in your specification table is not acceptable. A specific value should be provided.



 

IND 67,818 11/29/04 meeting

*Discussion during the meeting:*

The sponsor consented, and stated that an acceptance criterion for total impurities based on data that will be collected and validated.

3. Please revise the drug product regulatory specification to include the clobetasol propionate related substances identified in your stability data tables (or the COA sheets).

*Discussion during the meeting:*

The sponsor agreed, and stated that an acceptance criterion for clobetasol propionate related substances based on data that will be collected and validated.

4. Please revise the drug product specification to provide acceptance criteria of NMT [redacted] for any unspecified individual degradation product per ICH Q3B (R) (see attachment 1).

*Discussion during the meeting:*

The sponsor consented, and stated that an acceptance criterion for any unspecified individual degradation product per ICH Q3B based on data that will be collected and validated.

Other Issues

[redacted]

**Addendum:**

[redacted]



 

The sponsor responded there is no single ingredient that is critical to the dosage form.

**Addendum:**

In response to the concern expressed by the Clinical Team Leader regarding the exposure of children to this super potent corticosteroid, the sponsor is requested to provide a secondary container with child resistant closure.

**Pharmacology/Toxicology:**

**Sponsor's Nonclinical Question 1:**

Does the Agency agree that the proposed nonclinical development plan is sufficient to support an NDA submission and product approval?

**Agency's Response:**

The proposed nonclinical development plan may be adequate to support submission of an NDA under section 505(b)(2) of the FD&C Act along with reference to the approved NDA 21-142 and supporting literature information. The proposed nonclinical plan does not appear to be adequate to support an NDA submitted under section 505(b)(1) of the Act. Any NDA submitted under 505(b)(1) should have full reports of investigations which have been made to show whether or not such drug is safe for use. This includes complete nonclinical studies. Since NDA 21-142 did not contain complete reports of all nonclinical information, referring to NDA 21-142 will not be sufficient to support a new 505(b)(1) NDA.

**Addendum:**

These comments are based on the establishment of an adequate clinical bridge to a listed product (see clinical addendum).

**Clinical Pharmacology and Biopharmaceutics:**

No Clinical Pharmacology and Biopharmaceutics questions were identified in the briefing document. The Agency has the following comment:

The Sponsor is requested to measure plasma concentrations of clobetasol propionate under maximal use conditions in the target patients using a sensitive, validated analytical method. The results of the assay along with analytical method validation should be submitted with the original NDA package.

**Addendum:**

The Agency encourages submitting a protocol for review prior to initiation of the study.

**Clinical:**



 

IND 67,818 11/29/04 meeting

1. **Comments on Regulatory Status:**

The anticipated regulatory pathway for approval will be via a 505 (b) (2) application.

Although the sponsor may proceed to Phase 3 prior to the completion of the pediatric HPA axis suppression studies, doing so may necessitate performance of an open-label study in pediatric subjects to augment the safety database in the pediatric age range.

2. **Comments on the sponsor's drug/indication:**

The sponsor is pursuing an indication for topical treatment for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. For the indication of corticosteroid-responsive dermatoses (not restricted to scalp) it is recommended that a demonstration of efficacy and safety in both atopic dermatitis and psoriasis be provided.

Atopic dermatitis is largely a pediatric disease. Safety issues and disease prevalence are greatest in the pediatric population. Hence to pursue an indication for corticosteroid-responsive dermatoses (or the indication for atopic dermatitis alone), it will be imperative that the Sponsor study the safety and efficacy of their product in the pediatric atopic dermatitis population, where it is most needed and most likely to be used. It is expected that the sponsor's product, which contains clobetasol propionate, will readily beat vehicle with regard to efficacy. *Garnering approval will therefore rest primarily on solid demonstration of safety*. It may be possible to extrapolate safety information from the pediatric population to adults, but not the reverse. It is not clear that the sponsor's proposed atopic dermatitis trial (CPE.C.301), which will begin with subjects 18 years and older and open to younger subjects after completion of successive cohorts in the HPA axis suppression study, will provide sufficient safety data in pediatric subjects. Should the sponsor choose to initiate their study in adult subjects, an open-label safety study in pediatric subjects may be necessary to enrich the safety database for the pediatric age groups.

*Discussion during the meeting:*

*The sponsor indicated that they plan to pursue the indication of atopic dermatitis, and the remainder of the meeting discussion was predicated upon that assertion. The sponsor indicated that if they later decide to pursue psoriasis, they will accept the Agency's comments regarding psoriasis, which were not discussed further during the meeting.*

To establish safety and efficacy in the treatment of psoriasis, the Sponsor is requested to extend enrollment to pediatric subjects, pending completion of the HPA axis suppression study, analogous to the atopic dermatitis trial. Although psoriasis is not considered primarily a pediatric disease, because the sponsor is pursuing the broader indication of corticosteroid-responsive dermatoses, evaluation of safety in pediatric psoriasis subjects will be useful. Demonstration of safety in psoriasis will not rest as heavily on data from pediatric subjects as will be the case for atopic dermatitis.

3. **Comments on topical safety studies:**



 

IND 67,818 11/29/04 meeting

Dermal safety studies are needed for the final to-be-marketed new vehicle formulation. Generally, the required topical safety studies are cumulative irritancy (not less than 30 evaluable subjects), contact sensitization (not less than 200 evaluable subjects), photoallergenicity (not less than 50 evaluable subjects, and phototoxicity (not less than 30 evaluable subjects). These studies should be conducted with the final to-be-marketed vehicle formulation and are usually conducted in parallel with phase 3 studies. However, if phase 1/2 studies reveal an irritancy signal and the product is to be labeled as an irritant, cumulative irritancy testing may not be needed. Additionally, if no component of the Sponsor's product absorbs in the UVA, UVB, or visible light spectra, then phototoxicity and photoallergenicity studies may be waived (copies of the absorption spectra should be submitted to the IND).

**4. Comments on protocols submitted:**

Protocol number: CPE.C.301

Comments on overall study design:

- Approval will largely rest upon adequate demonstration of safety in the pediatric population.

Comments on Inclusion/Exclusion criteria:

- Please define or specify "intertriginous areas."

Comments on Endpoints:

- The primary endpoint is the proportion of subjects who have the following at week 2 (or end of treatment):
  - ISGA score of clear or almost clear ( 0 or 1, respectively), and
  - Score of 0 or 1 for both erythema and induration/papulation, and
  - Minimum improvement in the ISGA score of 2 grades from baseline to week 2 (or end of treatment).

The primary endpoint is acceptable.

- The secondary endpoint, "mean percent reduction in the sum of the scores of erythema, induration/population, lichenification, scaline and oozing/crusting from baseline to week 2 or end of treatment," is a computed score that is not clinically meaningful; it will not have regulatory utility. Preferred secondary endpoints would be the parameters of erythema, induration/papulation and lichenification dichotomized to success and failure, such as proposed for tertiary endpoints (second, third and fourth bullets under "Additional Evaluations" on p72 of 151 in the sponsor's briefing document).
- The proposed secondary endpoint, "mean percent reduction in the percent of BSA from baseline to week 2 (or end of treatment)" will not have regulatory utility.
- The sponsor is asked to confirm that the primary timepoint is week 2.
- Please clarify the intended use of the clinical photographs. If the sponsor intends to use photographs for marketing purposes, the Agency would like to participate in selection of photos that are representative of overall trial results.

Comments on Safety:

- Please actively assess for skin atrophy, striae, telangiectasia and pigmentation. Please provide static assessment scales for these safety parameters. Please include these

assessments in the Study Flow Sheet, and capture the data from these assessments on case report forms.
- Please follow any female subject who becomes pregnant during the trial to the conclusion of her pregnancy.
- Because the sponsor's product is expected to be used in a chronic intermittent fashion, the safety data needs of ICH E1A apply.

Protocol number: CPE.C.302

Comments on Inclusion/Exclusion criteria:
- Please include pediatric subjects in parallel with the ages included in trial CPE.C.302.
- Please specify what is meant by "intertriginous areas."

Comments on Endpoints
- The proposed primary endpoint is not acceptable. The proposed primary endpoint is the proportion of subjects who have the following at Week 2 (or end of treatment):
  - An ISGA score of clear or almost clear (0 or 1, respectively, and
  - A score of 0 or 1 for erythema and scaling, and
  - A score of 0 for induration
- Please add the following parameter to the primary endpoint: Minimum improvement in the ISGA score of 2 grades from baseline to week 2 (or end of treatment).
- Please add the phrase, "barely perceptible elevation," to the category descriptor for Almost Clear in the ISGA to amplify the phrase, "minimal plaque elevation ≈0.5mm."
- The sponsor is asked to confirm that the primary timepoint is week 2.
- The secondary endpoint, "mean percent reduction in the sum of the scores for target lesion signs of psoriasis (erythema, scaling, lichenification, scaling and induration) from baseline to week 2 (or end of treatment)," is a computed score that is not clinically meaningful; it will not have regulatory utility. Preferred secondary endpoints would be the parameters of erythema, scaling and induration dichotomized to success and failure, such as proposed for tertiary endpoints (first, second, and third bullets under "Additional Evaluations" on p122-123 of 151 in the sponsor's briefing document). "Plaque thickness" or "plaque elevation" may be more apt terms than "induration" for the third cardinal sign of psoriasis.
- The proposed secondary endpoint, "mean percent reduction in the percent of BSA from baseline to week 2 (or end of treatment)" will not have regulatory utility.
- Please clarify the intended use of the clinical photographs. If the sponsor intends to use photographs for marketing purposes, the Agency would like to participate in selection of photos that are representative of overall trial results.
- The Subject's Global Assessment Scale is not static and therefore subject to recall bias. It will not have regulatory utility.

Comments on Safety:
- Please actively assess for skin atrophy, striae, telangiectasia and pigmentation at baseline, Week 2 (or early termination) and post-treatment follow up. Please provide static assessment scales for these safety parameters. Please include these assessments in the Study Flow Sheet, and capture the data from these assessments on the case report forms.
- Please follow any female subject who becomes pregnant during the trial to the conclusion of her pregnancy.



 

- Because the sponsor's product is expected to be used in a chronic intermittent fashion, the safety data needs of ICH E1A apply.

**Addendum:**

The plan by which the sponsor intends to establish a biobridge to a listed clobetasol propionate, 0.05% product is not clear. For a 505 (b)(2) application, a biobridge is needed and could be provided by performing one three-arm clinical trial to demonstrate non-inferiority to the listed product and superiority to vehicle. Should the sponsor pursue the indication of atopic dermatitis alone, the biobridge may be achieved by a three-arm (sponsor's product, sponsor's vehicle, listed product) efficacy study in atopic dermatitis subjects 12 years of age and older, and safety needs may be achieved by a large, open-label study in younger subjects. Should the sponsor choose to pursue the indication of corticosteroid-responsive dermatoses, a three-arm psoriasis trial (sponsor's product, sponsor's vehicle, listed product) in subjects 12 years of age and older and a two-arm atopic dermatitis trial (sponsor's product vs. vehicle) weighted toward the younger ages could together provide the requisite biobridge and efficacy and safety data.

**Biostatistics:**

**Sponsor's Clinical Question # 2:**

Does the Agency agree with the design (subject population, study endpoints, and study evaluations) of the proposed Phase 3 clinical studies to support the proposed indication?

**Agency's Response:**

1. The two protocols, for different indications, postulate identical success rates and sample sizes. The Sponsor is requested to explain the source of the estimates of treatment effect used in the power calculations. To avoid problems with the final Phase 3 studies, the Sponsor is strongly encouraged to conduct Phase 2 dose ranging studies to identify the appropriate dose and duration of treatment for their product. Among other uses, such studies can provide estimates of treatment effects for the power calculations used for the subsequent Phase 3 trials. According to the Sponsor's calculations, identical specifications for the two trials lead to calculation of 80% power in one trial and to 90% power in the other.

*Discussion during the meeting:*

*At the meeting the sponsor indicated the estimates of treatment effect came from the similar drug Olux®.*

2. The Sponsor states that the primary endpoint is measured "from Baseline to Week 2 (or end of treatment)." For efficacy evaluations the primary endpoint should be evaluated at one time point. Efficacy evaluations carried out at different time points might require a multiplicity adjustment to control Type I error. Patients who attain clearance prior to the time specified for the primary endpoint (Week 2) might stop treatment for safety, but



 

should be evaluated at the time specified for the primary endpoint. For the Intent to Treat population, values associated with dropouts (if any) prior to Week 2 may be imputed.

3. As discussed by the Medical Officer, to insure that the final endpoint reflects an actual improvement, the primary endpoint in the psoriasis study should also reflect two unit decrease in the Investigator Static Global Assessment (as is specified in the atopic dermatitis study).

*Discussion during the meeting:*

*At the meeting the sponsor noted that they may not pursue the psoriasis indication at this time.*

4. Details of the randomization including blocksize, if any, should be included in the protocol. Actual treatment allocation should be included with the final submission of the NDA.

**Sponsor's Biostatistics Question:**

Does the Agency concur with the primary and secondary analyses in the Phase 3 protocols, Study CPE.C.301 and CPE.C.302.

**Agency's Response:**

1. The Sponsor defined sums of signs and symptoms scores (erythema, induration/ papulation, lichenification, scaling and oozing/crusting in the atopic dermatitis study and erythema, scaling, and induration in the psoriasis study) are not considered to be of regulatory utility. The Sponsor might use success on the individual signs and symptoms scores as secondary endpoints (see clinical comments). Unless the number of secondary endpoints is relatively small a multiplicity adjustment would be required.

2. The Sponsor also specifies analyses of additional endpoints under the heading of "Additional Evaluations". The Sponsor is reminded that if these are to be of potential use in labeling they should be clinically meaningful and should be included among the secondary endpoints. Some endpoints are supposed to be assessed with a descriptive analysis. If these are also of potential use in labeling they should be formally tested for treatment differences.

3. The Agency encourages the use of sensitivity analyses for assessing the impact of the missing data. The Sponsor is requested to submit details on the technique using sequential generalized logistic models.

*Discussion during the meeting:*

*At the meeting the role of sub-investigators at some study sites was raised. The sponsor clarified that each subject will be evaluated at each visit by the same investigator or sub-investigator.*

**Administrative Comments**

IND 67,818 11/29/04 meeting

1. 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).

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

3. The Sponsor is encouraged to submit its revised protocols for the treatment of corticosteroid-responsive dermatoses as Special Protocols through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.

4. The Sponsor is encouraged to request a Pre-NDA Meeting at the appropriate time.

Minutes Preparer: _____
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDDP, HFD-540

Chair Concurrence: _____
Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540

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

/s/

Stanka Kukich
12/22/04 03:00:48 PM
Sign off for Dr. Jonathan Wilkin, Division Director



 