Grading scale for Global Assessment of Response	
Score	Description of response
1	Completely clear, except for possible hyperpigmentation.
2	Almost clear; very significant clearance (about 90%); however, patchy remnants of dusky erythema and/or sparse fine scaling may be present.
3	Marked improvement; significant improvement (about 75%); however, a small amount of disease remaining, i.e., fine to coarse scales in some areas, definite erythema and/or barely perceptible plaque elevation.
4	Moderate improvement; intermediate between slight and marked; representing about 50% improvement.
5	Slight improvement; some improvement (about 25%); however, significant diease remaining, i.e., a moderate or greater amount of erythema, scaling, and/or plaque elevation.
6	No change. (Moderate to severe erythema, scaling, and plaque elevation).
7	Worse.

Pivotal study #2: Only one pivotal study was performed.

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on the proposed draft labeling?..... YES

Proposed indication from sponsor's draft labeling:

"OLUX Foam is a super-potent corticosteroid indicated for [redacted]

As designed, could the endpoints in pivotal trial #1 support the labeling? ..... YES

7. Are all data sets for pivotal efficacy studies complete for all indications requested? (This is not a stats question) ..... YES

8. Do all pivotal efficacy studies appear to be adequate and well controlled within current Divisional policies (or to the extent agreed to previously with the applicant by the Division?) for approvability of this product based on proposed draft labeling? ..... YES

PreIND Meeting Date: 2/19/98
EP2 Meeting Date: None
Agency response to Phase 3 protocols: NA
PreNDA Meeting Date: 4/26/99

Do the endpoints as described by the sponsor in pivotal study #1 conform to previous Agency committments? ..... YES

Do the endpoints as described by the sponsor in pivotal study #2 conform to previous Agency committments? ..... NA

Is the pivotal trial multi-centered? ..... YES
Are there adequate numbers of patients enrolled? ....Refer to Statistics

9. Has the applicant submitted the line listings in a format to allow reasonable review of the patient data? ..... YES

However, I was unable to locate an index of the line listings.

Has the applicant submitted line listings in the format agreed to previously by the Division? ... NA

10. Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? ..... NA

11. Has the applicant submitted all additional required case report forms (beyond deaths and drop-outs) previously requested by the Division? ..... NA

12. Has the applicant submitted the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? ..... YES

13. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? ..... NA

14. Has the applicant submitted draft labeling consistent with 21CFR 201.56 and 21CFR 201.57, current Divisional policies, and the design of the development package? ..... YES

15. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? ..... YES

16. Has the applicant complied with the requirements of the Pediatric Rule? .....

    a. Is this an indication that would be applicable to the pediatric population? ..... NO
    b. What pediatric ages are included in the protocol?
    c. Does the sponsor request pediatric labeling? .... NO

    The sponsor requests a full waiver of the Pediatric Study requirements because Clobetasol Foam a) does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients, and b) is not likely to be used in a substantial number of pediatric patients.

17. Financial disclosure of investigator - Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for investigators? ..... NO

    The sponsor states that the NDA is exempt from filing Financial Disclosure for Clinical Investigators, as the studies were completed prior to February 2, 1999.

18. From a clinical perspective, is this NDA filable? .. YES

Reviewer's comment: Have they shown that the drug has no UV absorbance, to permit a waiver of phototoxicity and photosensitization studies?

Reviewing Medical Officer

Dermatology Team Leader

connetics®
CORPORATION

September 15, 1999

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA #21-142 OLUX™
(clobetasol propionate) Foam, 0.05%

Response to Agency's Request for Information
- **Chemistry**
- **Biopharmaceutics**

Dear Dr. Wilkin:

The following is Connetics' response to the Agency's request for Chemistry and Biopharmaceutics information dated September 2, 1999, and the subsequent clarification to the Biopharmaceutics request dated September 3, 1999. For ease of review, the Agency's comments are in bold and our responses follow. As discussed with the Agency, Connetics' responses to the information requests regarding financial disclosure and data reformatting are not required prior to the September 27, 1999, NDA filing deadline; and therefore, will follow within the next few weeks.

Chemistry:

1. **Please confirm that the following facilities are ready for inspection or that they will be ready for inspection within a short period of time (please state when they will be ready):**

   a. **the drug substance manufacturing site,**
   b. **the drug product manufacturing site,**
   c. **the two release testing sites for drug product,**
   d. **the microbiology testing facility, and**
   e. **the site where each lot of the drug is released:**
      Connetics Corporation
      Quality Assurance Department
      3400 West Bayshore Road
      Palo Alto, CA 94303

3400 West Bayshore Road • Palo Alto, CA 94303 • USA • Telephone: (650) 843-2800 • Facsimile: (650) 843-2899

The names and addresses of the facilities referred to in the Agency's comment remain as given in Connetics' original NDA submission (7/28/99; pages 4-0004, 4-0017), and all are currently ready for inspection. The only activity occurring at Connetics Corporation in Palo Alto, CA, is review of batch records for release of drug product; no manufacturing or testing is performed at this site.

2. **On Volume 1.2, Page 04 0017, the sponsor refers to a manufacturing DMF [redacted]). This is a [redacted]. Please provide a reference to the correct DMF.**

The DMF number for CCL Pharmaceuticals (CCL) given on page 4-0017 of NDA #21-142 is incorrect, and we apologize for any confusion this may have caused. The correct number is [redacted] A letter authorizing FDA to reference CCL's [redacted], on behalf of Connetics Corporation is provided in Attachment 1.

Biopharmaceutics:
Request received on 9/2/99:
Please provide the assay methodology and validation for the HPA axis suppression study CPCD.C.003.

Clarification received on 9/3/99:
The Sponsor did not submit any information on the analysis of the serum cortisol levels during the HPA axis study, specifically was it a kit, was it done via an automated assay, what controls were used, what is the accuracy and reproducibility of the assay. Assuming it was an antibody based kit, this information should be available from the supplier regarding their historical accuracy controls. If it was done through an automated assay from a clinical laboratory, then they had to have some sort of control procedure in place to monitor performance.

The analysis of serum cortisol levels in the HPA axis suppression study (CPCD.C.003) was performed by [redacted] summary of the method employed is given in Attachment 2. The assay utilizes a [redacted] and a copy of the current package insert for this kit is provided in Attachment 3.

If you have any questions regarding this submission, please contact Dawn Parsell at (650) 843-2809 or me at (650) 843-2889.

Sincerely,

Claire J. Lockey
Vice President, Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 3, 1999. Number of Pages (including cover sheet) 1
TO: Ms. Dawn Parcell, Regulatory Affairs
COMPANY: Connetics Corporation
NUMBER: 650-843-2899
MESSAGE:

RE: NDA 21,142 Clobetasol Propionate Foam, 0.05%

Please find clarification for the Biopharm information request:

"The Sponsor did not submit any information on the analysis of the serum cortisol levels during the HPA axis study, specifically was it a kit, was it done via an automated assay, what controls were used, what is the accuracy and reproducibility of the assay. Assuming it was an antibody based kit, this information should be available from the supplier regarding their historical accuracy controls. If it was done through an automated assay from a clinical laboratory, then they had to have some sort of control procedure in place to monitor performance."

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

c: NDA 21,142
DIV FILES
HFD-540/BAKHAI
HFD-930/Bashaw
HFD-880/Noory

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 2, 1999.
TO: Ms. Dawn Parcell, Regulatory Affairs
COMPANY: Connetics Corporation
NUMBER: 650-843-2899
MESSAGE:

Number of Pages (including cover sheet) 5

RE: NDA 21-142 Clobetasol Propionate Foam, 0.05%

Please find request for information for this NDA. As discussed, the chemistry and biopharmaceutics information needs to be submitted before September 27, 1999, which is the filing date for this application.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

NDA 21,142
DIV FILES
HFD-540/BRATT
HFD-540/TURNJMAN
HFD-540/NOONY
HFD-[illegible]/FARR

NDA 21, 142 Olux (clobetasol propionate Foam), 0.05%

REQUEST FOR INFORMATION

Chemistry:

1. Please confirm that the following facilities are ready for inspection or that they will be ready for inspection within a short period of time (please state when they will be ready):

a. the drug substance manufacturing site,
b. the drug product manufacturing site,
c. the two release testing sites for the drug product,
d. the microbiology testing facility,
and
d. the site where each lot of the drug is released:

Connetics Corporation
Quality Assurance Department
3400 West Bayshore Road
Palo Alto, CA 94303

2. On Volume 1.2, Page 04 0017, the sponsor refers to a manufacturing [redacted]
Tnis is a [redacted]. Please provide a reference to the correct DMF.

Biopharmaceutics:

Please provide the assay methodology and validation for the HPA axis suppression study CPCD.C.003.

Administrative:

Financial Disclosure:

Please report proprietary interests and compensation affected by the outcome of the clinical studies. The Sponsor is referred to page 72173 of the December 31, 1998, amendment to the rule, for requirements for investigators participating in clinical studies, whether they are ongoing or completed, if the studies are to be used to support applications that are submitted on or after February 2, 1999.

If you have any questions regarding financial disclosure issues, please contact Linda Carter at 301-594-6758.

FDA Division of Biometrics

NDA# 21-142 Olux (Clobetasol Propionate Foam, 0.05%)
REQUEST FOR DATA
DATE: 8/31/1999

The followings are some suggestions and general recommendations to expedite the data evaluation procedure. These are not official policy statements and should not be construed as such. It is to be noted that FDA does not encourage submissions in one statistical package over another, this note is not meant to endorse SAS.

We would like to thank you in advance for cooperating in this matter, also to remind you that adhering to these simple instructions will only accelerate the review process which in turn will benefit you as the sponsor.

REQUEST FOR TRANSFER OF DATA:
Please provide the data for the Phase III pivotal study only.

1. Data Submission by Study Number:
   Efficacy and safety data sets should be submitted by study. Study number is to be carried as a common variable to facilitate pooling of the data across studies.

   A listing from PROC CONTENTS from each data library should be provided which lists all the data sets, clearly labeled for each study and variable type. ***For each study only Two data sets should be provided.***
   For example:
   Study # 1, Demographic Data & Efficacy Data
   Study # 1, Safety Data

   Study # 2, Demographic Data & Efficacy Data
   Study # 2, Safety Data

2. Uniformity of Data and Data Layout:
   All data should be named, coded and described in the same manner for all studies throughout the NDA.

   All files should include patient number, investigator number and treatment group as common variables. A useful data layout is to have one record per patient, with all visit information available in a single record.

   The patient numbers in all the data sets should be unique, so it would be possible to merge the data sets if necessary.

3. Description of Data:
   - A data dictionary which lists and describes the key safety and efficacy variables.
Example: TRT =treatment, INVID =investigator id#.

- A description of the values of the variables. Example: TRT (A=Investigational Drug, B=Placebo), SEX (1=male, 2=female).

4. Data Formats:
   All format libraries and variable labels should be provided, along with step-by-step outline of attaching the format catalogs to SAS data sets.

   If SAS transport files or compressed files are submitted, a step-by-step instruction set should be attached for conversion to .SSD or .SD2. As of now, we are using PC-SAS version 6.12 for Windows as our primary platform.

5. SAS Programs:
   The programs used to generate the results, and a description of their intended use, for each of the studies separately (no need for programs that create tables or pages.)

For each study please provide:

Demographic Data:
Example:

Patient Id
Investigator Id
Treatment Group
Age
Race
Gender
Baseline Clinical Evaluability
Any Concomitant Drug Use & Drug Type
Past History of Sickness
Smoker
Drinker
Number of Days in Study
Number of Days on Therapy

(All available related demographic variables)

Efficacy Data:
Example:

Patient Id
Investigator Id
Treatment Group
Visit Number
Days from start of treatment
Losses: (Culture, LTFU, ...)
Signs & Symptoms
Clinical Response at test of cure

(All the variables needed for the efficacy analyses)
Safety Data:
Example:

Patient Id
Investigator Id
Treatment Group
Visit Number
Days from Start of Treatment to Adverse Event
Adverse Event
List of Adverse Events
Death
Date of Death

(All the variables needed for the safety analyses)

Other comments:
Comments and Action Taken are not needed in the data sets. At this time, lab results are not needed.

MESSAGE CONFIRMATION

09/02/99 12:16

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 2, 1999. Number of Pages (including cover sheet) 5
TO: Ms. Dawn Parcell, Regulatory Affairs
COMPANY: Connetics Corporation
NUMBER: 650-843-2899
MESSAGE:

RE: **NDA 21-142 Clobetasol Propionate Foam, 0.05%**

Please find request for information for this NDA. As discussed, the chemistry and biopharmaceutics information needs to be submitted before September 27, 1999, which is the filing date for this application.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

THIS MESSAGE IS ADDRESSED AND MAY CONTAIN

connetics

FACSIMILE TRANSMISSION SHEET

Date: September 15, 1999

To: Kaylani Bhatt
Division of Dermatologic & Dental Drug Products

Fax: (301) 827-2075

From: Dawn Parsell

Subj: Clobetasol Propionate Foam, 0.05% (NDA #21-142)
Response to request for information

No. of pgs. (20) including transmission sheet

Dear Kaylani,

The following is a copy of Connetics' response to the Agency's request for Chemistry and Biopharmaceutics information (submission 2.1 to NDA #21-142).

I have spoken with the statistician who is reformatting the data as requested by the Agency; we anticipate submitting the reformatted data the week of September 20, 1999.

Best Regards,

Dawn

Dawn Parsell, Ph.D.
Associate Director, Regulatory Affairs

3400 W. Bayshore Road, Palo Alto, CA 94303. Telephone (650) 843-2800. Fax (650) 843-2899.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Connetics Corporation	September 15, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
650/843-2800	650/843-2899
APPLICANT ADDRESS *(Number, Street, City, State, County, and ZIP Code or Mail Code, and U.S. License number if previously issued)*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
3400 West Bayshore Road Palo Alto, CA 94303	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) #NDA 21-142

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Clobetasol Propionate, USP	OLUX™ Foam

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
(11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17 (1-oxopropoxy)-pregna-1,4-diene-3,20-dione

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Aerosol Foam	0.05%	Topical

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE
(check one) X NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGIC LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) X 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ORIGINAL APPLICATION X AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Response to a Request for Information

PROPOSED MARKETING STATUS (check one) X PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS X PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug substance is manufactured by manufactured by CCL Pharmaceuticals (see Section 4.A.2.d); this site is ready for pre-approval inspection. Drug product is released following approval by Connetics Corporation. The contact person for all sites is Claire J. Lockey, Vice President, Regulatory Affairs, Connetics Corporation, 3400 West Bayshore Road, Palo Alto, CA; (650) 843-2800.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Connetics Corporation (Clobetasol Propionate Foam, 0.05%), Palo Alto, CA 94303
NDA #20-934: Connetics Corporation [Luxiq™ (betamethasone valerate) foam, 0.12%], Palo Alto, CA 94303

FORM FDA 356h (4/97)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3 Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Claire J. Lockey Vice President, Regulatory Affairs	9/15/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3400 West Bayshore Road, Palo Alto, CA 94303	650/843-2800

Attachment 1

APPEARS THIS WAY
ON ORIGINAL

CCL Pharmaceuticals

Commercial Offices
Innovation House, 6 Seymour Court, Manor Park, Runcorn, Cheshire, England. WA7 1SY
Tel: +44 (0)1928 579322 Fax: +44 (0)1928 579827
E-mail: sales.pharm@ccl-industries.co.uk

3 September 1999

Drug Master File Staff
Food and Drug Administration
12420 Parklawn Drive, Room 2-14
Rockville, Maryland 20852

Dear Sir/Madam:

DMF NUMBER ASSIGNED: ———

Date of Submission: May 1 1995

Title of Submission: Type 1, Facility and Operating Procedure in Runcorn, United Kingdom

Holder of Submmission: CCL Industries

Agent(s): None

Relevant Sections:
1 - Company Information
2 - Administrative Information
3 - Organizational and Personnel Structure
4 - Buildings and Facilities
5(Pgs 62-68) - Production/Manufacturing Areas
6 - Quality Assurance

Please allow access to the above DMF in relation to any submission made by the following company:

Connetics Corporation
3400 West Bayshore Road
Palo Alto
CA 94303
USA

Thank you for your assistance in this matter.

Sincerely,

Steve Tickle
Technical Director

Attachment 2

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

Attachment 3

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 8

❖❖❖

Draft Labeling
(not releasable,

connetics

FACSIMILE TRANSMISSION SHEET

Date: September 9, 1999

To: Kaylani Bhatt and Olga Cintron
Division of Dermatologic & Dental Drug Products

Fax: (301) 827-2091

From: Dawn Parsell

Subj: Clobetasol Propionate Foam, 0.05% (NDA #21-142)
Request for clarification

No. of pgs. (1) including transmission sheet

Dear Kaylani and Olga,

We would like to request clarification regarding the Request for Data (Date 8/31/99) from the FDA Division of Biometrics received as part of the Agency's September 2, 1999 fax to Connetics.

It is our understanding that the Division would like the data from the Phase III study (Protocol CPCD.C.002) to be compiled into two data sets:

They don't want to merge the Demographic Data Set. The Biometrics Group sent it as

(1) Demographics and Efficacy, and
(2) Safety,

and that laboratory results need not be included in either set.

To comply with this request, we plan to merge the data presented in our Demographics and Efficacy data sets to create a new data set (1), and to merge the data presented in our Adverse Event and Vital Signs data sets to create a new data set (2). We do not plan to include laboratory results in the Safety data set.

We would appreciate confirmation that our plan is acceptable to the Division. We would also like to know how many copies of the disks containing the data sets we should send to the Agency. Thank you for your help.

Sincerely, Dawn

Dawn Parsell, Ph.D.
Associate Director, Regulatory Affairs

3400 W. Bayshore Road, Palo Alto, CA 94303. Telephone (650) 843-2800. Fax (650) 843-2899.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 2, 1999. Number of Pages (including cover sheet) 5
TO: Ms. Dawn Parcell, Regulatory Affairs
COMPANY: Connetics Corporation
NUMBER: 650-843-2899
MESSAGE:

RE: NDA 21-142 Clobetasol Propionate Foam, 0.05%

Please find request for information for this NDA. As discussed, the chemistry and biopharmaceutics information needs to be submitted before September 27, 1999, which is the filing date for this application.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

This request for info. was faxed to the sponsor needs to be processed.

NDA 21,142
DIV FILES HFD-540/Woory
HFD-540/Blatt HFD-580/Farr
HFD-540/Turnipman

NDA 21, 142 Olux (clobetasol propionate Foam), 0.05%

REQUEST FOR INFORMATION

Chemistry:

1. Please confirm that the following facilities are ready for inspection or that they will be ready for inspection within a short period of time (please state when they will be ready):

a. the drug substance manufacturing site,
b. the drug product manufacturing site,
c. the two release testing sites for the drug product,
d. the microbiology testing facility,
and
d. the site where each lot of the drug is released:

Connetics Corporation
Quality Assurance Department
3400 West Bayshore Road
Palo Alto, CA 94303

2. On Volume 1.2, Page 04 0017, the sponsor refers [redacted]
This is [redacted] Please provide a reference to the correct DMF.

Biopharmaceutics:

Please provide the assay methodology and validation for the HPA axis suppression study CPCD.C.003.

Administrative:

Financial Disclosure:

Please report proprietary interests and compensation affected by the outcome of the clinical studies. The Sponsor is referred to page 72173 of the December 31, 1998, amendment to the rule, for requirements for investigators participating in clinical studies, whether they are ongoing or completed, if the studies are to be used to support applications that are submitted on or after February 2, 1999.

If you have any questions regarding financial disclosure issues, please contact Linda Carter at 301-594-6758.

FDA Division of Biometrics

NDA# 21-142 Olux (Clobetasol Propionate Foam, 0.05%)
REQUEST FOR DATA
DATE: 8/31/1999

The followings are some suggestions and general recommendations to expedite the data evaluation procedure. These are not official policy statements and should not be construed as such. It is to be noted that FDA does not encourage submissions in one statistical package over another, this note is not meant to endorse SAS.

We would like to thank you in advance for cooperating in this matter, also to remind you that adhering to these simple instructions will only accelerate the review process which in turn will benefit you as the sponsor.

REQUEST FOR TRANSFER OF DATA:
Please provide the data for the Phase III pivotal study only.

1. Data Submission by Study Number:
   Efficacy and safety data sets should be submitted by study. Study number is to be carried as a common variable to facilitate pooling of the data across studies.

   A listing from PROC CONTENTS from each data library should be provided which lists all the data sets, clearly labeled for each study and variable type. ***For each study only Two data sets should be provided.***
   For example:
   Study # 1, Demographic Data & Efficacy Data
   Study # 1, Safety Data

   Study # 2, Demographic Data & Efficacy Data
   Study # 2, Safety Data

2. Uniformity of Data and Data Layout:
   All data should be named, coded and described in the same manner for all studies throughout the NDA.

   All files should include patient number, investigator number and treatment group as common variables. A useful data layout is to have one record per patient, with all visit information available in a single record.

   The patient numbers in all the data sets should be unique, so it would be possible to merge the data sets if necessary.

3. Description of Data:
   - A data dictionary which lists and describes the key safety and efficacy variables.
Example: TRT =treatment, INVID =investigator id#.

- A description of the values of the variables. Example: TRT (A=Investigational Drug, B=Placebo), SEX (1=male, 2=female).

4. Data Formats:
   All format libraries and variable labels should be provided, along with step-by-step outline of attaching the format catalogs to SAS data sets.

   If SAS transport files or compressed files are submitted, a step-by-step instruction set should be attached for conversion to .SSD or .SD2. As of now, we are using PC-SAS version 6.12 for Windows as our primary platform.

5. SAS Programs:
   The programs used to generate the results, and a description of their intended use, for each of the studies separately (no need for programs that create tables or pages.)

For each study please provide:

Demographic Data:
Example:

Patient Id
Investigator Id
Treatment Group
Age
Race
Gender
Baseline Clinical Evaluability
Any Concomitant Drug Use & Drug Type
Past History of Sickness
Smoker
Drinker
Number of Days in Study
Number of Days on Therapy

(All available related demographic variables)

Efficacy Data:
Example:

Patient Id
Investigator Id
Treatment Group
Visit Number
Days from start of treatment
Losses: (Culture, LTFU, ...)
Signs & Symptoms
Clinical Response at test of cure

(All the variables needed for the efficacy analyses)
Safety Data:
Example:

Patient Id
Investigator Id
Treatment Group
Visit Number
Days from Start of Treatment to Adverse Event
Adverse Event
List of Adverse Events
Death
Date of Death

(All the variables needed for the safety analyses)

Other comments:
Comments and Action Taken are not needed in the data sets. At this time, lab results are not needed.

MESSAGE CONFIRMATION

09/02/99 12:16

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 2, 1999. Number of Pages (including cover sheet) 5
TO: Ms. Dawn Parcell, Regulatory Affairs
COMPANY: Connetics Corporation
NUMBER: 650-843-2899
MESSAGE:

RE: **NDA 21-142 Clobetasol Propionate Foam, 0.05%**

Please find request for information for this NDA. As discussed, the chemistry and biopharmaceutics information needs to be submitted before September 27, 1999, which is the filing date for this application.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

THIS [illegible] IS ADDRESSED AND MAY CONTAIN

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: January 28, 2000	**DUE DATE:** May 29, 2000	**OPDRA CONSULT #:** 00-0029

TO: Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Kalyani Bhatt, Project Manager
HFD-540

PRODUCT NAME: Olux (clobetasol propionate foam, 0.05%) **NDA #:** 21-142	**MANUFACTURER:** Connetics Corporation 3400 West Bayshore Road Palo Alto, CA 94303

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), OPDRA conducted a review of the proposed proprietary name "Olux" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objections to the use of the name "Olux". We have made recommendations for labeling revisions, which are consistent with a previous consult completed for NDA 20-934, Luxiq (betamethasone valerate foam, 0.12%)

/S/ 3/28/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 3/29/00

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 23, 2000

NDA NUMBER: 21-142

NAME OF DRUG: Olux (clobetasol propionate foam, 0.05%)

NDA HOLDER: Connetics Corporation
3400 West Bayshore Road
Palo Alto, CA 94303

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for assessment of the proprietary name Olux.

Olux (clobetasol propionate foam, 0.05%) is a topical corticosteroid product. This product is indicated for the short-term treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp. Treatment should be limited to 2 weeks or less and with use of no more than 50 grams per week. Use in children under 12 years of age is not recommended. The usual dosage is twice daily application, once in the morning and once at night. The foam is supplied in a 100-gram aerosol can.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Olux to a degree where potential confusion between drug names could

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[ii] American Drug index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iv] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-99, and the electronic online version of the FDA Orange Book.

occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three (3) prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Olux. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

With regard to Olux, there were no product names identified that had significant look-alike or sound-alike properties to this name. However, as with a previous review concerning another Connetics topical foam product (Luxiq, NDA 20-934, dated 2/10/2000), there was a concern raised regarding the use of the nomenclature "Viafoam" for the following reasons:

[redacted] *" sounds and looks like the drug product name Vioform™,* an OTC product currently marketed by Novartis. Vioform is an antifungal cream and ointment with the active ingredient of 3% Clioquinol (iodochlorhydroxyquin). In accordance with 21 CFR 201.10 (c) (5), the labeling of a drug may be misleading if the proprietary name, designating a drug or ingredient, is similar in spelling or pronunciation of another proprietary name. In addition, 201.10(c)(4) states that the featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation may be misleading. *The* [redacted] *logo draws attention to the function of an inactive ingredient (foam drug vehicle).*

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 91 health care professionals (nurses, pharmacists, physicians) to determine the degree of confusion of Olux with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote inpatient orders and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Outpatient: Olux, Apply to scalp QD, #1, No refills	*Outpatient*: Olux, apply to scalp everyday. Dispense one, no refills.
Inpatient: Discharge pt home today Olux Apply to scalp QD	

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Olux" response	Other response
Written: Outpatient	31	19 (61%)	17 (89%)	2 (11%)
Inpatient	31	16 (52%)	15 (94%)	1 (6%)
Verbal: Outpatient	29	12 (41%)	9 (75%)	3 (25%)
Total	91	47 (52%)	41 (87%)	6 (13%)

Among participants in the two written prescription studies, the majority of the respondents (91%) provided the correct spelling of the drug name. The other responses were generally phonetic variations of the name "Olux".

Among the verbal prescription study participants, the majority of the respondents (75%) interpreted the name correctly. The other name interpretations were generally phonetic variations of "Olux".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Olux", the primary concerns raised were related to the use of the drug vehicle name, [redacted] which has strong look-alike and sound-alike properties as compared with Vioform, a currently marketed OTC antifungal product.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container label, carton labeling, and draft package insert for Olux, OPDRA has attempted to focus on safety issues relating to possible medication errors, but we have also completed a regulatory review of the labeling. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. GENERAL COMMENT

OPDRA has some safety concerns surrounding the use of the term [redacted] and a currently marketed OTC product named "Vioform" (see comments above).

B. CONTAINER LABEL

1. Please note that the "ASHP Guidelines on Preventing Medication Errors in Hospitals", Am J Hosp. Pharm, Vol. 50, Feb 1993, notes that important information such as drug name and strength should have the greatest prominence. *"Olux" and the established name* should be relocated to appear more central on the label and its prominence should be increased.

2. 21 CFR 201.10 states "the established name shall be in letters that are at least ½ as large as the

letters comprising the proprietary name and shall have a prominence with such proprietary name". Although it would appear that the established name meets this requirement, we recommend the *prominence of the established name,* and especially the phrase "foam 0.05%", be increased and revised to appear in the same font and appearance as Olux on all labels and labeling.

3. The *large logo "C"* which appears over the majority of the primary panel may be confused with a Controlled Substance Symbol (C) which is overlayed on scheduled drugs as required by the DEA.

4. The *"Rx Only"* statement should be moved to the primary display panel, because there is plenty of room and that is the Agency preference.

5. In accordance with 21 CFR 201.100(b)(1) all *inactive ingredient names* must be listed on the label if the product is not for oral use. The firm should be advised to list them on the label in alphabetical order.

6. The *net quantity statement* should not have greater prominence than the product strength. We recommend that the prominence of the product strength be increased and that the net quantity not be highlighted.

B. CARTON AND PACKAGE INSERT LABELING

See comments above, as applicable.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS

A. From a safety perspective, OPDRA has no objections to the use of the proprietary name "Olux". However, we do not recommend the use of [redacted] nomenclature and offer recommendations on labeling revisions.

B. OPDRA recommends the above labeling revisions that might lead to the safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/ 3/28/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-142
HFD-540; Division Files/Kalyani Bhatt, Project Manager
HFD-540; Jonathan Wilkin, Division Director
HFD-040; Mark Askine, Senior Regulatory Review Officer, DDMAC
HFD-430; Marilyn Pitts, Safety Evaluator, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Peter Honig, Director, OPDRA (electronic copy)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (electronic copy)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:OPDRA/Jerry Phillips/ Sammie Beam			FROM: Kalyani Bhatt, Project Manager HFD-540 301-827-2049	
ATE 28-00	IND NO.	NDA NO. 21-142	TYPE OF DOCUMENT N (111) 1C	DATE OF DOCUMENT 7-29-99
NAME OF DRUG Olux Foam (0.05% clobetasol propionate)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 5-29-00 (10 Month User Fee Date)

NAME OF FIRM: Connetics Corporation, 3400 West Bayshore Road, Palo Alto, CA 94303

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISION RICK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

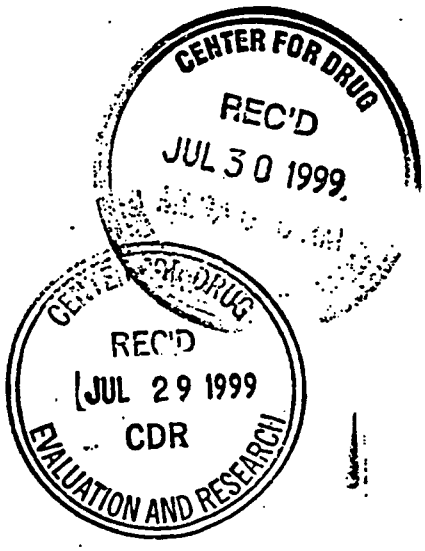
V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

SIGNATURE OF REQUESTER Kalyani Bhatt HFD-540, X7-2049	METHOD OF DELIVERY (Check one) E-mail & internal mail X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

connetics™



July 28, 1999

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
Attn: HFD 540
12229 Wilkins Avenue
Rockville, MD 20852

RE: Original New Drug Application #21-142
Clobetasol Propionate Foam, 0.05%

Dear Sir/Madam:

Enclosed is an original New Drug Application (NDA) for clobetasol propionate foam, 0.05%, being submitted under the Federal Food, Drug and Cosmetic (FD&C) Act Sec. 505(b)(2) and 21 CFR §314.54. The trade name we are suggesting for this product is OLUX™ Foam, as reflected in our proposed draft labeling; however, our final drug product is referred to as "Clobetasol foam" throughout this marketing application. We propose that Clobetasol foam carry class labeling with the indication for the short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp. Clobetasol foam will be marketed as a prescription drug.

Clobetasol propionate (Clobetasol), the active ingredient in Clobetasol foam, is a synthetic analog of prednisolone with a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity*, and its effects are well-known in animals and humans. Topical Clobetasol has been marketed internationally since 1973. Clobetasol was first approved for marketing in the U.S. in 1985 for topical whole body use for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Connetics Corporation's (Connetics) Clobetasol foam is a new topical dosage form of Clobetasol that has cosmetic advantages over other currently marketed formulations of Clobetasol (*i.e.*, solutions, creams and ointments), in that it is neither runny nor greasy. When the foam is applied, body heat causes the foam structure to break down and deposit the active ingredient in a vehicle most closely resembling that of a solution. This is particularly advantageous when used on hairy areas such as the scalp. The foam dosage form provides controlled application of a small amount of product over the lesion site, rather than spreading over the surrounding areas of the skin. The ease of localized

* Pakes GE, Kamm AR. Topical Clobetasol Propionate. In: Maibach HI, Surber C (eds). *Topical Corticosteroids*. Basel, Karger; pp. 370-387; 1992.

application and the improved cosmetic aspects of Clobetasol foam may be expected to lead to better patient compliance and satisfaction.

The active ingredient and excipients (with the exception of the propellant) of Clobetasol foam are all compendial ingredients with a history of safe use in topical pharmaceutical and cosmetic products. The drug product is a hydroalcoholic, thermolabile foam packaged in an aluminum can pressurized with a hydrocarbon propellant (propane/butane). In the can, the drug product is a clear solution; the foam is formed when the solution is dispensed from the can.

Clobetasol drug substance is manufactured at . All manufacturing and packaging operations of the drug product are performed for Connetics at CCL Pharmaceuticals (CCL) in Runcorn, U.K. Copies of Drug Master File (DMF) "letters of authorization" for these two manufacturers are attached to this cover letter for your convenience. Also appended is a DMF authorization letter from . A DMF is not available for ; however, a letter from providing a description of the materials used in the for Clobetasol foam is also attached. All of the materials are on FDA's GRAS (Generally Regarded As Safe) list.

At the Pre-IND Meeting on February 19, 1998, Connetics and representatives from the Food and Drug Administration (FDA) agreed that submission of a 505(b)(2) application containing data demonstrating comparable bioavailability of Clobetasol foam to the currently marketed dosage forms of Clobetasol would be sufficient for approval. (Copies of minutes from this meeting prepared by both FDA and Connetics are included in the "Prior Agreements" attachment to this cover letter.) The clinical package agreed upon at this meeting included the following three studies:

- a comparative vasoconstrictor study;
- a comparative Phase III safety and efficacy study in scalp psoriasis; and
- a comparative HPA axis suppression study.

Connetics conducted these clinical studies under . A summary of the results of these studies was presented to the Agency at a Pre-NDA Meeting held on April 26, 1999. (A copy of FDA's minutes and a copy of Connetics' minutes from this meeting are included in the "Prior Agreements" attachment to this cover letter.) The results of the clinical studies support Connetics' claim that Clobetasol foam is comparable to currently marketed Clobetasol products as follows:

- Results from a vasoconstrictor assay demonstrate that Clobetasol foam, like most other Clobetasol formulations, is a super-high-potency corticosteroid.
- The efficacy of Clobetasol foam in treating scalp psoriasis is superior to that of the Vehicle foam and not inferior to that of a currently marketed Clobetasol solution.

- Clobetasol foam is generally safe and well-tolerated and shows a safety profile similar to that of Clobetasol solution in subjects using the product to treat scalp psoriasis.

- Clobetasol foam has no greater effect on the HPA axis than Clobetasol ointment, as measured by the cosyntropin-stimulated change in plasma cortisol response.

- Clobetasol foam is efficacious, safe, and well-tolerated under normal conditions of clinical use.

Under the FD&C Act Section 505(b)(2) and 21 CFR §314.54, Connetics will refer to and depend upon Glaxo Wellcome's (Glaxo) NDAs for topical Clobetasol products (*i.e.*, Temovate Cream, 0.05%, and Temovate Ointment, 0.05%, NDAs #19-322 and #19-323, approved in 1985; Temovate Scalp Application, 0.05%, NDA #19-966, approved in 1990; Temovate Gel, 0.05%, and Temovate E Cream, 0.05%, NDAs #20-337 and #20-340, approved in 1994). These products have been demonstrated to be safe and effective in the treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Additionally, on February 28, 1999, Connetics received marketing clearance for another topical foam drug product, Luxiq™ (betamethasone valerate) foam, 0.12% (NDA #20-934), for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp. The excipients in Clobetasol foam are the same as those used in Luxiq. The safety profile of Luxiq was comparable to that of other currently marketed betamethasone valerate formulations, and likewise, the safety profile of Clobetasol foam does not differ substantially from that of the currently marketed Clobetasol dosage forms.

It was agreed at the Pre-NDA Meeting that no human dermal irritation nor sensitization studies were necessary to support this 505(b)(2) application since the final product will contain clobetasol-related impurities or degradation products at levels less than 1% of the drug substance at the end of shelf-life. Likewise, photoallergenicity and phototoxicity studies were waived since the drug substance has no absorbance in the visible, UVA, and UVB ranges.

The Nonclinical Pharmacology and Toxicology Section of this NDA (Section [5]) includes a summary of the Clobetasol nonclinical studies from Glaxo's Temovate Summary Basis of Approval documents, as well as a review of the published literature on Clobetasol nonclinical pharmacology and toxicology. Section [5] also includes a summary of the preclinical irritation and sensitization studies conducted on Luxiq, and cross-references the Luxiq NDA #20-934. It was agreed at the Pre-NDA Meeting that no additional preclinical studies were necessary to support this NDA.

A risk assessment has been performed on the aerosol propellant (propane/butane) of Clobetasol foam, and a summary of the results of this assessment, as well as the risk assessment report, are also included in Section [5].

In addition to the documents included in the attachments labeled "Prior Agreements" and "Letters of Authorization," the following are also appended to this cover letter:

- Form FDA 356h;
- Patent Information and Patent Certification (originals submitted in Sections [13] and [14]);
- Debarment Certification (original submitted in Section [16]);
- A completed User Fee Cover Sheet (Form FDA 3397) indicating that a user fee is not applicable (original submitted in Section [18]);
- Claimed exclusivity for Clobetasol foam (also submitted in Section [19]);
- Financial disclosure for clinical investigators (also submitted in Clinical Data Section 8.A.6, List of Investigators, and Section [19]);
- Pediatric study requirement (also submitted in Clinical Data Section 8.B, Overview of the Clinical Program, and Section [19]).

Please be advised that material and data contained in this submission are considered confidential.

If you have any questions concerning this NDA for clobetasol propionate foam, 0.05%, please do not hesitate to call Dawn Parsell at (650) 843-2809 or me at (650) 843-2889. Please direct all correspondence regarding this NDA to me at the address or facsimile number on the first page of this cover letter.

Sincerely,

Claire J. Lockey
Vice President
Regulatory Affairs

Enclosures

cc: Olga Cintron, Project Manager (4 desk copies of Volume 1)

Cintron - 540

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 26, 1999. Number of Pages (including cover sheet) 7
TO: Dawn Parsell, Ph.D., Associate Director, Regulatory Affairs
COMPANY: Connetics Corporation
NUMBER: 650-843-2899

MESSAGE:

RE: ——— **Clobetasol Propionate Foam, 0.05%**
Pre-NDA Meeting Minutes dated 4/26/99.

A copy of our meeting minutes is enclosed. The external constituents are responsible for notifying CDER of any significant differences in their understanding of the meeting outcomes (as reflected in the minutes).

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

cc: ———

HFD 540 DIV FILES

APR 26 1999

MEETING MINUTES

Date: April 26, 1999. **Time:** 1:00 pm **Location:** N-225 **Meeting ID:** 3913

Drug: Clobetasol Propionate Foam, 0.05%

Proposed Indication: [redacted]

Sponsor: Connetics Corporation

Type of Meeting: Pre-NDA

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder: Olga Cintron, R.Ph.

Sponsor participants:

Thomas J. Franz, M.D., Vice President, Clinical Research, Connetics
Claire J. Lockey, Vice President, Regulatory Affairs, Connetics
Russell Kawahata, Ph.D., Senior Director, Pharmaceutical Sciences, Connetics
Max Nygaard, Regulatory Affairs Associate II, Connetics
John Hannigan, Biostatistician Consultant, Connetics

FDA participants:

Jonathan Wilkin, M.D., Division Director, HFD-540
Martin Okun, M.D., Ph.D., Medical Officer, HFD-540
Paul Brown, Ph.D., Pharmacologist/Toxicologist, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-540
Ernest Pappas, Chemist, HFD-540
Saleh A. Turujman, Ph.D., Chemist, HFD-540
Neal Sweeney, Ph.D., Microbilogy Reviewer, HFD-805
Dennis Bashaw, PharmD, Biopharmaceutics Team Leader, HFD-880
Ping Gao, Ph.D., Biostatistician, HFD-725
R. Srinivasan, Ph.D., Biostat Team Leader, HFD-880
Olga Cintron, R.Ph., Project Manager, HFD-540

Meeting Objective:

To provide comments and regulatory guidance on the content and format of the Sponsor's proposed NDA submission.

Discussion points:

With reference to the March 26, 1999, meeting briefing package, the Agency provided the following comments:

Chemistry, Manufacturing, and Controls:

1. Answer to Question #1: Yes. We agree that submission of 12 months of stability data from CCL and 3 months from —— , supports a fileable 505(b)(2) application for Clobetasol Propionate Foam, 0.05%. However, we encourage you to have at least 6 months of stability data from —— at the time of the NDA submission.

2. Answer to Question #2: Conditionally, no. Additional stability data should be submitted within 7 months post submission of the NDA.

3. Answer to Question #3: This question will be addressed by the microbiologist.

4. Answer to Question A (faxed by the Sponsor on 4/20/99): We emphasize that method validation is performed on the test methods and not the product. The Sponsor clarified that the word "retains" refer to the samples set aside for methods validation.

5. Question B: The CMC information should be submitted similar to the information as submitted for the Luxiq NDA.

6. Labeling: The proposed labeling address the flammability of the product under the WARNING section for Clobetasol foam. Are you going to submit data on its flammability?

Microbiology:

1. Answer to Question #3: We agree that the Antimicrobial Effectiveness Test does not need to be a release specification. However, antimicrobial preservative effectiveness should be demonstrated for the drug product formulated with an amount of preservative (ethanol) less than or equal the minimum specified as acceptable. This information should be included in the NDA.

2. For testing the stability of the preservative system of the drug product, the first three production lots should be tested for antimicrobial preservative effectiveness at the start and end of the stability period, and at one point in the middle of the stability test period if the test period equals or exceeds two years. The first three production batches should be assayed for the chemical content of the preservative at all appropriate test points. Upon demonstration of chemical content commensurate with antimicrobial effectiveness in the first three production batches, chemical assays may be adequate to demonstrate the maintenance of the specified concentrations of preservative for subsequent lots placed into stability testing. Preservative effectiveness testing of the first three production lots should be performed as a post approval commitment.

3. The microbial limit test acceptance criteria [Total viable count (aerobic, yeasts, molds) <100 cfu/g; E.coli, S. aureus, P. aeruginosa, Salmonella species all absent) for the drug product are acceptable. Please note the current USP <1111> proposal [Pharm. Forum, March/April 1999] of <100 cfu/g for total aerobic microbial count, and <50 cfu/g for total combined molds and yeast. Microbial limits acceptance criteria may be accordingly revised to meet the finalized USP microbial limits acceptance criteria.

Pharmacology/Toxicology:

1. Answer to Question #11: Yes. At the Pre-IND meeting the pharmacology and toxicology comments from the Division stated that if additional safety concerns arose during the clinical trials then further nonclinical testing might be required to support an NDA.

   The summaries of the clinical studies results presented in the current submission suggest that additional safety concerns did not arise during these studies. Therefore, no additional nonclinical studies are recommended to support the filing of a 505(b)(2) NDA for clobetasol propionate foam.

2. Answer to Question #12: Yes. The Sponsor should provide a review of the existing pharmacology and toxicology data on clobetasol and the foam vehicle in the NDA.

3. Additional comment: The specification of 0.01 mole% for [redacted] in the propellant should be maintained for the clobetasol propionate foam formulation as it is for the betamethasone valerate formulation.

Biopharmaceutics:

1. Answer to Question #6.D: The sponsor has adequately addressed the outstanding pharmacokinetic issues.

   With respect to the small number of subjects to be exposed to test drug in the HPA axis suppression study, the Sponsor subsequently doubled the number of subjects from 6 to 12 in each group.

   With respect to the timing of the blood sampling for HPA response, the Sponsor pointed out that the current guidance and directions for the test allows for assessment at either the 30 or 60 min timepoint.

2. Answer to Question B: The proposed formatting of the data is acceptable. The results of the HPA axis suppression study should be provided in EXCEL as well as SAS formats.

Clinical:

1. Answer to Question #4: Agency decision regarding fileability will be made subsequent to examination of submitted NDA volumes. It is reasonable for Sponsor to expect that criteria similar to those used in deciding the fileability of NDA 20-934 will be used in deciding

whether the studies supporting this NDA submission do support a fileable 505(b)(2) application.

2. Answer to Question #5: Agency agrees that no human dermal irritation/sensitization studies, nor clinical photoallergenicity or phototoxicity studies are necessary for filing the clobetasol propionate foam NDA. Human skin irritation/sensitization studies will be waived, unless CMC profiles show impurities or degradation products greater than 1% of the drug substance. Photoallergenicity/phototoxicity studies will be waived if the drug substance has no absorbance in visible, UVA, or UVB light.

3. Answer to Questions #6A,6B: The principal focus of this meeting is to ensure that the form and content of the NDA is such that it can be filed and subsequently reviewed effectively. To answer these questions satisfactorily, the NDA and the Sponsor's proposed label for this product must be reviewed and considered in context. Answering these questions definitively, which touch upon issues related to the review process itself, at this time is premature.

4. Answer to Questions #6C, 7: NDA submission should include submission of data in a manner that enables assessment of outcomes in the I.T.T. population, which is defined by the statistics reviewer, of treatment "success" at day 15, defined as subjects who had (a) an Investigator's Global Assessment Score of completely clear or almost clear, and (b) a plaque thickness score of zero, and (c) a scaling score of 0 or 1, and (d) an erythema score of 0 or 1. To be counted as a "success", subjects must meet all 4 of the above-stated criteria. Rest of question as per Statistics.

5. Answer to Question #6D: As per Biopharm.

6. Answer to Questions #8,9,10: Answering these questions definitively, which touch upon issues related to the review process itself, at this time is premature.

7. Other issues:

   A. Please submit CRFs for all patients who are lost to follow-up or who are early discontinuations. Additional CRFs may be requested during the course of the review process.

   B. Please include in the submission the primary efficacy analysis [as defined in the answer to question (6C,7)] broken down by investigator.

   C. Please include in the submission an index that would enable the reviewer to make the association between investigator's verbatim terminology used to describe an adverse event and the preferred term used for coding the adverse event in the submission's adverse event tables.

Biostatistics:

1. Answer to Questions # 6.C and #7: Agree with comments by medical officer.

2. SAS data sets: Please submit in SAS 6.12 for windows format. Data sets should have a unique patient identifier, so that the data sets can be easily merged.

3. ITT population includes all randomized patients who were dispensed with study medication. There need not be a post baseline efficacy measurement.

Divisional Comments

Pediatric Rule
The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, became effective April 1, 1999, requires the following:

For pre-NDA meetings:

1. Under 21CFR, Section 312.47, the Sponsor is required to inform the Agency about the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness. The meeting package submitted for the pre-NDA meeting must now include the status of needed or ongoing pediatric studies.

For NDA applications:

2. Under 21 CFR, Section 314.50, the NDA application is required to include the following:

   (d) (7) Pediatric Use Section. Requires that an NDA contain "a section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (3) and (5), and information required to be submitted under Section 314.55."

3. Under 21 CFR, Section 314.55 Pediatric Use Information.
   (a) Required assessment. "Except as provided in paragraphs (b), (c), and (d), each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective...." Orphan drugs are exempted from this requirement.

4. For additional information, please refer to the following CDER web site, www.fda.gov/cder/pediatric

Financial Disclosure:

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 the following CDER web site, www.fda.gov/cdrh/modact/fr112098a.html

Labeling:

If you have an Information for Patients leaflet/labeling, please submit with the NDA.

Post meeting corrigenda:

Further clarification of the threshold for qualification of impurities/degradation products:

Impurities that are equal to or greater than 1% of the drug substance should be qualified. The Sponsor is referred to the ICH Guidance for Industry Q3B Impurities in New Drug Products.

Signature, minutes preparer: /S/ 4/26/99

Chair concurrence (or designated signatory): /S/

APPEARS THIS WAY
ON ORIGINAL

cc:
HFD-540/Div File
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Okun 4/26/99.
HFD-540/Brown 4/26/99.
HFD-540/Jacobs
HFD-880/Bashaw 4/26/99.
HFD-540/DeCamp 4/26/99.
HFD-540/Pappas 4/26/99.
HFD-725/Srinivasan 4/26/99.
HFD-725/Gao 4/26/99.
HFD-805/Sweeney 4/26/99.
HFD-540/Cintron

JUL 6 1998

MEETING MINUTES

Date: February 19, 1998. Time: 2:30 pm Location: N-225

Type of Meeting: Pre IND/End of Phase 2 Meeting ID: 2216

Drug: Clobetasol Propionate Foam, 0.05%

Sponsor: Connetics Corporation

FDA participants: Jonathan Wilkin, M.D., Division Director, HFD-540
Susan Walker, M.D., Clinical Team Leader, HFD-540
Martin Okun, M.D., Medical Officer, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-830
Paul Brown, Ph.D., Pharmacologist/Toxicologist, HFD-540
Shahla Farr, M.S., Statistician, HFD-725
R. Srinivasan, Ph.D., Biostatistics Team Leader, HFD-725
D. Wang, Pharm. D., Biopharmaceutics Reviewer, HFD-880
Dennis Bashaw, Pharm. D., Biopharmaceutics Team Leader, HFD-880
Olga Cintron, R.Ph., Project Manager, HFD-540

Sponsor participants: W. Scott Harkonen, M.D., Senior Vice President, Product Development and Operations, Connetics
Thomas J. Franz, M.D., Vice President, Clinical Research, Connetics
Claire J. Lockey, Vice President, Regulatory Affairs, Connetics
Russell Kawahata, Ph. D., Senior Director, Pharmaceutical Sciences, Connetics
Ananda Gubbi, Ph. D., Senior Biostatistician, Connetics
Jacqueline Kalbach, Manager, Regulatory Affairs, Connetics
Dawn Parsell, Ph. D., Clinical Scientist, Connetics
Lesley Pickford, Assoc. Dir., Pharm/Tox, Connetics

Objectives:

1. To discuss and obtain feedback on the questions outlined in the January 30, 1998, request for Pre IND meeting submission.

2. To discuss the sponsor's development plans for clobetasol propionate foam, 0.05%, for the topical treatment of the pruritic and inflammatory manifestations of corticosteroid-responsive dermatoses.

Discussion:

The Sponsor's pre meeting briefing package included several questions regarding the development plan and regulatory strategy to obtain approval for the proposed formulation. The sponsor intends to obtain approval of clobetasol propionate foam by submitting a 505 (b)(2) application. Please refer to sponsor's briefing package for specific questions. The Agency addressed the sponsor's questions as follows:

Chemistry, Manufacturing, and Controls:

- No specific chemistry, manufacturing, and control issues were discussed. The Sponsor will be requesting a meeting or teleconference to discuss the CMC issues once more stability data of the proposed product becomes available.

- The Agency stated that the advice given at this time is provisional since the CMC information could reflect on all disciplines, and that the FDA team will be present at the meeting to discuss CMC issues. (Question #9)

Pharmacology/Toxicology:

- If the pharmacology and toxicology information submitted in the IND are sufficient to establish the safety of clobetasol foam and the drug product does not contain unqualified impurities or degradants, then additional non clinical pharmacology and toxicology studies are unlikely to be needed to permit initiation of the clinical trials. If unanticipated safety concerns arise during clinical trials, then additional non clinical studies may be needed to support an NDA. (Question #7)

- The IND and the NDA applications should include a review of the available pharmacology and toxicology information on clobetasol propionate and the foam vehicle to permit the assessment of the safety of the proposed drug product. (Question #8)

Biopharmaceutics:

Regarding the HPA axis suppression study:

- The duration of the study should equal the length of treatment. The Sponsor is encouraged to consider a 4 week study if the Sponsor intends to subsequently submit an application for 4 weeks of clinical use.

- Response variables proposed by the Sponsor are considered adequate by the Agency provided there is the additional analysis suggested below:

The Sponsor should compare cosyntropin-stimulated cortisol levels after 14 days to stimulated levels at baseline (delta). The 90% confidence intervals should be constructed for these comparisons using the standard bioequivalence method, although this comparison is not for bioequivalence purpose.

- The Sponsor should assure maximum body surface exposure of drug according to the labeling.

Clinical:

- An appropriate comparative efficacy study design would include a four arm comparison, using the reference product as a comparator and including a placebo arm (active foam, placebo foam, active comparator, placebo comparator). The company has determined the comparator to be the Clobetasol Propionate Solution 0.05%. Assessment of the overall scalp should be made, instead of assessment of a specific target lesion. (Question #2)

- The primary endpoint Investigator's Global Assessment should be a dichotomous static variable. The criteria for placing a subject into an assessment level should be clearly defined for the clinical investigators, such that the distinction between Cleared and Almost Cleared is apparent. Subjects who are completely cleared or almost cleared, should ultimately be included in the 'success' category for analysis and all others in the 'failure' category.

- The results of the analysis of the secondary endpoint variables Erythema, Scaling, and Plaque Thickness, based on the changes from baseline to day 15 in each of the scores of signs, should reflect the results of the global static assessment.

- The intent of the vasoconstrictor assay in the 505 (b)(2) application is to determine potency, not comparative bioavailability. A single dose-duration [redacted] design is adequate. Comparisons should be made with multiple drug products in adjacent classes in order to adequately establish the steroid class of the clobetasol foam product. (Question #4)

- An HPA axis suppression study should use a cosyntropin stimulation test. The subjects should receive an amount of foam per week equal to the weekly upper limit of total dosage permitted in the final package labeling. The area treated must be clinically involved skin. Final package labeling will reflect the percentage of body surface area applied in the HPA axis suppression study, and final package labeling's proposed duration of treatment will reflect the duration and outcome of the HPA axis suppression test.

- The study should be performed in children, if the sponsor plans to claim use in children.

- The final package labeling will reflect the clinical trials. Whole body class labeling would not be supported by a single study in scalp psoriasis. Body psoriasis is a more appropriate paradigm than scalp psoriasis for supporting class labeling, and it includes a greater chance to enroll pediatric patients. (Question #3)

- HPA axis suppression testing should precede clinical trials to demonstrate an acceptable duration for the clinical pivotal trial. Sponsor should then demonstrate superiority over vehicle and non inferiority to the comparator at 4 weeks in the pivotal clinical trial. (Question #5)

- Human skin irritation studies will be waived for the proposed formulation, unless CMC profile shows impurities or degradation products. Photoallergenicity and phototoxicity studies will be waived if the drug product has no absorbance in visible, UVA, or UVB light. (Question #6)

<u>Biostatistics:</u>

- For approval, the sponsor should demonstrate:
  - Statistical superiority of Clobetasol Propionate Foam, 0.05%, to its own vehicle and,
  - Statistical non-inferiority of Clobetasol Propionate Foam, 0.05% to the currently marketed comparator (Clobetasol Propionate Solution 0.05%).

- To demonstrate non-inferiority of the foam formulation to the solution, a 95% confidence interval for the difference between Clobetasol Propionate Foam and the comparator should be constructed:
  - The confidence interval should not fall below zero, and
  - The foam formulation should not be 10% worse than the solution.

- If the two vehicle arms are not statistically different, they can be combined for the purposes of statistical analysis.

<u>Microbiology:</u>

- The "Proposed Drug Product Specifications" should include specifications for both total aerobic microbial count (bacteria) and total combined molds and yeast count.

- Antimicrobial Preservative Effectiveness specification should also be included in the Proposed Drug Product Specifications.

Regulatory:

- The submission of a 505(b)(2) application is an acceptable option to obtain approval for the proposed drug product. (Question #1)

The meeting ended cordially.

Signature, minutes preparer: /S/ Date: 2/6/98.
Signature, Chair: /S/ Date: 2/6/98

APPEARS THIS WAY
ON ORIGINAL

cc:
Pre IND Div Files
HFD-540/Wilkin
HFD-540/Okun 2/19/98.
HFD-540/DeCamp
HFD-540/Pappas
HFD-725/Srinivasan 2/19/98.
HFD-725/Farr 2/19/98.
HFD-540/Brown 2/19/98.
HFD-880/Bashaw 2/25/98.
HFD-880/Wang 2/25/98.
HFD-540/Walker 2/19/98
HFD-540/Cintron
HFD-604/Hare

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FORWARD PLANNING MEETING MINUTES

NDA 21-142	**Olux (clobetasol propionate) Foam, 0.05%**
Date:	August 31, 1999.
Sponsor:	Connetics Corporation, Inc.
Pharmacologic class:	corticosteroid
Type:	3S
Indication:	Short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp.
Active ingredient:	clobetasol propionate
Filing Date:	September 27, 1999.
Regulatory Due Date:	[redacted]
User Fee Due Date:	May 29, 2000. (10 month)

DEC 28 1999

Attendees:

Jonathan Wilkin, M.D., Director, HFD-540
Marty Okun, M.D., Ph.D., Medical Officer,HFD-540
Saleh Turujman, Ph.D., Chemist, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-540
Paul Brown, Ph.D., Pharmacologist/Toxicologist, HFD-540
Abby Jacobs, Ph.D., Pharm/Tox Team Leader, HFD-540
Shahla Farr, Statitistician, HFD-725
R. Srinivasan, Ph.D., Biostatistics Team Leader, HFD-725
Sue Chih Lee, Ph.D.,Biopharmaceutics, HFD-880
Assadollah Noory, Biopharmaceutics Reviewer, HFD-880
Olga Cintron, R.Ph., Project Manager, HFD-540

The meeting was convened to determine the fileability of NDA 21-142. All disciplines presented their comments in terms of general content and format requirements with respect to their section of the new drug application.

From a preliminary evaluation of the general content and format as well as the CMC microbiology, pharmacology and toxicology, clinical and statistical section of the application, it was recommended that NDA 21-142 be filed.

From a biopharmaceutic standpoint, a potential fileability issue was identified. The sponsor did not provide the assay methodology and validation data for the HPA axis suppression study CPCD.C.003. Chemistry reported that the sponsor did not provide a statement of readiness for inspection for the following sites: DS, DP manufacturing sites, two realease testing sites for the product, the nmicrobiology testing facility and the site where each lot of drug is released. [redacted] This needs to be clarified.

It was concluded that NDA 21-142 be filed provided the sponsor submit the aforementioned information before September 27, 1999.

Expected date of draft reviews if filed:

Chemistry	March 30, 2000
Pharmacology	October 29, 1999
Biopharmaceutics	November 30, 1999
Biostatistics	March 30, 2000
Clinical	TBD
Microbiology (CMC)	September 30, 1999

Addendum to the minutes:

On September 2, 1999, the Agency faxed a chemistry and biopharm request for information. The Sponsor responded to the informational request on September 15, 1999. The response was found acceptable by both chemistry and biopharm.

/S/ 12/28/99

Olga Cintron, R.Ph., Project Manager, HFD-540

APPEARS THIS WAY
ON ORIGINAL

Attachments (Checklists)

cc:
Original NDA 21-142
HFD-540/DIV FILE
HFD-540/Wilkin
HFD-540/CHEM/Turujman
HFD-540/TL CHEM/DeCamp
HFD-540/PHARM/Brown
HFD-540/TL PHARM/Jacobs
HFD-725/BIOSTAT/Farr
HFD-725/TL BIOSTAT/Srinivasan
HFD-540/MO/Huene/Okun
HFD-880/SR BIOPHARM/Bashaw
HFD-880/BIOPHARM/Noory
HFD-540/SUPV PROJ MGR/Kozma-Fornaro
HFD-540/PROJ MGR/Cintron

FORWARD PLANNING MEETING CHECKLIST

August 31, 1999

NDA 21-142 **Clobetasol Propionate foam, 0.05%**

Indication: Short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp.
Sponsor: Connectics Corporation
Type: 3S
Filing Date: Sept 27, 1999
User Fee Date: May 29, 2000 (10-month)
Regulatory Due Date: ~~———~~

FILEABILITY

On initial overview of the NDA application:

PROJECT MANAGEMENT:

(1) Do any of the following apply to this application (i.e., if YES , the application MUST BE REFUSED TO FILE under 314.101 (e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application?
NO.

(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)?
NO.

(c) Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?
NO.

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.101(d) and there is the potential for filing over protest):

(a) Does the application contain a completed application form as required? under 314.50 or 314.55?
YES.

(b) On its face, does the application contain the sections of an application? required by regulation and Center guidelines?
YES. (Clinical, Biopharm, Statistics, Microbiology, Pharm/Tox, Chemistry)

(c) Has the applicant submitted a complete environmental assessment, which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is under 25.24 of the CFR?
THE SPONSOR SUBMITTED MATERIAL SAFETY DATA SHEETS AND IS REQUESTING CATEGORICAL EXCLUSION. LOCATED IN VOLUME 2, PAGE 04-0431.

(d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?
YES. INTEGRATED SUMMARY OF EFFECTIVENESS IS LOCATED IN VOLUME 7, 08-0045 AND THE INTEGRATED SUMMARY OF SAFETY IS LOCATED IN VOLUME 7, 08-0118 OF THE NDA.

(e) Is the NDA indexed and paginated?
YES.

(f) On its face, is the NDA legible?
YES.

(g) Has the applicant submitted all required copies of the submission and various sections of the submission?
YES.

(h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?
YES.

(i) Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?
YES. STATEMENT LOCATED IN VOLUME 4 05-0066.

(j) If required, has the applicant submitted carcinogenicity studies?
NO. CARCINOGENICITY STUDIES WERE NOT REQUIRED.

(k) On its face, does the application contain at least two adequate and well-controlled clinical trials?
THIS APPLICATION IS BEING CONSIDERED A 505(B)(2) APPLICATION. THE SPONSOR IS RELYING ON THE AGENCY'S FINDING FOR SAFETY AND EFFICACY AND HAS ONLY SUBMITTED THE DATA NEEDED TO SUPPORT THE CHANGE IN DOSAGE FORM. THE FOLLOWING STUDIES WERE SUBMITTED TO SUPPORT THE CHANGE: A COMPARATIVE VASCONSTRICTOR STUDY, A COMPARATIVE PHASE 3 SAFETY AND

EFFICACY STUDY IN SCALP PSORIASIS AND A COMPARATIVE HPA AXIS SUPPRESSION STUDY.

(l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?
YES. LOCATED IN VOLUME 7, 08-0190.

(m) Have all articles/study reports been submitted whether in English or translated into English?
YES.

(n) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?
YES, LOCATED IN VOLUME 1.1.

(o) Has the applicant submitted the required FRAUD POLICY notice?
YES. LOCATED IN VOLUME 1, PAGE 16-001.

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?
NOT APPLICABLE.

(q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?
YES. STATED IN VOLUME 7 PAGE 08-0018. THE CUT-OFF DATES FOR THE LITERATURE REVIEW OF SAFETY AND CLINICAL STUDIES CONDUCTED WITH CLOBETASOL FOAM ARE MAY 1999 AND NOVEMBER 1998, RESPECTIVELY.

(r) If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions?
NO APPLICABLE.

(3) From a project management perspective, is this NDA fileable? If "no". please state on the reverse why it is not.

THIS APPLICATION IS FILEABLE FROM A PROJECT MANAGEMENT PERSPECTIVE.

/S/ 8-23-99
Project Manager

/S/ 8/24/99
Supervisory Project Manager

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS FILING REVIEW

NDA:	**21-142**	**SUBMISSION DATE: July 28 1998**
PRODUCT:	**Clobetasol Propionate Foam, 0.05%**	
BRAND NAME:	**Olux™**	
APPLICANT:	**Connetics Corporation**	
REVIEWER:	**A. Noory**	

Filing Review

Olux™ is a foam product for topical use on the scalp, it contains clobetasol propionate, 0.05%, a synthetic corticosteroid. Clobetasol solution, cream, and ointment are currently on the market for topical application. As part of this NDA, the applicant has submitted the results of the following studies. A comparative vasoconstrictor study using Olux™ versus five currently marketed clobetasol products. An HPA axis suppression study comparing the clobetasol foam to clobetasol ointment. The applicant has not provided the assay validation report for the HPA axis suppression study (CPCD.C.003).

Recommendation:
Due to lack of assay methodology and validation for cortisol in the HPA axis suppression study (CPCD.C.003), NDA 21-142 is not fileable from the Division of Drug Evaluation III, OCPB standpoint.

/S/ 8/30/99

Assadollah Noory
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm.D. /S/ 8/30/99

Original: NDA 21-142
CC:
HFD-540/DIV. File
HFD-5540/Proj. Mgr/Bhatt
HFD-880 (Noory)
HFD-880 (Bashaw)
HFD-880 (Lazor)
(CDR. Attn. B. Murphy)

NDA FILEABILITY CHECKLIST

NDA Number: 21-142 **Applicant: Connetics Corporation** **Date: 7/28/99**
Drug Name: OLUX (clobetasol propionate) Foam, 0.05%

OCT 31

IS THE CMC SECTION OF THE APPLICATION FILABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?		X	No CFN; See attached draft to EES and Questions to EES
5	Is a statement provided that all facilities are ready for GMP inspection?			
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		Complies with USP
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		FDA agreed to 12 month stability data in pre-NDA, data is provided 4A2.1
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Reviewing Chemist: Saleh A. Turujman, Ph.D. SAT 8/30/99 Date: 8/30/99

Team Leader Wilson H. DeCamp, Ph.D. /S/ Date: /S/ 8/31/99

cc:
Original NDA 21-142
HFD-540/Division File
HFD-540/Chem/Turujman
HFD-540/ChemTL/DeCamp
HFD-540/PM/Bhatt
HFD-830/DivDir/Chen

NDA Number: 21-142 **Applicant: Connetics Corporation**
Drug Name: OLUX (clobetasol propionate) Foam, 0.05%

Have all DMF References been identified?

DMF Number	Holder	Description	LOA Included	Status
			Yes 3/4/98	Last reviewed 4/2/99; Found acceptable
			Yes 6/24/99	Need explanation
			Yes 6/24/99	Not reviewed

APPEARS THIS WAY
ON ORIGINAL

Division of Dermatologic and Dental Drug Products (HFD-540)

Pharmacology/Toxicology Checklist for NDA Forward Planning Meeting

Date: August 31, 1999
Reviewer: Paul C. Brown
NDA Number: 21-142
Sponsor: Connetics Corporation
Product Name: OLUX™ Foam
Drug Substance(s): Clobetasol Propionate Foam, 0.05%
Indication:

Route of Administration: topical to the scalp
Date CDER Received: July 29, 1999
User Fee Due Date (if filed): May 29, 2000
Expected Date of Draft Review (if filed): October 29, 1999

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner that would 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) Based upon a cursory review, does the presentation of data appear to be appropriate (consider tables, graphs, completeness of study reports, inclusion of individual animal data, appropriateness of data analysis, etc.)?
Yes

(5) Are all necessary nonclinical studies completed and submitted in this NDA?

Yes

(6) Please itemize the pivotal nonclinical studies included in the NDA and indicate any important nonclinical studies that were omitted.
This NDA is for an active ingredient that is found in several other previously approved drug products. The current sponsor is referring to these other NDA's for nonclinical safety information according to the FD&C Act Section 505(b)(2). The sponsor has submitted no new pharmacology or toxicology studies. The sponsor has included a review of relevant pharmacology and toxicology information for clobetasol propionate, copies of reviews of the previously approved NDA's and copies of published pharmacology and toxicology information about clobetasol propionate. The sponsor has also referred to their other NDA (20-934) for LUXIQ betamethasone valerate foam. This product was formulated with the same foam vehicle as OLUX. NDA 20-934 contained nonclinical irritation and sensitization studies.

(7) Based upon a cursory review, do the pivotal nonclinical studies appear to have been adequately designed (e.g., appropriate numbers of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?
See question 6 above

(8) As appropriate, were the test materials utilized in the pivotal nonclinical studies identical to the drug product or drug substance proposed for commercial use (including impurity profiles)? If not, or if this matter is unclear, please comment.
The exact formulation was not tested in nonclinical studies. The same foam vehicle was tested in NDA 20-934.

(9) Based upon a cursory review, do the excipients appear to have been adequately qualified?
Yes

(10) Was the route of administration used in the nonclinical studies the same as the intended clinical route of administration?
No new studies were conducted but previous studies with the foam vehicle and with betamethasone valerate foam were topical studies.

(11) Has proposed draft labeling been submitted?
Yes

(12) From a pharmacology/toxicology perspective, should this NDA be filed? If not, or if you have additional concerns, please indicate your recommendations in the form of draft comments that may be transmitted to the sponsor.
Yes

/S/
Reviewing Pharmacologist — 8-30-99 Date Signed

/S/
Pharmacology Team Leader — 8-30-99 Date Signed

APPEARS THIS WAY
ON ORIGINAL

SEP 18 1999

Memorandum of Teleconference

Date: September 14, 1999

Time: 4:30PM

Application Number: NDA 21-142

Teleconference Members:

Dawn Parcell, Connetics Corporation

FDA-Division of Dermatologic and Dental Products:

Olga Cintron, Project Manager
Kalyani Bhatt, Project Manager

Subject:

The applicant faxed the attached clarification request regarding the request for Data from the Phase III study to the Agency. The agency stated that the statistician had read the fax and is in agreement with the applicant's proposal with regard to the data presentation. One copy of the diskette is sufficient.

The agency inquired the status of the Biopharm and Chemistry info. The applicant indicated that it was being submitted the next day (9-15-99). and that it was going to be faxed on the afternoon of 9-14-99.

Note: The applicant called on 9-15-99 and indicated that the SAS data sets will be submitted on the week of Sept. 20, 1999. The statistical Consultant Company has been affected by Hurricane Floyd. There was no need to merge the Demographics, Efficacy and safety study with the data for Adverse Event and Vital Signs data. The agency also requested the

applicant to fax the information for Biopharm and Chemistry to review and to send the other data on disk for the statistician to review ASAP.

Minutes Prepared By: /S/

cc:

NDA 21-142
HFD 540 Div File
HFD 540/Cintron
HFD 540/Bhatt

Drafted: Sept 17, 1999

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 26, 2000 Number of Pages 3

TO: Claire J. Lockey/Dawn Parsell
COMPANY: Connetics Corporation
FAX #: 1-650-857-1193

MESSAGE: NDA 21-142 Olux Foam 0.05%.
Congratulations! Please see approval letter.

FROM: Kalyani Bhatt,
TITLE: Project Manager
PHONE #: 301-827-2049
FAX #: 301-827-2075/2091