CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-400

CORRESPONDENCE

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

ORIGINAL

PENEDERM

ORIG AMENDMENT

RS

March 28, 1994

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-520, Room 12B-45
Rockville, MD 20857

RE: New Drug Application 20-400
For: Acticin™ (tretinoin) Gel, 0.025%

Dear Dr. Lumpkin:

Pursuant to Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Section 314.50, Penederm Incorporated herewith submits responses to the deficiencies and questions cited in your letter dated November 23, 1993. The new drug product contains the active drug substance, tretinoin, at a concentration of 0.025%, in an ethanolic gel vehicle. Previous information concerning this formulation has been submitted to the Agency under New Drug Application #20-400, Investigational New Drug Application (IND)
Abbreviated New Drug Application (ANDA)

Eight copies of this seven-volume resubmission are being provided at the request of the Agency. The volumes have been labelled for distribution as follows:

- Archival Copy
- Chemistry Copy
- Microbiology Copy
- Biostatistics Copy
- Nonclinical Pharmacology/Toxicology Copy
- Biopharmaceutics Copy
- Clinical Copy
- Desk Copy

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Your prompt review of this document is appreciated. Please contact Barry M. Calvarese, M.S., Executive Director, Regulatory Affairs for further information regarding this application.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Regulatory Affairs
Penederm Incorporated

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
358-0100
415-378-6488

PENEDERM

October 28, 1997

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: **NDA #20-400, Avita™ Gel, 0.025% - Minor Amendment**
Updated Final Printed Labeling and Safety Update

Dear Dr. Wilkin:

Reference is made to your letter dated January 14, 1997, granting tentative marketing clearance to Avita™ (tretinoin gel) Gel, 0.025% for the treatment of acne vulgaris. That letter specified that a minor amendment containing final printed labeling and a safety update should be submitted to the Agency at least 90 days before January 27, 1998.

Reference is also made to our minor amendment of May 9, 1997 which contained our proposed revised package insert and patient instructions. No additional changes have been made to the current proposed labeling.

With regard to a safety update, Penederm has not performed any new studies with Avita Gel, 0.025%. There is no new information available on the product.

This letter is submitted in triplicate. Please call me at 650-638-3008 if you have any questions or comments.

Sincerely,

John W. Quigley, PhD
Senior Vice President
Research and Development

desk copy: Olga Cintron, RPh

ORIGINAL

ORIG AMENDMENT

A2

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

PENEDERM

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

July 12, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Tretinoin Gel 0.025% (Avita™)
Response to Nonapprovable Letter dated June 26, 1996

Dear Dr. Wilkin:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Section 314.120, Penederm Incorporated herewith submits an NDA amendment to address the responses to the deficiencies and comments cited in your NDA nonapprovable letter dated June 26, 1996.

Penederm believes that all outstanding issues have been addressed, and that there is no valid scientific or regulatory reason for the agency to withhold approval of Avita Gel 0.025%. Penederm has responded to all of the comments pertaining to Chemistry, Manufacturing, and Controls, and pertaining to the Carcinogenicity Advisory Committee Recommendations.

Following the recommendation of the Agency, an additional clinical study has been performed, consisting of three treatment arms (Avita Gel 0.025%, Retin-A Gel 0.025%, and Vehicle Gel). This study, included in this submission, provides another well-controlled and independent study demonstrating evidence of clinical superiority of Avita Gel over Vehicle Gel. Penederm believes that this study provides substantial evidence that Avita Gel will have the effects that are represented in the proposed labeling. Also, following the recommendation of the Agency, in this clinical study, adverse events as related to race were monitored.

As previously described in a June 9, 1994 letter to Dr. Lumpkin, Penederm is committed to the initiation of a Phase 4 dermal study of tretinoin gel within four months after final approval of both the gel and cream formulations.

Six copies of Penederm's response are being provided:

FDA Archive	FDA Pharmacology/Toxicology
FDA Clinical	FDA Chemistry, Manufacturing, and Controls
FDA Statistical	FDA Desk Copy

Included in each of the above copies is a disk containing the Clinical/Statistical Report for Clinical Study PDC 004-022 in WordPerfect® 5.1 format (Volume 1).

Note: The conversion of documents from Microsoft Word 6.0 for the Macintosh to DOS WordPerfect 5.1 may result in distortion of some graphic elements. However, all text should be readable and identical to the hard copies provided.

Also included in the FDA Archive and FDA Statistical copies is a disk containing the SAS data sets for Clinical Study PDC 004-022. The SAS data disk may be found in the Clinical/ Statistical Report, Section 5, Appendix C.12, Data Management User's Guide (Volume 10). All statistical calculations were performed on PC-compatible computers containing Intel Pentium chips (free of the floating point error present in earlier versions of the Pentium chip).

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the applicable provisions of 18 USC, Section 331(j) and/or 21 CFR 312.130.

Sincerely yours,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

RESPONSE TO CLINICAL COMMENTS

As recommended by the Agency, Penederm Incorporated has completed a new clinical trial, PDC 004-022, consisting of three treatment arms (Avita Gel, Retin-A Gel, and Vehicle). Six hundred seventy-five patients were enrolled in Clinical Study PDC 004-022, where efficacy and cutaneous tolerance were assessed at Baseline and Days 7, 14, 28, 56, and 84. In addition, this clinical trial monitored adverse events as they related to race.

The submitted information now includes two independent, well-controlled investigations (PDC 004-003 and PDC 004-022) providing substantial evidence that Avita Gel will have the effects as represented in the proposed labeling. Both pivotal studies clearly show statistically significantly greater reductions than Vehicle in the mean percent improvement for all three lesion parameters after 12 weeks of treatment (Day 84). Furthermore, in both studies, the lesion count improvements are paralleled by a significantly better response than Vehicle in Physician Global Assessment. These significant findings are observed in all four primary efficacy parameters and are maintained in both the Per Protocol (± 3-day window for Day 84 visit) and ITT-LOCF populations for both studies.

With regard to Clinical Study PDC 004-022, a Per Protocol analysis using a ± 7-day window for the Day 84 visit was conducted and no differences between the ± 3-day Per Protocol population were observed. Therefore, the ± 7-day Per Protocol data is not presented in the integrated clinical/statistical report but is provided on the SAS data disk.

Please note that three of the clinical sites were located in Canada. Penederm shared the sponsorship and monitoring responsibility for these sites with Penederm's Canadian distributor, located in Montreal. Also, please note that there is inconsistent use of conventions for dating documents at the Canadian sites. Although most investigators used a numerical system typical of that used in the United States, in which the month is given first, followed by the day, and then the year (e.g., 12/05/95), some investigators used a numerical system in which the day is given first, followed by the month, and then the year (e.g., 5/12/95).

With regard to the updated safety report, the only new information available since the last submission is the adverse event data from Clinical Study PDC 004-022, summarized in the following tables. Please refer to the integrated clinical/statistical report for PDC 004-022 for additional data related to new safety information.

Table 1
Avita Gel 0.025% Safety Information Update

Clinical Study PDC 004-022
Adverse Events Possibly, Probably, or Definitely
Related to Treatment (N = 218)

Adverse Event	Number of Patients with AE	Number of AE	Severity		
			Mild	Moderate	Severe
Total	46	102	19	79	4
Cyst	1	1	0	1	0
Application Site Reaction	45	99	17	78	4
Contact Dermatitis	1	1	1	0	0
Blepharitis	1	1		0	0

Table 2
Avita Gel 0.025% Safety Information Update

Clinical Study PDC 004-022
Patients Terminating Early Due to an Adverse Event (N = 218)

Number of Patients	Adverse Event	Severity
1	Application Site Reaction:	
	Facial Burning	Severe
	Facial Dryness	Moderate
	Facial Peeling	Moderate

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

PENEDERM

December 13, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ Gel 0.025%
NDA #20-404, Avita™ Cream 0.025%, 0.05%, and 0.1%
Storage Conditions

Dear Dr. Wilkin:

This letter is to summarize the discussions of yesterday morning with Dr. Nahid Rejali, Ms. Robin Anderson, and myself regarding the storage conditions for Avita Cream and Avita Gel.

As mentioned in the conversation, Penederm agrees to modify the storage statement in the labeling by including the words, The modified labeling for both products will read as follows:

Please do not hesitate to call us if additional clarification is required.

Sincerely,

Bhaskar Chaudhuri, PhD
Executive Director
Pharmaceutical Sciences

copy: Ms. Robin Anderson
Dr. Nahid Rejali

ORIGINAL

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

BL
NDA ORIG AMENDMENT

PENEDERM

May 9, 1997

NDA NO. _____ REF NO. _____
NDA SUPPL FOR _____

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: **NDA #20-400, Avita™ Gel, 0.025% - Minor Amendment**
Proposed Revised Package Insert and Patient Instructions

Dear Dr. Wilkin:

Reference is made to your letter dated January 14, 1997, granting tentative marketing clearance to Avita™ (tretinoin gel) Gel, 0.025% for the treatment of acne vulgaris. There are several changes which the Sponsor wishes to make in the Package Insert and Patient Instructions; these proposed changes are the subject of this amendment.

Included in this submission are:

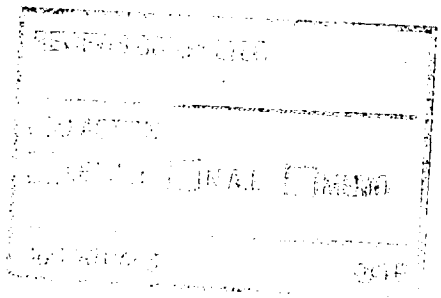
1. Form FDA 356h
2. Form FDA 3397
3. The current Package Insert and Patient Instructions (from FDA), with numbered lines
4. Summary of proposed changes to the Package Insert and Patient Instructions
5. The proposed revised Package Insert and Patient Instructions (PN308.01A) and a disk copy in WordPerfect® 5.1 format
6. The proposed revised Package Insert and Patient Instructions, with numbered lines

This amendment is submitted in triplicate. Please call me if you have any questions or comments about this submission.

Sincerely,

John W. Quigley, PhD
Senior Vice President
Research and Development

cc: Ms. Olga Cintron, RPh



ORIGINAL

RM INCORPORATED
RIDGE DRIVE, SUITE A
, CA 94404

-358-0101

PENEDERM

January 24, 1997

NEW CORRESPONDENCE

CENTER FOR DRUG
REC'D
JAN 27 1997
MEGA DOC RM
EVALUATION AND RESEARCH

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ Gel 0.025%
NDA #20-404, Avita™ Cream 0.025%

Dear Dr. Wilkin:

The letters listed below (originals attached) were sent to Ms. Olga Cintron via fax on the actual dates of the correspondence. However, the originals were not submitted at that time.

- Letter dated 1/13/97 for NDA #20-400 and NDA #20-404: Penederm's agreement with the Labeling and Patient Instructions for both NDAs.
- Letter dated 1/13/97 for NDA #20-400 and NDA #20-404: Penederm's commitment to initiate a Phase 4 study with Avita Gel 0.025% (NDA #20-400) after final approval and to submit the data to NDA #20-404.
- Letter dated 1/14/97 for NDA #20-400: Penederm's commitment to further develop Analytical Method for tretinoin degradation products.
- Letter dated 1/14/97 for NDA #20-404: Penederm's commitment to further develop Analytical Method for tretinoin degradation products.

This correspondence is submitted in triplicate. Should you have any questions or require additional information, please call me at 415-638-3017.

Sincerely,

Bhaskar Chaudhuri, PhD
Executive Director
Pharmaceutical Sciences

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

PENEDERM

NEW CORRESPONDENCE

January 14, 1997

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room # N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA # 20-400, Avita™ Gel 0.025%

Dear Dr. Wilkin:

As stated in our correspondence to FDA dated June 26, 1996, based on the suggestion of the Agency, Penederm is committed to further develop Analytical Method to cover the tretinoin degradation products as part of a Phase IV study. This will encompass photo-isomerization, autoxidation, and photo-oxidation products in the tretinoin gel.

Results from the study will be submitted as part of the Annual Report to the Avita Gel NDA (# 20-400).

Should you have any questions or require additional information, please call me at 415-638-3017.

Sincerely,

Bhaskar Chaudhuri, Ph.D.
Executive Director
Pharmaceutical Sciences

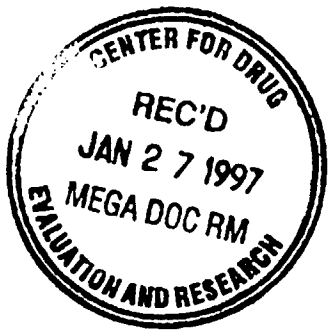
REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

PENEDERM



January 13, 1997

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room # N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA # 20-400, Avita™ Gel 0.025%
NDA # 20-404, Avita™ Cream 0.025%

Dear Dr. Wilkin:

Based on our initial review, Penederm agrees with the Labeling and the Patient Instructions, as supplied to us, for both the Avita Gel (NDA # 20-400) and also the Avita Cream (NDA # 20-404).

Should you have any questions or require additional information, please call me at 415-638-3017.

Sincerely,

Bhaskar Chaudhuri, Ph.D.
Executive Director
Pharmaceutical Sciences

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

PENEDERM

NEW CORRESPONDENCE

January 13, 1997

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room # N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA # 20-400, Avita™ Gel 0.025%
NDA # 20-404, Avita™ Cream 0.025%

Dear Dr. Wilkin:

As stated in our correspondence to FDA dated June 9, 1994, Penederm is committed to initiating a Phase 4 with Avita™ Gel 0.025% after final approval.

Upon completion of the carcinogenicity study, Penederm commits to submit the final report to the Avita Gel NDA (# 20-400) and also the Avita Cream NDA (# 20-404).

Should you have any questions or require additional information, please call me at 415-638-3017.

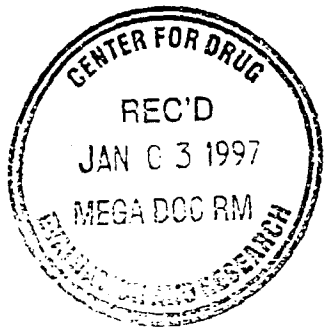
Sincerely,

Bhaskar Chaudhuri, Ph.D.
Executive Director
Pharmaceutical Sciences

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

DERM INCORPORATED
ESIDE DRIVE, SUITE A
CITY, CA 94404
58-0100
415-358-0101

ORIGINAL
NEW CORRESP
IC



January 2, 1997

Jonathan Wilkin, MD, Director
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ Gel 0.025%
Patent Certification Amendment (IV to III)

Dear Dr. Wilkin:

In accordance with 21 CFR Sections 314.94 (a)(12)(i)(A)(3) and (viii), Penederm Incorporated ("Penederm") submits this amended certification from Paragraph IV to III concerning Patent No. 4,247,547 covering the referenced listed drug, tretinoin, Retin-A. Penederm certifies that the patent for the referenced listed drug, Retin-A, expires on January 27, 1998 and that Penederm does not intend to market Avita Gel in interstate commerce prior to January 28, 1998.

Sincerely,

John W. Quigley, PhD
Senior Vice President
Research and Development

PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
415-358-0100
AX 415-358-0101

PENEDERM

December 16, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ (tretinoin) Gel 0.025%
Revised Nonconfidential Environmental Assessment

Dear Dr. Wilkin:

Pursuant to discussions with Ms. Mary Jean Fornaro and Dr. Tony DeCamp, Penederm Incorporated is submitting a revised Nonconfidential Environmental Assessment for NDA #20-400. These modifications do not change the essence of the environmental assessment in any way.

This information is submitted in triplicate. Please contact us if you have any questions or require additional information for this application.

Sincerely,

John Quigley, PhD
Senior Vice President
Research and Development

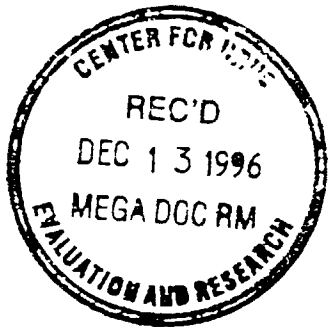
Desk Copy: Dr. Tony DeCamp

DERM INCORPORATED
AKESIDE DRIVE, SUITE A
ER CITY, CA 94404
58-0100
15-378-6488

ORIGINAL

NEW CORRESPONDENCE

December 12, 1996



Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ Gel 0.025%
NDA #20-404, Avita™ Cream 0.025%, 0.05%, and 0.1%
Disk Copies of Patient Instructions

Dear Dr. Wilkin:

Penederm Incorporated has sent a disk under separate cover to Mr. Hal Blatt which contains electronic copies of the Patient Instructions for Avita Gel 0.025% and Avita™ Cream 0.025%, 0.05%, and 0.1% in WordPerfect® 6.1 for Windows '95 format.

If you have any questions or require additional information, please call me at 415-638-3008.

Sincerely,

John Quigley, PhD
Senior Vice President
Research and Development

desk copy: Mr. Hal Blatt

FILE/NEWS COMPLETED

DOC ACTION:
LETTER

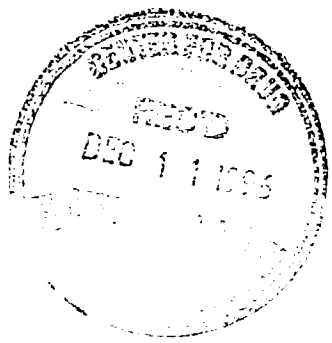
INITIALS DATE

ORIGINAL

PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
TER CITY, CA 94404
358-0100
415-358-0101

PENEDERM

NEW CORRESPONDENCE



December 10, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ Gel 0.025%
NDA #20-404, Avita™ Cream 0.025%, 0.05%, and 0.1%
Disk Copies of Package Insert Labeling

Dear Dr. Wilkin:

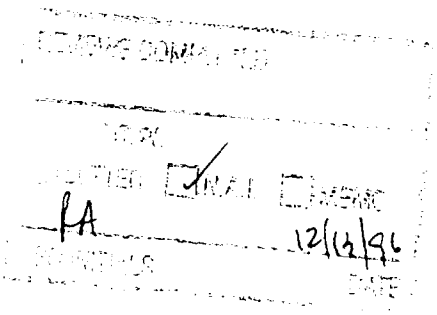
Penederm Incorporated has sent a disk under separate cover to Mr. Hal Blatt which contains electronic copies of the Package Insert for Avita Gel 0.025% and the Package Insert for Avita™ Cream 0.025%, 0.05%, and 0.1% in WordPerfect® 6.1 for Windows '95 format.

If you have any questions or require additional information, please call me at 415-638-3008.

Sincerely,

John Quigley, PhD
Senior Vice President
Research and Development

desk copy: Mr. Hal Blatt



ORIGINAL

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

PENEDERM

November 20, 1996

BC

NDA ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ (tretinoin) Gel 0.025%
Environmental Assessment (Confidential and Nonconfidential)

Dear Dr. Wilkin:

At the request of the Agency, Penederm Incorporated is submitting an updated Environmental Assessment for NDA #20-400. Two versions of the Environmental Assessment are provided; one is confidential; and one is nonconfidential.

This information is submitted in triplicate. We consider all the information contained in this application proprietary. Please be advised that the confidentiality of the enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Please contact us if you have any questions or require additional information for this application.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

Desk Copy: Dr. Nahid Rejali (Room N238)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
5-358-0100
X 415-358-0101

PENEDERM

NEW RSLahiri 11/23/96

November 18, 1996

CENTER FOR DRUG REC'D NOV 19 1996 MEGA DOC RM EVALUATION AND RESEARCH

NEW CORRESPONDENCE

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ Gel 0.025%
Disk Copies of PDC 004-022 Final Report

Dear Dr. Wilkin:

Penederm Incorporated has sent two disks under separate cover to Dr. Roy Blay which contain electronic copies of Clinical Study Report PDC 004-022 in the following formats:

- 004-022.W51 WordPerfect 5.1 for DOS
- 004-022.DOS MS-DOS Text
- 004-022.WPW WordPerfect 5.x for Windows
- 004-0022.MAC Microsoft Word 6.0.1 for the Macintosh (separate disk)

If you have any questions or require additional information, please call me at 415-378-6479.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

copy to: Dr. Roy Blay

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

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

ORIGINAL
ORIG AMENDMENT
AE

PENEDERM

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

July 12, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Tretinoin Gel 0.025% (Avita™)
Response to Nonapprovable Letter dated June 26, 1996

Dear Dr. Wilkin:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Section 314.120, Penederm Incorporated herewith submits an NDA amendment to address the responses to the deficiencies and comments cited in your NDA nonapprovable letter dated June 26, 1996.

Penederm believes that all outstanding issues have been addressed, and that there is no valid scientific or regulatory reason for the agency to withhold approval of Avita Gel 0.025%. Penederm has responded to all of the comments pertaining to Chemistry, Manufacturing, and Controls, and pertaining to the Carcinogenicity Advisory Committee Recommendations.

Following the recommendation of the Agency, an additional clinical study has been performed, consisting of three treatment arms (Avita Gel 0.025%, Retin-A Gel 0.025%, and Vehicle Gel). This study, included in this submission, provides another well-controlled and independent study demonstrating evidence of clinical superiority of Avita Gel over Vehicle Gel. Penederm believes that this study provides substantial evidence that Avita Gel will have the effects that are represented in the proposed labeling. Also, following the recommendation of the Agency, in this clinical study, adverse events as related to race were monitored.

As previously described in a June 9, 1994 letter to Dr. Lumpkin, Penederm is committed to the initiation of a Phase 4 study of tretinoin gel within four months after final approval of both the gel and cream formulations.

Six copies of Penederm's response are being provided:

FDA Archive	FDA Pharmacology/Toxicology
FDA Clinical	FDA Chemistry, Manufacturing, and Controls
FDA Statistical	FDA Desk Copy

Included in each of the above copies is a disk containing the Clinical/Statistical Report for Clinical Study PDC 004-022 in WordPerfect® 5.1 format (Volume 1).

Note: The conversion of documents from Microsoft Word 6.0 for the Macintosh to DOS WordPerfect 5.1 may result in distortion of some graphic elements. However, all text should be readable and identical to the hard copies provided.

Also included in the FDA Archive and FDA Statistical copies is a disk containing the SAS data sets for Clinical Study PDC 004-022. The SAS data disk may be found in the Clinical/ Statistical Report, Section 5, Appendix C.12, Data Management User's Guide (Volume 10). All statistical calculations were performed on PC-compatible computers containing chips

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the applicable provisions of 18 USC, Section 331(j) and/or 21 CFR 312.130.

Sincerely yours,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

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

ORIGINAL
NEW CORRESP
NO

PENEDERM

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS DATE 7/31/96

June 28, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 0 1 1996
HFD-

Re: NDA #20-400, Tretinoin Gel 0.025% (Avita™)

Dear Dr. Wilkin:

Penederm Incorporated acknowledges the receipt of your June 26, 1996 nonapprovable letter regarding the above-referenced drug product. Pursuant to 21 CRF 314.20, we are providing notification of our intent to file an amendment. We expect to submit the amendment within the next three (3) weeks.

We consider all the information contained in this letter proprietary and confidential. This letter is submitted in triplicate.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

ORIGINAL

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

PENEDERM

June 13, 1996

BC
NDA ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Tretinoin Gel 0.025% (Avita™)

Dear Dr. Wilkin:

At the request of Dr. Nahid Rejali (Reviewing Chemist), we are providing the following information:

1. Revised Quality Standards for Tretinoin Drug Substance and Finished Product
2. Methods for Tretinoin Drug Substance and Finished Product, BHT, and Ethanol
3. Method Validation Reports for the above Methods
4. Studies Performed on the Degradation Products

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the applicable provisions of 18 USC, Section 331(j) and/or 21 CFR 312.130.

This information is submitted in triplicate. Please call me at 415-378-6479 if you have any questions or require additional information.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

Desk Copy: Dr. Tony DeCamp

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

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

PENEDERM

June 3, 1996

BC
NDA ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Tretinoin Gel 0.025% (Avita™)

Dear Dr. Wilkin:

At the request of Dr. Nahid Rejali (Reviewing Chemist) on May 31, 1996, we are providing the following information:

1. Finished Product Specifications

   An overview summarizing revisions to the finished product specifications is provided. The current, revised Finished Product Release and Stability Quality Standards are also included.

2. 18-Month Stability Data

   Current stability data for Lots HKC, HKD, and HKE which include the 18-month time point are provided. Please note that specifications in the stability tables reflect the earlier version of the Quality Standard.

This information is submitted in triplicate. Please call me at 415-378-6479 if you have any questions or require additional information.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
[illegible]58-0100
FAX 415-358-0101

ORIGINAL
NEW CORRESP
NC

PENEDERM

May 31, 1996

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Tretinoin Gel 0.025% (Avita™)

Dear Dr. Wilkin:

At the request of Dr. Nahid Rejali (Reviewing Chemist), we have provided the following information:

1. Statement for Withdrawal of Non-Conforming Batches

   This statement was provided in the original submission dated 9/24/93 (page 2-0247). A copy is also included in this package.

2. Description of Crimps

   This information was provided in the amendment dated 12/16/94 (page 0-0083). A copy is also included in this package.

3. Revised Non-Confidential Environmental Assessment

   The current, revised Non-Confidential Environmental Assessment dated May 30, 1996 is provided in this package.

This information is submitted in triplicate. Please call me at 415-378-6479 if you have any questions or require additional information.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

CENTER FOR DRUGS
REC'D
JUN 03 1996
HFD
EVALUATION AND RESEARCH

PENEDERM INCORPORATED
220 LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
-358-0100
415-358-0101

PENEDERM

May 9, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Tretinoin Gel 0.025% (Avita™)

Dear Dr. Wilkin:

At the request of Mr. Peter Cooney (reviewing Microbiologist) on May 8, 1996, please find enclosed the Microbial Limits test results for Tretinoin Gel 0.025%, Lot Numbers 73026, 73798, and 75735.

Please call me at 415-378-6479 if you have any questions or require additional information.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

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

PENEDERM
DUPLICATE
NEW CORRESP

February 22, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-400, Avita™ (Tretinoin) Gel 0.025%
NDA #20-404 Avita™ (Tretinoin) Cream 0.025%, 0.05%, 0.1%

Dear Dr. Wilkin:

The purpose of this letter is to address the approvability of NDA #20-400 and NDA #20-404. As you know, both NDAs have been subjected to a protracted five-year review process that has vacillated between the Generic Drug Division and the Division of Dermatologic and Ophthalmologic Drug Products Division. The two March 1995 nonapprovable letters for these NDAs were vague in reference to past agreements between Penederm and the agency regarding the path to approval for these drug products. Reference is made to our April 20, 1995 meeting, where we agreed to the key regulatory/ clinical issues related to approval of the Avita Gel and Cream NDAs.

Penederm was recently informed that a meeting will be held within the Dermatologic Division on February 26th to discuss the Avita Gel and Cream NDA amendments. The following summary of the major agreements confirmed at our April 20, 1995 meeting is provided to recap the approval requirements that were fully addressed in our recent amendments.

1. Avita Gel has been accepted as a 505(b)(2) NDA for which one clinical study showing bioequivalence or two pivotal studies showing superiority to vehicle would be sufficient for approval:

2. All cream strengths, if otherwise acceptable, would be approvable as line extensions of the gel approval, requiring only a single study showing separation from vehicle.

3. The 0.05% cream strength would be approvable as a bracketed strength between 0.025% and 0.1% cream.

In response to the nonapprovable letters, Penederm corresponded on May 19, 1995, August 7, 1995, and November 14, 1995 seeking specific clarification of issues very generally stated in the March nonapprovable letters. Such clarification was important in order for Penederm to submit an amendment that addressed the issues of the nonapprovable letters based on a mutual understanding of the regulatory history unique to these two NDAs. After sending these letters, Penederm was persistent in following up with FDA to seek acknowledgment on our approach to addressing the nonapprovable letters before filing the amendments. In spite of our persistence and patience, no formal acknowledgment was received regarding the gel common investigator issue, the use of a 90% confidence interval for establishment of bioequivalence, and the justification of the high strength cream.

We are quite concerned with the lack of response to our letters of August 7, November 14, and December 6, 1995. Three very fundamental confirmations were requested in these letters:

1. Though we acknowledge the potential common investigator issue, there is sound statistical rationale for discounting concerns about potential bias in this particular instance. There is FDA precedent for accepting a study with a common investigator, provided satisfactory proof of non-bias can be presented.

2. That if the gel is approved, all cream strengths would be approved as line extensions of the gel provided that at least one study showed separation from vehicle.

3. That our justification for the 0.1% cream meets medical and regulatory standards for higher strength approvals, and is therefore approvable.

In December, we made a decision to file the amendments based on what we interpreted as positive feedback from a November 1995 meeting that included Doctors Lumpkin, Bilstad, Weintraub, Williams, and Harkins. At your request, we delayed that submission so that FDA would receive the amendments in January 1996, after first sending a letter dated December 6th outlining our approach to addressing the issues of the amendments. It is our understanding that you will respond in writing to this series of inquiries to clarify and substantiate the approval requirements that have been agreed upon over the course of the last five years.

Penederm's current understanding of the status of these NDAs, based on telephone updates from senior division personnel (refer to attachment), lead us to believe that the current amendments will likely address all substantive issues related to a timely approval. We believe that these amendments contain the necessary information to resolve the issues cited in the nonapprovable letters, but still require formal acknowledgment of the past agreements and regulatory approval path for these NDAs.

We appreciate your continued dedication and efforts to resolve these issues. We look forward to your timely response and encourage you to contact us if you have any questions or comments regarding these NDA applications.

Sincerely,

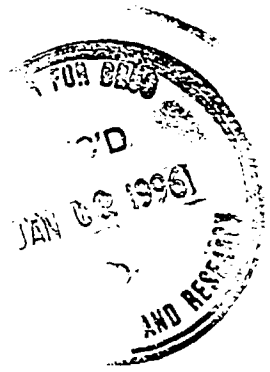
Barry Calvarese

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
650-358-0100
415-358-0101

ORIGINAL

PENEDERM



December 28, 1995

Kennerly Chapman
Project Manager
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 2, Room N229
9201 Corporate Blvd.
Rockville, MD 20850

Noted KLC 1/24/96

Re: NDA 20-400 Amendment Cover Letter and Index
NDA 20-404 Amendment Cover Letter and Index

Dear Ms. Chapman:

Enclosed with this letter please find a desk copy of the Acticin Gel and Acticin Cream NDA amendment cover letters and table of contents. Please call me if you have any questions regarding these amendments. We look forward to working with you and your colleagues to resolve any remaining issues related to approval of the Acticin Gel and Cream NDAs.

Your time and efforts are greatly appreciated.

Sincerely,

Barry Calvarese

Barry Calvarese
Executive Director
Clinical/Regulatory Affairs

ORIGINAL

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
5-358-0100
FAX 415-358-0101

PENEDERM

December 22, 1995

AZ

NDA ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Division Document Room
Rockville, MD 20857

Re: NDA #20-400, Tretinoin Gel 0.025%

Dear Dr. Wilkin:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Section 314.120, Penederm Incorporated herewith submits an NDA amendment to address the responses to the deficiencies and questions cited in your NDA nonapprovable letter dated March 29, 1995.

Please be advised that Penederm wishes to change the trade name of Tretinoin Gel 0.025% to AVITA™ (from ACTICIN™). However, to be consistent with previous submissions, we have continued to refer to the new drug product as Acticin.

Penederm would like to use a combined (cream and gel) physician insert. Text for this combined insert is included in this submission.

Regarding physician and patient inserts, we have questions that we would like clarified:

1. Is the patient insert a required document for AVITA cream and gel products? If this is a requirement, is it acceptable to adapt similar language to the current Retin-A patient insert?

2. If it is required, what is an acceptable format? Our preference is to have the option for either separate or attached physician and patient inserts.

If a patient insert is required, one copy will be included in each trade carton along with the physician insert. Copies of the patient insert and the physician insert will be included in each sample carton of two-gram tubes.

Please be advised that Penederm is removing

Therefore, which has been qualified as a GMP facility, will be the only manufacturer of Avita Gel 0.025% listed in this NDA.

This amendment includes updated safety information, as required by 21 CFR 314.50(d)(vi)(b), in the form of four new study reports. These reports have been submitted to IND .

Reference is made to our correspondence dated May 19, 1995, June 12, 1995, July 19, 1995, August 7, 1995, and August 24, 1995.

Penederm believes that all outstanding CMC issues have been addressed and that there is no valid scientific or regulatory reason for the agency to withhold approval of Acticin Gel 0.025%. Penederm has demonstrated in two independent clinical trials that Acticin Gel 0.025% is safe and efficacious, although one pivotal study may be required for a 505(b)(2) NDA. Penederm's reanalysis to account for the common investigator utilizes identical methods to account for the common investigator that the agency has permitted for other products. Further, Penederm has demonstrated equivalence to Retin-A under a 90% confidence interval, thus, providing further support that Acticin is safe and effective.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

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

PENEDERM

NEW CORRESPONDENCE

December 15, 1995

Dr. Abigail Jacobs
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-540
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

Dear Dr. Jacobs:

Enclosed please find a protocol draft for a study entitled "Dermal Carcinogenicity Study of Acticin (Tretinoin) Gel 0.025% in Mice", and a description of the study dose groups. As you may recall, this is a Phase IV study that Penederm has agreed to initiate after receiving approval of its Acticin Gel and Cream products. We plan to submit this protocol as part of the amendment for NDA #20-400, Acticin (tretinoin) Gel 0.025%.

As per your suggestion, I called Dr. Syed Alam on July 28, 1995, to discuss some of the specifics of this protocol with him. During that conversation, Dr. Alam suggested that the protocol be reviewed by the Carcinogenicity Assessment Committee (CAC) prior to being finalized. Penederm would welcome the comments of the CAC. It is my understanding that CAC normally reviews the protocol within two weeks of receipt.

A final protocol will be prepared in consultation with a selected contract laboratory after we receive your comments. Penederm is considering the following laboratories to conduct this study:

Please contact me if you have any questions.

Sincerely,

Gregory S. Wagner, Ph.D.
Director, Pharmacology and Toxicology

ORIGINAL

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

at the opened meeting
N.S.

PENEDERM

December 6, 1995

NEW CORRESPONDENCE

Jonathan Wilkin, MD
Director, Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control
5600 Fishers Lane
HFD-540, Room 12B-30
Rockville, MD 20857

RE: NDA 20-400, Acticin Gel 0.025%
NDA 20-404, Acticin Cream 0.025%, 0.05%, 0.1%

Dear Dr. Wilkin:

On November 28th, Ms. Kennerly Chapman informed Penederm by phone of the status of the above-referenced NDAs based on her notes of an October FDA meeting that included Drs. Lumpkin, Williams, Weintraub, Bilstad and Harkins. Ms. Chapman's recommendations and conclusions were confirmed in a November 29th phone call with Dr. Ralph Harkins.

Based on these conversations, Penederm will submit amendments to these two NDAs with a clear understanding of the following:

- Penederm should submit a thorough amendment for each NDA that addresses all deficiencies in the nonapprovable letters dated March 29, 1995.

- Penederm and the Topical Drug Product Division should begin working together to finalize package labeling and the physician package insert.

- A 90% confidence interval is acceptable for assessment of bioequivalence.

- Pivotal Clinical Study requirements for Acticin Gel include one study demonstrating bioequivalence to the innovator product or two studies demonstrating statistical separation from vehicle.

- CDER will consider reviewing/ labeling within the next three months.

Additionally, Penederm confirms the agreement with the Topical Drug Product Division regarding the clinical trial requirements for Acticin Cream 0.025%, 0.05% and 0.1%; Acticin Cream is a line extension of Acticin Gel and requires only one pivotal study showing statistical separation from vehicle. This requirement was introduced by the Anti-Infective Division at an April 21, 1993 meeting and verified at an April 20, 1995 meeting with the Topical Drug Product Division. Also, Penederm has provided justification for the 0.05% and 0.1% strengths of the cream formulation in our November 14, 1995 letter. An identical version of this justification will be provided in the Acticin Cream amendment.

Penederm looks forward to working with you to resolve any issues related to the approval of Acticin Gel and Cream. Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
0 LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
5-358-0100
X 415-358-0101

PENEDERM

September 11, 1995

Jonathan K. Wilkin, M.D.
Director, Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

Hold
ONR
10/4/95

RE: Acticin Gel 0.025%, NDA 20-400

Dear Dr. Wilkin:

It was a pleasure talking to you on September 6th regarding your decision to cancel our September 8th meeting regarding the Acticin Gel clinical issues cited in my August 7, 1995 letter. Although we were very disappointed to hear that our meeting was canceled, we are looking forward to resolving the issues regarding bioequivalence and the common investigator analysis as soon as possible. We look forward to rescheduling our meeting in the very near future.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese
Executive Director
Clinical/Regulatory Affairs

cc: Michael Weintraub, MD HFD 800
(includes August 7, 1995 letter)

PENEDERM INCORPORATED
[illegible]0 LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
-358-0100
...X 415-358-0101

PENEDERM

ORIGINAL

August 24, 1995

NC

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

Re: NDA #20-400, Acticin (Tretinoin) Gel 0.025%

Dear Dr. Wilkin:

Reference is made to our New Drug Application for Acticin (tretinoin) Gel 0.025%. This letter serves as confirmation of the meeting scheduled for September 8, 1995, at 2:00 p.m. in the 17B-45 conference room.

Attached is a proposed agenda for the meeting. We would like to discuss the issues cited in my letter to you dated August 7, 1995 (copy enclosed).

Representing Penederm will be:

Lloyd Malchow
President/CEO, Penederm

Peter Hutt
Covington and Burling

John Quigley, PhD
Vice President, Research & Development

Jenning Lin, PhD
Senior Biostatistician
Pharmaco:LSR

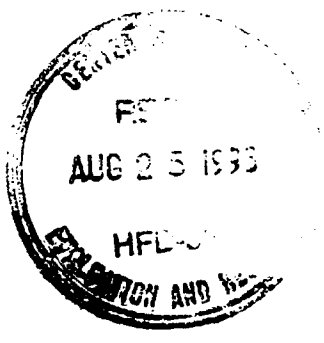
Barry Calvarese, MS
Executive Director, Clinical/Regulatory Affairs

This information is submitted in triplicate. In addition, 11 desk copies of this briefing package are being provided under separate cover to Ms. Sandy Childs. If there are any questions, please call me at 415-378-6479.

Sincerely,

Barry Calvarese, MS
Executive Director, Clinical/Regulatory Affairs

cc: Ms. Sandy Childs, HFD-540 (11 copies)



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

PENEDERM

ORIGINAL

19 May 1995

8/11/95
Telecon held 6/19/95
to discuss these issues
per resolution.
N. [illegible]

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

Re: NDA 20-400, Acticin Gel 0.025%
NDA 20-404, Acticin Cream 0.025%, 0.05%, 0.1%

Dear Dr. Wilkin:

Thank you for meeting with John Quigley and me regarding the clinical issues cited in your March 29, 1995 nonapprovable letter. The following summary is our understanding of the key points made by you and your colleagues during our April 20, 1995 meeting:

- Clinical Study PDC 004-003 (three-arm gel study) provides satisfactory evidence of efficacy versus vehicle, and would be acceptable as one of two studies for that purpose. Since PDC 004-015 (Acticin versus vehicle) used an investigator common to PDC 004-003, PDC 004-003 and PDC 004-015 are not considered to be independent studies.

- FDA still concurs with the concept that, if either the gel or the cream were approved, the non-approved form could then be approved as a line extension with only one efficacy study. With the current data sets, and the concerns over investigator effects in the cream, FDA was not sure that the current cream study would be sufficient as the only study for the cream. They were confident that, if we did an additional efficacy or equivalence study on cream, we would be able to use the gel study, PDC 004-003, as the only gel study.

- One study would be sufficient for approval if equivalence was demonstrated. FDA believes that PDC 004-003 does not demonstrate equivalence.

- FDA's definition of equivalence is that the lower bound of the 95% confidence limit of Acticin must fall within 20% of the mean of the Retin-A value

- The use of the two-sided 95% confidence interval is policy. It may be possible to use a different method, but this would involve the use of historical Retin-A controls, and would require extensive historical survey and analysis.

- Although the subject of a different NDA, the Acticin cream study, PDC 004-011, falls into a similar situation. One study which shows equivalence, or two well-controlled and independent studies which demonstrate efficacy versus vehicle, is/are required.

- FDA has questions over investigator Cullen's vehicle effect in the five-arm cream study (PDC 004-011). The reviewing medical officer's comments were sent to Penederm on May 12, 1995.

As discussed in that same meeting, it is our intention to file amendments to the Acticin gel and cream NDAs to fulfill the requirements summarized in the preceding paragraphs. Before filing these amendments, Penederm wants to discuss progress on further analysis of the Acticin gel data so that the amendments reflect mutually agreed-upon analyses for key statistical issues. This progress is summarized by issue, as follows:

Issues Related to Acticin Gel - Common Investigator

The presence of a common investigator in two pivotal studies is not without precedent. Very recently, the Topical Drug Product Division (then the Anti-Infective Division) addressed this issue during its review of a New Chemical Entity NDA (refer to Lamisil NDA #20-192, Summary Basis of Approval, pp. 111-125). Since the question of independence would appear to be of primary importance, the Acticin data has been reanalyzed in a manner that tests whether the results from Dr. Jarratt's site may have unduly influenced the two Acticin pivotal studies.

In Tables 2.1 to 2.3 (Attachment 1), Dr. Jarratt's patients were pooled from both gel studies (PDC 004-003 and PDC 004-015) and compared to pooled data (PDC 004-003 and PDC 004-015) from the remaining investigators, Drs. Lucky and Jones, to test whether Dr. Jarratt's data unduly influenced the results of both studies. Pooling is an acceptable approach because the study protocols were identical with regard to inclusion/exclusion criteria, dosing and the timing of the clinical efficacy endpoint visit (Day 84). The studies were well-separated in time. Clinical Study PDC 004-003 was initiated on September 19, 1990, and was completed on February 13, 1991. Clinical Study PDC 004-015 was initiated on September 28, 1992, and was completed on January 13, 1993. Investigator Cullen's data were removed from the analysis of Clinical Study PDC 004-003 as suggested by the FDA biostatistician's concern over the small number of highly influential vehicle patients in this data set. Data were analyzed using an ANOVA model in SASPROC GLM for the lesion count variables.

Please note that the Last-Observation-Carried-Forward Intent-to-Treat (LOCF-ITT) analytical approach was used since it accounts for treatment failures, lost to follow-ups, and other unknown factors that may influence outcomes or the original randomization of the trial. The fundamental idea behind the LOCF-ITT approach, which is consistent with the FDA memorandum dated November 5, 1985, "Forms and Content of NDA Reviews: Strategies for the Efficacy Analysis," is that exclusion of some patients who were randomized to treatment may induce bias which favors one treatment group more than another. A sensitivity analysis in the form of a LOCF-ITT analysis compared to an analysis of the evaluable group demonstrates results with similar direction, and therefore is considered to be robust. Penederm agrees with the LOCF-ITT approach as the most valid and least biased view of the data and assumes that FDA continues to support this approach.

Tables 2.1 to 2.3 of the pooled Lucky/Jones data show a statistically significant Acticin effect when compared with the vehicle, as does the pooled Jarratt data in the same table. The analyses of the two groups demonstrated statistically significant effect of Acticin over its vehicle in percent decrease of total lesions, percent decrease of total non-inflammatory lesions, percent decrease of total inflammatory lesions, and in the investigator's global assessments. These two groupings can be interpreted as two independent samples that prove the conclusion that Acticin is effective when compared to its vehicle.

A meta-analysis of all data, submitted in the refiled NDA on March 28, 1994, also supports this conclusion. Additionally, the results of the LOCF-ITT analysis of both Acticin gel studies as they were conducted, which were submitted to the gel NDA on October 28, 1994, also meet the study criteria to prove the superiority of Acticin gel over vehicle. Refer to Tables 1.1 to 1.4 in Attachment 1.

If FDA concurs that the issues on the gel common investigator would be adequately addressed by the preceding discussion, then the cream amendment could be considered as a line extension to gel. Since only a single study is required for such a line extension, Penederm believes that the current cream data set constitutes one study that proves Acticin cream is effective when compared to its vehicle. The apparent vehicle effects of investigator Cullen, while counter-intuitive, are not unusual for a highly variable disease such as acne in a fairly small set of data from one site. Indeed, the recognition of this variability is the basis for large, multiple-site studies. Even if the Cullen data set is included in the analysis of Clinical Study PDC 004-011, the Acticin cream group still shows statistically significant separation from its vehicle.

In conclusion, we feel that substantial evidence of Acticin gel's superiority over vehicle in two well-controlled studies has been established using statistical treatment of the data in a manner consistent with CDER policy for other topical drug products. We would like to schedule a teleconference or face-to-face meeting to discuss the supplemental analysis of the Acticin gel clinical data and our intention to rely on these conclusions for the forthcoming amendment. The submission of the Acticin cream amendment is subject to the outcome of the gel discussions.

Issues Related to Acticin Gel Equivalence

While Penederm continues to prefer that Acticin gel efficacy vs. vehicle be established through the aforementioned two independent studies, the option presented by FDA of pursuing an equivalence rating to Retin-A has merit provided that the standard of equivalency is firmly established. With regard to equivalence, neither Penederm nor any of its regulatory consultants is aware of the statistical policy cited (95% confidence level, 20% of the mean of the Retin-A values). Penederm does not believe that this 95/20 standard is as relevant to measures of effectiveness of topical acne drug products as it may be to pharmacokinetic metrics of systemic drugs.

The statistical analysis of the Acticin gel data do show that a 95% confidence interval for the difference in mean percent change in the total lesion count between Acticin and Retin-A is outside of the 20% interval of the Retin-A mean. It is important to note that the observed mean percent changes for Acticin are within 1% of Retin-A for total lesions.

The inability to fit within the 20% interval of Retin-A would appear to be a consequence of the high variation within the treatment groups at baseline and the follow-up efficacy visits. Meeting the definition for equivalence in this case becomes a problem of treating the broad spectrum of study-eligible patients. Measures with high variation, such as lesion counts, are then harder to use for definitions of equivalence, even when the real difference is small. Thus, these statistical methods, useful in analysis of pharmacokinetic metrics for which high variations are uncommon, do not appear to be appropriate for use with highly variable clinical endpoints.

The small amount (less than 3%) by which the 95% confidence interval exceeds the 20% interval for Retin-A represents a difference of less than three total lesions. This is based on an estimate that the mean number of total lesions at baseline is approximately 93. The mean percent decrease is 40.5% for Acticin and 41.2% for Retin-A. The 20% interval for Retin-A can be viewed as a range of lesions, based on an expected decrease of approximately lesions.

The inference using the 95% confidence interval for Acticin is that the Acticin decrease from baseline may be no more than 10.4 lesions different from that expected from Retin-A. For non-inflammatory lesions, the difference is no more than 1.5 lesions between the 95% confidence interval and that expected from the 20% of Retin-A. These results support the conclusion that for practical clinical purposes, Acticin treatment results in lesion reduction that is equivalent to treatment with Retin-A.

The clinically insignificant differences detected between Retin-A and Acticin gel in the average percent change in lesion counts using the two-sided 95% confidence interval are well within the intraobserver variability reported in the literature for acne lesion counts (Burke, B.M., Cunliffe W.J. (1984) The Assessment of Acne Vulgaris - The Leeds Technique, *British Journal of Dermatology*, 111, 83-92).

Based on these known variabilities of topical acne drug evaluation, equivalence between Acticin gel and Retin-A gel has been established within what is regarded to be a clinically relevant range, although CDER has not established written, interim bioequivalence guidelines for topical acne products. Penederm believes that the current data substantiates that Acticin is clinically equivalent to Retin-A.

Penederm is prepared to teleconference with you at your earliest convenience to solicit your input on the statistical approach of the pooled data groups as outlined in this letter for comparing Acticin gel to its vehicle. The Acticin NDA amendment is of utmost priority to Penederm, and we wish to be responsive to your concerns in our filing.

Your time and efforts are greatly appreciated.

Sincerely,

Barry Calvarese

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

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

PENEDERM

17 April 1995

[redacted]

N-
4/5/95
hand
[illegible]

Kennerly Chapman
Project Manager
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

Dear Ms. Chapman,

Thank you for the telephone call earlier today. I attempted to call you back shortly after we talked. Upon further reflection, even though it is short notice, we would like to take the opportunity to meet with FDA on April 20, 1995.

Our objective for the meeting is to discuss clinical issues identified in your March 29, 1995 non-approvable letters for NDA #20-400 (Tretinoin Gel 0.025%) and NDA #20-404 (Tretinoin Cream, 0.025%, 0.05% and 0.1%). Mr. Barry Calvarese will contact you on Tuesday, April 18th, to determine if April 20th is still available and acceptable to FDA.

Penederm appreciates your prompt response to our request for a meeting.

Sincerely,

John W. Quigley, PhD
Vice President
Research and Development

cc: Barry Calvarese

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

PENEDERM

April 7, 1995

Jonathan Wilkin, M.D., Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA 20-400
All-trans-retinoic acid, Acticin Gel 0.025% topical formulation

Dear Dr. Wilkin:

Penederm Incorporated acknowledges the receipt of your March 29, 1995 nonapprovable letter regarding the above referenced drug product. Pursuant to 21 CFR 314.20, we are providing notification of our intent to file an amendment. Furthermore, in accordance with 314.20(d), we request a conference at your office to discuss in detail the deficiencies cited in your letter. We propose to have this meeting within the first 15 calendar days of May 1995. We expect to submit an amendment within two (2) weeks of our proposed May 1995 conference.

We consider all the information contained in this letter proprietary and confidential.

Your time and efforts are greatly appreciated.

Sincerely,

Barry Calvarese

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

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

PENEDERM

March 9, 1995

FAXED
Mac 3/9/95

Kennerly Chapman
Project Manager
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA 20-400, Acticin Gel 0.025%
NDA 20-404, Acticin Cream 0.025%, 0.05%, 0.1%

Dear Ms. Chapman:

Penederm Inc. has compiled data, as suggested by the reviewing chemist, to demonstrate the equivalence of batches manufactured at the two manufacturers listed in the above referenced NDAs, We are now ready to withdraw from NDAs 20-400 and 20-404 and to have listed as the sole manufacturer of Acticin gel and cream.

We seek your guidance on how to proceed. Will it help the NDA review process if we submit a request to within the next few days? Are there any other requirements that need to be considered before proceeding?

I plan to call you within the next two days to discuss this issue in order to summarize our proposal to from the Acticin gel and cream NDAs.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

TOTAL P.01

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

PENEDERM

1/30/95
hated.

January 17, 1995

Jonathan Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA 20-400, Acticin (tretinoin) Gel 0.025%
CMC Amendment

Dear Dr. Wilkin:

Please find enclosed information regarding the CMC amendment submitted to the aforementioned NDA on December 16, 1994. The information on the changes from the original NDA are itemized and summarized below:

- Addition of as a manufacturing site

  - The differences in the manufacturing processes used at (discussed in pages 0033 and 0035 of the Amendment) versus the one used originally at are further clarified in Table I of this letter

  - A description of the facilities of is provided on page 0026 of the CMC Amendment

- Updated stability tables for batches manufactured at both manufacturing sites

  - Additional data generated after the original NDA filing have been provided for the batches made at

- New data obtained from the batches made at have been included

The above information is summarized in Table II of this letter

- Special *in-vitro* studies performed to compare the products manufactured at

  - An *In-vitro* release study (across synthetic membranes) and an *in vitro* percutaneous absorption study have been performed. The data are presented in pages 0048 through 0084 of the amendment

- Updated specifications (Quality Standard) and analytical methods for raw materials and finished product

  - Updated specifications for raw materials

    Tretinoin - Changed sampling requirement; requalification does not require ID testing

    Hydroxypropyl cellulose - Changed testing method for from

  - Updated specifications for product

    All specifications for Bulk Product Release (page 0086), Finished Product Release (page 0090) and Finished Product Stability (page 0182) were updated to reflect the following, as applicable:

    i) clarification of specification for total degradant
    ii)Tretinoin content changed from % Label Strength to % as required by USP 23
    iii) Deleted statement regarding tretinoin being heat and light sensitive and reference to
    iv) Changed Storage from between
    v) Changed crimp code to package code.
    vi) Changed label and package appearance to product appearance.
    vii) Deleted Part II. Contract Manufacturer.
    viii) Revised Sampling Requirements

  - Updated analytical methods

    Figures updated and reference added (page 0093)

    Clarified temperature control for sonification; increased sample dilution volume but same final concentration (page 0098)

- Environmental assessment for new manufacturing site

  - Amendment contains report of the environmental assessment done at

Please call me if you have any further questions.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
[illegible]TER CITY, CA 94404
58-0100
415-358-0101

ORIGINAL

PENEDERM

NEW CORRESPONDENCE

September 27, 1994

Jonathan Wilkin, M.D.
Director, Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

MHI 6/4/96
RB

RE: New Drug Applications 20-400, 20-404
For: Acticin™ (tretinoin) Gel, 0.025%
Acticin™ (tretinoin) Cream, 0.025%, 0.05%. 0.1%

Dear Dr. Wilkin:

Enclosed, please find two copies (Biometrics copy and Archive copy) of SAS data sets for clinical studies PDC 004-003, PDC 004-011 and PDC 004-015. These disks were requested by Beth Turney of the Biometrics group.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

EDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
TER CITY, CA 94404
358-0100
415-358-0101

PENEDERM

ORIGINAL

BS

July 26, 1994

Kennerly Chapman
Consumer Safety Officer
Division of Topical Drug Products
HFD 521, Room 12B-05
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fischers Lane
Rockville, MD 20857-1706

RE: NDA 20-400, Acticin (tretinoin) Gel 0.025%

Dear Ms. Chapman:

It was a pleasure talking to you on 6/2/94 regarding the need for the following:

- Last observation carried forward analysis of clinical studies PDC 004-003 and PDC 004-015

Two copies of the report and tables are provided, one for the Biostatistical reviewer and an archive copy.

Please call me if you have any further questions.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

NEDERM INCORPORATED
0 LAKESIDE DRIVE, SUITE A
OSTER CITY, CA 94404
5-358-0100
X 415-358-0101

PENEDERM

ORIGINAL

BZ

June 17, 1994

Kennerly Chapman
Consumer Safety Officer
Division of Anti-Infective Drug Products
HFD 521, Room 12B-05
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fischers Lane
Rockville, MD 20857-1706

RE: NDA 20-400, Acticin (tretinoin) Gel 0.025%

Dear Ms. Chapman:

It was a pleasure talking to you on 6/2/94 regarding the need for the following:

- Copies of case report forms for Penederm clinical study PDC 004-003 subjects

- An explanation of the differences between excipients PDT002-001 and PDT002-002.

- We are compiling information regarding the racial demographics of research subjects who participated in clinical studies PDC 004-003 and PDC 004-015. We expect to send this information to you by August 1, 1994.

Please call me if you have any further questions.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

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

PENEDERM

June 9, 1994

Murray M. Lumpkin, M.D.
Director, Division of Anti-Infective Drug Products
HFD 520, Room 12B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fischers Lane
Rockville, MD 20857-1706

RE: Acticin (tretinoin) Gel NDA 20-400, 0.025%
Acticin (tretinoin) Cream NDA 20-404, 0.025%, 0.05%, 0.1%

Dear Doctor Lumpkin:

Recently, a request was made by the Anti-Infective Division to confirm, in writing, Penederm's commitment to conduct a phase 4 study on Acticin Gel. Such a study would be conducted exclusively on Acticin gel, since it is agreed that the Acticin cream formulations are a line extension of the gel drug product formulation and as such would not require a dermal carcinogenicity study.

Penederm is committed to initiating a phase 4 study within four months after final approval of both the gel and cream formulations. We understand that the requirement for a study is a new policy and will be applied to all topical retinoid drug formulations regardless of their status (New drug or generic).

We look forward to working with the Anti-Infective Division to develop a protocol for the phase 4 study.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

INCORPORATED
E DRIVE, SUITE A
Y, CA 94404
)
-01[illegible]
)

trip

PENEDERM

BM

June 3, 1994

dated
rec'd
6/13/94

Murray M. Lumpkin, M.D.
Director, Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fischers Lane
HFD-520, Room 12B-45
Rockville, MD 20857

RE: New Drug Application 20400
For: Acticin™ (tretinoin) Gel, 0.025%

Dear Dr. Lumpkin:

Enclosed, please find eight copies of the response to question 15(D) of your letter dated November 23, 1993.

15. With regard to PDC 004-015:

D. In the listing of adverse events by center, enrollment date should be included.

This response was not included in our resubmission of NDA 20400 dated March 28, 1994.

Sincerely,

Barry M. Calvarese
Executive Director
Regulatory/Clinical Affairs

PDC 004-015
Adverse Events

RM INCORPORATED
KESIDE DRIVE, SUITE A
CITY, CA 94404
0100
-0101

ORIGINAL PENEDERM

ORIG AMENDMENT
BS

March 30, 1994

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-520, Room 12B-45
Rockville, MD 20857

RE: New Drug Application 20400
For: Acticin™ (tretinoin) Gel, 0.025%

Dear Dr. Lumpkin:

On March 28, 1994, pursuant to Section 505 (b) (2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Section 314.50, Penederm Incorporated submitted responses to the deficiencies and questions cited in your letter dated November 23, 1993. An appendix was inadvertently omitted from the statistical section. Eight copies of Appendix F.1, Repeated Measurement Analysis of Absolute Lesion Counts for PDC 004-003 (without the interaction), are enclosed for inclusion into the response. This appendix consists of pages 18-0241A through 18-0241CC of response S-18 and should be inserted after page 18-0241.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Regulatory Affairs

RM INCORPORATED
ESIDE DRIVE, SUITE A
CITY, CA 94404
)100
358-0101

ORIGINAL

PENEDERM

1/21/94
Noted. Penederm has subsequently decided to perform a human contact sensitization study utilizing the final formulation of Acticin gel cream.

November 1, 1993

Rosemary Cook
Project Manager
HFD 520, Room 12B-05
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

Hold
1/25/94

RE: NDA 20400, Acticin™ (tretinoin) Gel, 0.025%

Dear Ms. Cook:

It was a pleasure talking to you today regarding Penederm's recent NDA submission for Acticin Gel 0.025%. As you requested, we are providing you with a status report for a recently completed sensitization study.

With the exception of polyolprepolymer-2, all excipients in the Acticin Gel formulation are not sensitizers and are identical to those present in the Retin-A formulation. The drug active, tretinoin, is known to not cause sensitization. The pharmacological action of tretinoin causes local irritation, in the form of erythema, peeling and itching and it was determined unwarranted to conduct a contact sensitization study on the final formulation, given that both the excipients and the drug active have been previously characterized.

To augment the existing animal and human sensitization data submitted in the application, we have recently completed a standard repeated human insult patch study on 100 subjects on polyolprepolymer-2 (PDT 002-002), and the report for this study will be forwarded to you as soon as it is available (November 8, 1993). This study shows that polyolprepolymer-2 does not cause sensitization in humans.

Please contact me if you have any additional comments or questions.

Sincerely,

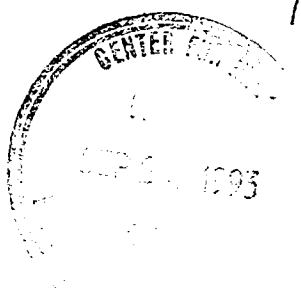
Barry M. Calvarese
Executive Director,
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
5-358-0100
AX 415-358-0101

ORIGINAL

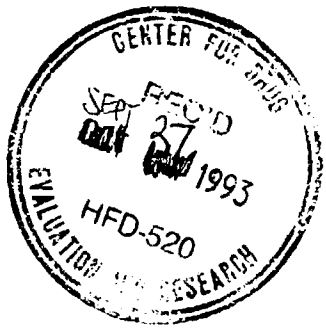
20-400

N



September 24, 1993

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-520, Room 12B-45
Rockville, MD 20857



RE: New Drug Application
Acticin™ (tretinoin) Gel, 0.025%

Dear Dr. Lumpkin:

Pursuant to Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Section 314.50, Penederm Incorporated herewith submits an original New Drug Application (NDA) for Acticin™ (tretinoin) Gel, 0.025%. The new drug product contains the active drug substance, tretinoin, at a concentration of 0.025%, in an ethanolic gel vehicle. Previous information concerning this formulation has been submitted to the Agency under Investigational New Drug Application (IND)

Because of the generic equivalence of the Acticin gel formulation to Retin-A®, the Innovator product, an Abbreviated New Drug Application (ANDA) was submitted for this product in May of 1991, and was accepted for filing in August of 1991. At an August 13, 1992 meeting attended by representatives of the Office of Generic Drugs, the Office of Compliance, the Division of Anti-Infectives, CDER, and the Sponsor, the Agency determined that this submission was not acceptable for review as an ANDA due to the presence of a new excipient not present in the innovator product and not previously approved as an ingredient in a new drug. Although the sponsor did not at that time agree, and continues to disagree with that interpretation, the ANDA was withdrawn at the request of the Agency and the Sponsor agreed to modify the application to an NDA-type submission based on these discussions with the Agency on the understanding of an expedited review.

The Division of Anti-Infectives, CDER, has provided a comprehensive review and preliminary evaluation of the ANDA documents which were submitted, and, via letter and subsequent discussions, has identified additional requirements to permit substantive review of the proposed application. As a result, the Sponsor has provided additional clinical and toxicological information in this NDA submission to augment what was originally supplied. The Sponsor believes that the enclosed submission represents necessary and sufficient information for the approval of Acticin™ (tretinoin) Gel, 0.025%.

Based upon the equivalence of Acticin to the Innovator Retin-A formula, which has been on the market for two decades with the same acne indication, we are submitting this NDA application pursuant to section 505(b)(2) (literature based NDA) of the Food, Drug and Cosmetic act.

The complete NDA is submitted in the following volumes:

SECTION	ARCHIVAL COPY Vol #	REVIEW COPY Vol #
Application Summary	1.1.1	///
Chemistry	1.2.1-2	1.1.1 & 1.2.1-2
Pharmacology	1.3.1-7	1.1.1 & 1.3.1-7
Clinical	1.4.1-7	1.1.1 & 1.4.1-7
Statistical	1.5.1-6	1.1.1 & 1.5.1-6
Sample & Labeling	1.6.1	1.6.1
Total No. of Volumes	24	///

In addition, two additional desk copies of Section 1, Volume 1.1.1 are being included at the request of the Agency.

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

The continued expedited review of this application is appreciated. Please contact Barry M. Calvarese, M.S., Executive Director, Regulatory Affairs for further information regarding this application.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs

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

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

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; August 31,1989.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
24 Sep 93	24 Sep 93
DIVISION ASSIGNED	NDA/ANDA NO ASS
520	20-408

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314)*.

NAME OF APPLICANT
Penederm Incorporated

DATE OF SUBMISSION SEP 24 1993

TELEPHONE NO. *(Include Area Code)*
(415) 358-0100

ADDRESS *(Number, Street, City, State and Zip Code)*
320 Lakeside Drive
Suite A
Foster City, CA 94404

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Tretinoin Gel	Acticin-TM

CODE NAME *(If any)*	CHEMICAL NAME
	All-trans-retinoic acid

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Gel	Topical	0.025%

PROPOSED INDICATIONS FOR USE

Indicated for topical application in the treatment of acne vulgaris.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND#
DMF#
DMF#
DMF#

SEP 29 1993 RECEIVED

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION
☒ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

0001

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*