CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-400

ADMINISTRATIVE DOCUMENTS

NDA 20-400

Penederm Incorporated
Attention: Barry Calvarese, M.S.
Executive Director, Clinical/Regulatory Affairs
320 Lakeside Drive, Suite A
Foster City, CA 94404

Dear Mr. Calvarese:

Please refer to your September 24, 1993, new drug application (NDA) and your resubmission dated March 28, 1994, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avita (tretinoin gel) Gel, 0.025%.

Please also refer to our not approvable letter dated March 29, 1995. We also acknowledge receipt of your additional communications dated April 7 and 17, May 19, August 7 and 24, September 11 and 27, and December 6, 15, 20, and 22, 1995; and February 22 and May 9, 1996.

We have completed our review of this application, as amended, and find that the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Any resubmission of this application should also include an updated safety report as specified under 21 CFR 314.50(d)(5)(vi)(b).

In addition, although not the basis for the non-approval of this application, the following comments and requests should be addressed in any resubmission of this application:

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Until the safety and effectiveness of this drug product have been established, we reserve comment on the proposed labeling.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Dermatologic and Dental Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting should be requested 15 days in advance.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact Dr. Roy Blay, Project Manager, at (301) 827-2020

Sincerely yours,

6/26/96 /S/

Jonathan K Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-400
HFD-540\Div. Files
HFA-100
HFD-105/Weintraub
HFC-130
HFD-5
HFD-540\DDIR\Wilkin
HFD-540\MO\Slifman
HFD-540\CHEM\Rejali
HFD-2\Lumpkin
HFD-80
HFD-540\PROJ MGR\Blay

Concurrence:
HFD-540\DEP DIR\Katz\6.26.96
HFD-540\CHEM SUPV\DeCamp\6.26.96
HFD-540\PHARM SUPV\Jacobs\6.26.96
HFD-160\MICRO SUPV\Cooney
HFD-880\BIOPHARM SUPV\Bashaw
HFD-725\BIOSTAT SUPV\Harkins
HFD-540\PROJ MGT SUPV\Cook

drafted: RB/June, 26, 1996/c:\royblay\letters\nda\approval\20400.001
r/d Initials: RAB
final:

NOT APPROVABLE (NA)

NDA 20-400

Penederm Inc.
Attn: Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs
320 Lakeside Drive, Suite A
Foster City, CA 94404

MAR 29 1995

Dear Mr. Calvarese:

Please refer to your September 24, 1993, new drug application (NDA) and to your resubmission dated March 28, 1994, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acticin (tretinoin gel) Gel, 0.025%.

We acknowledge receipt of your amendments and correspondence dated March 30, June 2, 3, 9, 17, July 26, August 2, 8, 25, October 7, 28, November 16, December 16, 1994; January 17, and March 9, 1995.

We have completed our review of this application, as amended, and find that the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are as follows:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Please note that we cannot approve this application until we are informed that all sites involved in manufacture of the bulk drug and drug product have been found to be in compliance with good manufacturing procedures and are able to perform the production procedures specified in this NDA application.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Until the safety and effectiveness of this drug product has been established, we reserve comment on the proposed labeling.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Topical Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting should be requested at least 15 days in advance.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action, the Food and Drug Administration (FDA) may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

Should you have questions regarding this application, please contact Ms. Kennerly K. Chapman or Ms. Joanne A. Holmes of the Project Management Staff, at 301-594-4877.

Sincerely yours,

3/29/95 /s/

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-400
HFD-2/Lumpkin
HFR-PA200/LOS-DO
HFD-500
HFD-80
HFA-100
HFC-130
HFD-5
HFD-540
HFD-540/DDir/Wilkin
HFD-540/SMO/Chambers
HFD-540/MO/Labib
HFD-540/MO/Slifman
HFD-540/Chem/Rejali
HFD-540/Pharm/Sheevers/rd3/21/95
HFD-520/Micro/Utrup
HFD-426/Biopharm/Pelsor/rd/3/21/95
HFD-710/Biostat/Harkins
HFD-540/PMS/Chapman/n20400.na2

Concurrence only:

HFD-540/SChem/DeCamp/rd3/21/95; 3/24/95
HFD-540/ActSPharm/Jacobs/rd3/21/95
HFD-540/SPMS/Cook/rd3/20/95

Revised: Chambers 3/24/95
Revised: Chapman 3/27/95
NOT APPROVABLE

NDA 20-400

Penederm Incorporated
Attention: John Quigley, Ph.D.
Senior Vice President, Research and Development
320 Lakeside Drive , Suite A
Foster City, CA 94404

JAN 14 1997

Dear Dr. Quigley:

Please refer to your September 24, 1993, new drug application (NDA) and your resubmissions dated March 28, 1994, and July 12, 1996, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Avita™ (tretinoin gel) Gel, 0.025%.

Please refer to our not approvable letters dated March 29, 1995, and June 26, 1996.

We acknowledge the receipt of your amendments and additional communications dated May 31, June 3, 13 and 28, July 12 and 31, November 18 and 20, December 10, 12, 13 and 16, 1996, and January 2, 1997.

This new drug application provides for the treatment of acne vulgaris.

We have completed the review of this application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the enclosed revised draft labeling dated January 13, 1997. Accordingly, the application is tentatively approved under 21 CFR 314.105. This determination is contingent upon information available to the Agency at this time, and is therefore subject to change on the basis of new information that may come to our attention. The listed reference drug product upon which you base your application is subject to a period of patent protection. Therefore, final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3) may not be made effective until the period has expired, i.e., January 27, 1998. This action is based upon current information in your application.

At least 90 days prior to January 27, 1998, please submit an amendment to this application identifying changes, if any, in the conditions under which your product was tentatively approved. This information should include updated final printed labeling, and a safety update as appropriate. This submission should be designated as a minor amendment in your cover letter. In addition to, or instead of, the amendment requested above, the Agency may, at any time prior to the final date of approval, request that you submit an amendment containing the information described above.

Failure to submit any such amendment requested by the Agency will prompt a review of the application that may result in rescission of the tentative approval letter.

We remind you of your Phase 4 commitments specified in your submissions dated June 9, 1994, July 12, 1996, and in the facsimile of your letter dated January 14, 1997. These commitments, along with any completion date agreed upon, are listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, related to these Phase 4 commitments must be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Any significant change in the conditions outlined in this new drug application requires Agency review before final approval may be granted.

Prior to the issuance of the final approval letter by the Agency your product is NOT deemed approved and will not be included in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list published by the Agency. Should you believe that there are

grounds for issuing the final approval letter prior to January 27, 1998, you should amend your application accordingly.

The introduction or delivery for introduction into interstate commerce of this drug before the effective approval date is prohibited under section 301(d) of the Act (21 U.S.C. 331(d)).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Olga Cintron, R.Ph.
Project Manager
301-827-2020

Sincerely yours.

1/14/98 /S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA 20-400
HF-2/MedWatch (w/draft labeling)
HFD-2/MLumpkin (w/draft labeling)
HFD-92 (w/draft labeling)
HFD-105/OFFICE DIR/Weintraub (w/draft labeling)
HFD-540/DIV FILE (w/draft labeling)
HFD-540/CSO/Cintron (w/draft labeling)
HFD-540/MO/Labib (w/draft labeling)
HFD-540/CHEM/Mokhtari (w/draft labeling) 1-8-97
HFD-540/PHARM/Alam (w/draft labeling) 1-9-97
HFD-725/STAT/Farr (w/draft labeling) 1-8-97
HFD-880/BIOPHARM/Sun (w/draft labeling)
HFD-40 (w/draft labeling)
District Office (w/draft labeling)
HFD-613 (w/draft labeling)
HFD-735 (w/draft labeling)
HFD-005/Axelrad (w/draft labeling)

Concurrence:
HFD-540/PHARM TL/Jacobs (w/draft labeling) 1-9-97
HFD-540/CHEM TL/DeCamp (w/draft labeling) 1-8-97
HFD-540/SUPV PROJ MGR/Kozma-Fornaro (w/draft labeling)
HFD-880/BIOPHARM TL/Bashaw (w/draft labeling) 1-9-97
HFD-160/MICRO TL/Cooney (w/draft labeling) 1-8-97
HFD-560/Katz (w/draft labeling) 1/10/97
HFD-725/BIOSTAT TL/ Srinivasan (w/draft labeling) RS 1/01/09/97

TENTATIVE APPROVAL
PHASE 4 COMMITMENT

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 6, 1996

FROM: Nancy Sager, Team Leader, Environmental Assessment Team

SUBJECT: NDA 20-400 and 20-404

TO: Nahid Mokhtari-Rejali, Ph.D, HFD-540

The review and unsigned FONSI are being returned to you with the following comments:

Note: The EA reviewed is a desk copy received directly from Penderm dated May 31, 1996 (a fax copy of this submission was provided by the division). Confidential EAs provided by division are identified by page numbers 0 0433-0 0448 (NDA 20-404) and 0 0208-0 0221 (NDA 20-400).

EA:

1. Information has to be provided for the drug substance manufacturing site (format item 6). Since it is a foreign manufacturer, a certification of compliance is sufficient (see Industry Guidance for appropriate certification language).

2. On page 8 of the EA (last sentence) a compliance statement for is referenced but the compliance statement is not included.

3. There are no format items 12, 13 or 14 which are required for the abbreviated EA format for topical drugs (25.31a(b)(3)).

FONSI:
A minor revision is attached to this memo. The FONSI should be resigned since it appears to predate the submission by the applicant.

Note to the record:

Based on the production information provided in the EA the following amount of retinoic acid will be used:

Cream
(20400# x 0.1%) + (35700# x 0.05%) + (45900# x 0.025%) = 50 lbs of retinoic acid (~23 kg)

Gel
(34000# x 0.025) = 8 lbs (~4 kg)

c.c.
EA file NDA 20-400
EA file NDA 20-404

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
X 415-358-0101

PATENT INFORMATION

Penederm Incorporated pursuant to 21 U.S.C. § 355 (b) (1) herewith claims and certifies the following composition related to use patents for the Penederm topical tretinoin gel product which is the subject of this application.

U.S. Patent # 4,971,800	Expires - November 20, 2007
U.S. Patent # 5,045,317	Expires - November 3, 2008
U.S. Patent # 5,051,260	Expires - September 24, 2008

9/16/93
Date

Harris Goodman
Chairman and CEO
Penederm Incorporated

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

PENEDERM

PATENT CERTIFICATION

In the opinion of Penederm Incorporated and to the best of our knowledge, the following is an accurate account of all patents claiming gel compositions containing the listed drug substance, tretinoin, for which Patent Certification in accordance with 21 U.S.C. § 355 (b) (2) (A) must be provided.

Patent No.	3,729,568	Expired	April 24, 1990
Patent No.	4,247,547	Expires	January 27, 1998

Additionally, there is no exclusivity period listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for the listed drug. Therefore, no exclusivity exists.

Patent Certifications are provided on the following pages for the above referenced patents.

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

PENEDERM

PARAGRAPH A (II) CERTIFICATION

Penederm Incorporated certifies that Patent No. 3,729,568 expired on April 24, 1990.

9/16/93
Date

Harris Goodman, Ph. D.
Chairman and CEO
Penederm Incorporated

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

PENEDERM

PARAGRAPH A (IV) CERTIFICATION

Penederm Incorporated certifies that Patent No. 4,247,547 will not be infringed by the manufacture, use, or sale of Acticin™ (tretinoin) Gel, 0.025% for which this application is submitted.

Furthermore, Penederm Incorporated will provide notice to each owner of Patent No. 4,247,547 and to the holder of the approved application for Retin-A® (tretinoin) Gel, 0.025% in accordance with 21 U.S.C. § 355 (b) (3) (A) and (B).

9/16/93
Date

Harris Goodman
Harris Goodman, Ph.D.
Chairman and CEO
Penederm Incorporated

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

PENEDERM

DEBARMENT STATEMENT

Penederm Incorporated herewith certifies that the services of any persons debarred under Section 306 (a) or (b) were not and will not be used in any capacity, in conjunction with this application.

Signed: _____ Date: 9/16/93

John W. Quigley, Ph.D.
Vice-President
Research and Development

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-400 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Avita (tretinoin gel) Gel, 0.025% Action: (AP) AE NA

Applicant Penederm Therapeutic Class 35

Indication(s) previously approved acne vulgaris

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application _____

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

X 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form. Pediatric patients down to age 13 were studied Acne is not common below 13 years of age. The procedure is the same as in those 7 18 years old.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

_____ _____ January-20-98.

Signature of Preparer and Title (PM, CSO, MO, other) Date

1/28/98

cc: Orig NDA/PLA #: 20-400
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

FULL APPROVAL

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

The drug needs to be investigated in the [illegible]
age bracket of the pediatric population (e.g. 7-14 years of age)
:) pathophysiological processes mimic that of the adult
population.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-400 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Avita (tretinoin gel) Gel, 0.025% Action: (AP) AE NA

Applicant Penederm Therapeutic Class 5S

Indication(s) previously approved ACNE VULGARIS

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application _____

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4 NA 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

4 NA 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form. Pediatric patients down to age 13 were studied. Acne is not common below 13 years of age. The process is the same as in those > 18 years.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

_____ _____

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # [illegible]
HF[illegible] /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

1/14/9

Tent. Approv

NOTE: **A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**

5/95

The drug needs to be investigated in the upper age bracket of the pediatric population (EG., > 14 YEARS OF AGE) the pathophysiological processes mimic that of the adult population.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-402 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: AVITA (TRETINOIN 0.05%) GEL Action: AP AE NA

Applicant PERIDERM Therapeutic Class _____

Indication(s) previously approved _____

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___ N/A

Indication in this application ACNE VULGARIS

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written request to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

_____ 6/25/96 6/21/96 _____

Signature of Preparer and Title (PM, CSO, MO, other)

6/26/96

cc: Orig NDA/PLA # 20-402
HFD-540/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

THE DRUG ~~SHOULD~~ DOES NOT NEED TO BE INVESTIGATED IN THE UPPER AGE BRACKET OF THE PEDIATRIC POPULATION (E.G., > 14 YEARS OF AGE) IF THE PATHOPHYSIOLOGICAL PROCESSES MIMIC THAT OF THE ADULT POPULATION.

6/26/96

June 2, 1996

NDA 20-400 and 20-404, Avita Gel and Avita Cream

The Pharmacology review of March 3, 1996, by Dr. Hilary Sheevers reiterates the remaining pharmacology (CAC) issues initially addressed in the August 22, 1994, pharmacology review by Dr. Sheevers. These CAC issues were sent to the sponsor by facsimile on April 6, 1996, and are reiterated in the non-approval letters dated June, 26, 1996, for both of these NDAs.

6/20/96

2

MAY 12 1994

Review and Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products (HFD-540)

NDA 20-400 (original Submission, dated 3/28/9)

Drug Name: Acticin Gel, 0.025%

Category: Anti-acne

Sponsor: Penderm Inc.,

Number of Vols.: 7

Date CDER Received: 3/29/94

Date Assigned: 4/15/94

Date Review Started: 5/11/94

Date 1st Draft Completed: 5/11/94

Date Review Accepted by Supervisor: 5/11/94

Note: This is a memorandum of a telecon with Mr. Barry Calvarese. I asked him about his failure to address the carcinogenicity study with the gel product as a phase IV study. His answer was that the subject was not presented as a question; it was rather a statement. When I explained that it is a question that needs to be addressed by him, preferably before the fileability date, he said that he did not think it needed an answer at this time. They are still planning to ask for a waiver. He also said that he talked to Dr. Lumpkin at a Meeting in San Francisco, and, according to Mr. Calvarese, Dr. Lumpkin had said that it would not be necessary to do a dermal carcinogenicity study.

I have no idea how the question was placed to him. It is conceivable that Dr. Lumpkin said something that was misinterpreted.

I told Mr. Calvarese that I do think the issue is important, and

needs to be addressed at this time or as soon as possible. At his request, I agreed to ask Ms. Cook to explain to him the issue of a commitment on his part to the recommended study would be necessary before the approval of the Application, if and when it is approved.

/S/ Syed N. Alam, Ph.D.
Pharmacologist

cc:
HFD-340
HFD-502/
HFD-540/ 5/12/94
HFD-540/Pharm/Alam
HFD-540/MO/Labib
HFD-520/Micro/
HFD-540/Chem/Rejali
HFD-540/CSO/Cook
HFD-540/f/t init by SAlam 5/11/94

Memo to File

NDA 20-400/20-404 (Labeling) December 26/1996

Subject: Review of the proposed draft labeling for Avita[R]

In the proposed draft labeling, both the Carcinogenicity and the Pregnancy sections need revisions. Clearly, the Sponsor has used the labeling for Retin-A as a model for this proposed labeling for Avita, the obvious reason being a common active ingredient in both the preparations, namely, the all-trans-retinoic acid (tretinoin). However, since the marketing of Retin-A about 25 years ago, much new information on reproductive toxicity of tretinoin has become available. Thus, the statement that

is not true anymore. Also, it is necessary to clearly differentiate the oral and topical teratogenic effects of tretinoin in various species. Most of this new information has been included in the labeling of Renova[R], another formulation containing tretinoin as the active ingredient. The labeling of the present formulation should follow that of Renova and not of Retin-A. It is to be noted that the Sponsor is committed to performing a

study as a phase 4 study. The following changes in the labeling are proposed.

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

There are, however, no adequate and well-controlled studies in pregnant women. Avita should not be used during pregnancy.

/S/

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/TL/Concur/Jacobs 12/31/96

cc:

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TLPharm/Jacobs

HFD-540/MO/Labib

HFD-540/Chem/Rejali

HFD-540/CSO/Blatt

ANDA: 74-071, -238, -239, -240

MEETING WITH SPONSOR
MEETING DATE: April 4, 1993

0.025% TRETINOIN GEL

Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404

REVIEWER: Ene Ette, M.S., Ph.D.

==========

BIOPHARM. ISSUES:

The Division of Biopharm. recommends that the Sponsor should carry out a pharmacokinetic study in healthy volunteers to determine the penetration of tretinoin. Given the variability in the population at large (and blood supply to the skin in the in vivo system), in vitro studies cannot completely predict the in vivo situation.

The Sponsor should also provide evidence via simulation using physiologically-based modelling to evaluate fetal exposure of all-trans retinoic acid.

Ene Ette, M.S., Ph.D.

FT initialed by N. Fleischer, M.S.,Ph.D. 4/27/93

cc: ANDA 74-071, -238, -239, -240, HFD-520 (Clinical Division), HFD-426 (E. I. Ette, N. Fleischer), Chron, Drug, Reviewer's file.

MEMO OF TELECONFERENCE

Meeting Date: 12/12/96 Time: 2PM Location: N-238

Sponsor: Penederm, Inc.

NDA: 20,400 and 24,404

Meeting Type: Telecon regarding labeling

Meeting Chair: Nahid Mokhtari-Nejali/Chemistry Reviewer/ HFD-540

Meeting Recorder: Robin Anderson/Project Manager/HFD-540 RA

FDA Attendees:
HFD-540:
Robin Anderson, Project Manager
Nahid Mokhtari-Nejali/Chemistry Reviewer/

Sponsor Attendees:
Bhaskar Chaudhrin

Subject: Labeling

Sponsor advised to add to the label.

Sponsor agreed to fax statement of understanding regarding this issue to Robin Anderson.

cc:
NDA 20,400
NDA 20,404
HFD-540/Division file
HFD-540/Mokhtari-Nejali
HFD-540/Blay

MEMORANDUM OF A TELECONFERENCE CONVERSATION

November 4, 1996

Between: Bhaskar Chauduri, Director, Pharmaceutical Sciences
(415)-638-3017

And: Nahid Mokhtari-Rejali, Ph.D., Chemist
HFD-540

Subject: Update EA Package

On May 4, 1996, I called Bhaskar to ask him to provide the full package of environmental assessment. He promised to send the package in two weeks.

Consult #602 (HFD-540)

AVITA tretinoin gel and cream

The LNC found no look alike/sound alike conflicts nor misleading aspects in the proprietary name.

The LNC has no reason to find the proposed proprietary name unacceptable.

/S/ _____ 5/23/96 . Chair
CDER Labeling and Nomenclature Committee

Minutes of Teleconference

Date: ~~May~~ 6, 1996, 3:45PM
Sponsor: Penederm
Agent: Acticin Gel, NDA 20-400
Purpose: Convey Exec. CAC Recommendations and Suggestions

FDA Attendees:

Hillary Sheevers, Ph.D., Pharmacologist
Roy Blay, Ph.D., Consumer Safety Officer

Sponsor Attendees:

Greg Wagner, Regulatory Affairs

Dr. Sheevers pointed out that the recommendations were items that the Exec. CAC believes should be incorporated into the protocols while the suggestions were items that were worthy of consideration but would not necessarily have to be incorporated into the protocols.

Recommendations:

Mid and low doses should be at 1/3 and 1/9 of the high dose. Dr. Sheevers recognized the potential for irritation at certain doses and said that it had been a point of discussion by the CAC.

Dr. Sheevers noted that all formulations should be prepared in the clinically used vehicle. Also, physical exams should be performed on the animals prior to initiation of the study. A minimal survival rate should be determined prior to the study; i.e., at what mortality level should the study be terminated (a statistician should be consulted).

Suggestions:

Two additional controls were also suggested: (1) an untreated control, and (2) a vehicle control without polyoprepolymer-2. Inclusion of these controls would make for a 6-arm study.

The sponsor should collect laboratory data on AST, ALT glucose, and BUN values. Blood samples should be collected and examined at baseline.

Lung, liver thymus, kidney, skin, and heart specimens should be collected from all dosing groups and examined. Organs from the high and low dose groups should be examined histopathologically.

The discussion ended with Dr. Sheevers indicating her willingness to discuss any and all issues related to the comments from the CAC. Specific formal commentary by the sponsor should be submitted to the IND.

The conversation ended amicably.

The CAC comments will be faxed to Mr. Wagner.

Ack: HSheevers, 3.5.96

cc:
NDA Arch
NDA 20-400
HFD-540/Sheevers/Blay

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: June 2, 1994

FROM: Kennerly K. Chapman, Project Manager, HFD-521
(301) 443-0257

TO: Barry Calvarese, Regulatory Affairs

SUBJECT: Acticin Cream/Gel

IND/NDA: NDA 20-400, 20-404

SPONSOR: Penederm

Subsequent to our June Pre-Rounds meeting this Project Manager contacted Mr. Calvarese to request the following:

Clinical:
(Gel)
1. CRF's on 9 patients (study 003) that were given antibiotics and considered "evaluable" Numbers:

2. Racial Demographics on patients do not appear in the NDA or on the CRF. If the sponsor does not have this information already on file, then we would request that they go back to the individual PI to get this information off the records. This is a safety issue, and, does not necessarily have an impact on the efficacy of the product.

Comment: Mr. Calvarese stated that racial demographics is routinely done, however, would call back to clarify where this information may be obtained.

Statistics:

1. A 'Last observation forward' analysis is not contained in the NDA. This needs to be submitted.

Comment: Mr. Calvarese indicated he would contact Beth Turney to get specifics from her and clarify what study(ies) she was referring to in this request. Additionally, 4 disks are being sent in response to an earlier request from B. Turney. The enrollment date previously excluded from the March 1994 amendment will be submitted. (ref. #15D in RF letter.)

Pharmacology:
(Cream)

1. Additional information (internal specs, characterization, etc.) on the exipients: PDT-002-002 and PDT-002-001.

2. Phase IV commitment letter on the studies to be conducted should be submitted.

Comment: Mr. Calvarese agreed to submit this by the 30 June 1994.

Biopharm:

1. A copy of the submission prior to the RF letter (reviewer shredded) should be submitted for review.

Comment: A commitment was made to submit this by 13 June 1994.

The conversation ended cordially.

cc:
Orig NDA 20-400 (20-404)
HFD-540
HFD-540/MO/Slifman
HFD-540/Pharm/Sheevers
HFD-540/Chem/Rejali
HFD-540/Micro/King
HFD-540/Stat/Turney
HFD-540/Biopharm/Sun
HFD-540/PMS/Chapman 6/16/94