CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

PHARMACOLOGY REVIEW(S)

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

NDA 20-404.BM (Amendment, dated 12/11/96)

Drug Name: Avita™ Cream 0.025%, 0.05%, and 0.1%

Active Ingredient: Tretinoin

Category: Retinoid

Indication: Acne vulgaris

Sponsor: Penederm Inc., Foster City, CA

Number of Vols.: One

Date CDER Received: 12/12/96

Date Assigned: 12/19/96

Date 1st Draft Completed: 12/29/96

Date Review Accepted by Supervisor:

Preclinical Studies

None has been submitted in this amendment.

Comments

Although this submission has been marked "info" only, the CSO (Ms. Olga Cintron) has asked me to review this for comments on ongoing carcinogenicity study with the Avita gel. Specifically she wanted to know if the Sponsor would have to commit to a phase 4 dermal carcinogenicity study with the cream formulation now that the gel formulation is under litigation for a possible patent infringement.

Since we have considered the cream as a line extension of the gel form, the data generated with

the gel can still be used for the cream formulation. It will not be necessary to perform a separate carcinogenicity study with the cream dosage form.

It is recommended that the carcinogenicity data from the gel study be submitted to the cream NDA for safety evaluation of the topical Avita cream.

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 1/10/97

HFD-540/TL/Concur/Jacobs 1/13/97

cc:
NDA 20-404

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TLPharm/Jacobs

HFD-540/MO/Labib

HFD-540/Chem/Rejali

HFD-540/CSO/Blay

AUG - 2 1996

HFD 540
Blay

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

NDA: 20-404.AZ (Amendment, dated 7/12/96)

Drug Name: Avita[R] (Tretinoin Cream 0.025%, 0.05%, 0.1%)

Category: Retinoid

Indication: Acne vulgaris

Sponsor: Penederm Inc., Foster City, CA

Number of Vols.: One

Date CDER Received: 7/16/96

Date Assigned: 7/18/96

Date Review Started: 7/31/96

Date 1st Draft Completed: 7/31/96

Date Review Accepted by Supervisor:

Related Submissions: IND

Review Objective: To examine the Sponsor's response to FDA's nonapprovable letter of 6/26/96.

Comments:

This application for the cream formulation of Avita[R] is a "line extension of the Avita[R] gel" (NDA

The responses, contained in this amendment, are the same as those submitted for NDA

and have been reviewed (Pharmacology Review, dated 7/30/96).

Evaluation:

There are no outstanding preclinical issues related to the approval of this application.

The proposed revised mouse dermal carcinogenicity protocol for the gel formulation is satisfactory. It was agreed previously that the study will be performed only with the gel formulation as the the cream formulation is a line extension only.

No pharmacology action is indicated.

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 8/2/96

HFD-540/TL/Concur/Jacobs 7/31/96

cc:
NDA 20-404

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/SPharm/Jacobs

HFD-540/MO/Labib

HFD-540/Chem/rejali

HFD-540/CSO/Blay

June 2, 1996

NDA 20-404, 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.

a.g. 6/26/96

AUG 22 1994

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

NDA#: 20-404

Date Submitted: March 28, 1994
Date CDER Received: March 29, 1994
Date Assigned: May 17, 1994
Date Review Completed: July 13, 1994
Date Accepted by Supervisor:

Sponsor: Penederm Inc.
320 Lakeside Drive, Suite A
Foster City, CA 94404

Name of Drug: Acticin Cream 0.025
Generic Name: Tretinoin
Chemical Name: All-trans retinoic acid
Names Used in Studies:

Identifying Name	Other Names
Acticin 0.1% Cream	PDT 004-046
Acticin 0.05% Cream	PDT 004-045
Acticin 0.025% Cream	PDT 004-044
Acticin Cream Vehicle	PDT 004-054
Acticin 0.025% Gel	PDT 004-002
Acticin Gel Vehicle	PDT 004-006
Retinoic Acid Solution 0.2%	PDT 004-055
Retin-A® 0.1% Cream	PDT 004-031
Retin-A® 0.025% Gel	PDT 004-003
Polyolprepolymer-2	PDT 002-001, PDT 002-002, TopiCare Delivery Compound, TopiCare 35A

Pharmacological Category: Retinoid

Indication: Acne vulgaris

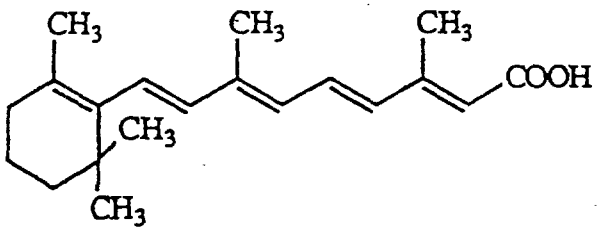
Route of Administration: Topical dermal

Recommended Dosage: Once nightly, "thin layer over effected area", multiple 6-week treatments may be necessary, exposure is considered chronic

Related IND:
Related NDA: Acticin 0.025% Gel Formulation: NDA
Related ANDA:

Related Drugs: Retin-A®: R. W. Johnson Pharmaceuticals; IND (gel, liquid, ointment, cream) NDAs 16-92-001 (solution), 16-002 (swab), 17-340-001 (emulsion, cream), 17-522-001 (emulsion, cream), 17-579-001 (gel); Renova® (NDA 19-963)

Structural Formula:



Formulations: The formulations are virtually identical to Retin-A®, except for the addition of polyolprepolymer-2. Other formulations were sometimes used in testing; they are presented in Appendix A.

Acticin (tretinoin) Cream, 0.025%
Penederm Formulation PDT 004-044

mg/g	Ingredient	% w/w
	Tretinoin, USP	
	Purified water, USP	
	Stearic acid, NF	
	Polyolprepolymer-2	
	Isopropyl myristate, NF	
	Polyoxyl 40 stearate, NF	
	Propylene glycol, USP	
	Stearyl alcohol, NF	
	Xanthan gum, NF, Food Grade	
	Sorbic acid, NF	
	Butylated hydroxytoluene, NF or F.C.C.	

*The sponsor will manufacture the drug product with a % overage.

Formulations (continued):

Acticin (tretinoin) Cream, 0.05%
Penederm Formulation PDT 004-045

mg/g	Ingredient	% w/w
	Tretinoin, USP	
	Purified water, USP	
	Stearic acid, NF	
	Polyolprepolymer-2	
	Isopropyl myristate, NF	
	Polyoxyl 40 stearate, NF	
	Propylene glycol, USP	
	Stearyl alcohol, NF	
	Xanthan gum, NF, Food Grade	
	Sorbic acid, NF	
	Butylated hydroxytoluene, NF or F.C.C.	

*The sponsor will manufacture the drug product with a [redacted]% overage.

Acticin (tretinoin) Cream, 0.1%
Penederm Formulation PDT 004-046

mg/g	Ingredient	% w/w
	Tretinoin, USP	
	Purified water, USP	
	Stearic acid, NF	
	Polyolprepolymer-2	
	Isopropyl myristate, NF	
	Polyoxyl 40 stearate, NF	
	Propylene glycol, USP	
	Stearyl alcohol, NF	
	Xanthan gum, NF, Food Grade	
	Sorbic acid, NF	
	Butylated hydroxytoluene, NF or F.C.C.	

*The sponsor will manufacture the drug product with a [redacted]% overage.

Index of Preclinical Studies:

The following studies were not reviewed previously and are presented in detail.

In Vitro Percutaneous Absorption Study
Toxicity/Irritation Tests:
- Acute Toxicity (LD_{50})
- 14-Day Dermal Toxicity and Irritation in Mice
- 7-Day Dermal Irritation in Guinea Pigs
- Primary Skin Irritation in Guinea Pigs
- Primary Eye Irritation in Rabbits
- 13-Week Dermal Toxicity and Irritation Test in Rabbits
- 91-Day Dermal Irritation and Toxicity Study

Reproduction Studies:
- Pilot Teratology Study in Rabbits
- Segment II Teratology in Rabbits

Mutagenicity Tests:
- Ames Assay
- Mouse Lymphoma Assay
- Mouse Micronucleus Bone Marrow Erythrocyte Assay *(In Vivo)*

The following studies were reviewed previously by Dr. Syed Alam and are summarized in this review:

In Vitro Percutaneous Absorption Studies in Human Cadaver Skin
Primary Skin Irritation Studies in Rabbits
Repeat Skin Irritation Studies in Guinea Pigs
Skin Hypersensitivity Studies in Guinea Pigs
Comedogenicity Study in Rabbits
28-Day Percutaneous Studies in Rabbits

Introduction:

The active ingredient in Acticin Cream formulations is tretinoin, a natural metabolite of Vitamin A (retinol) that has been used for over 20 years for acne vulgaris; the dermal form is currently on the market as Retin-A® gel or cream. The exact mechanism of action for tretinoin remains unknown, although evidence suggests a three-fold effect: the drug decreases cohesiveness of follicular epithelial cells and thus decreases microcomedo formation; tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells, which tends to cause extrusion of comedones; and third, tretinoin decreases sebum production.

Several adverse reactions are associated with Retin-A® use. The drug may cause skin irritation so severe that use must be discontinued, although the skin reactions are reversible. Retin-A® is also considered teratogenic in animals (pregnancy category C). Carcinogenicity

testing for Renova® (another tretinoin formulation) was negative, although the assay for photocarcinogenicity in CD-1 mice was positive.

Acticin Cream formulations are identical to Retin-A® Cream formulations, except for the addition of polyolprepolymer-2, a new and unknown ingredient that adds emollient qualities and reduces irritation (according to the sponsor). Polyolprepolymer-2 is a polyurethane glycol moiety formed by the linkage of polypropylene glycol units with dicyclohexylmethane di-isocyanate. The sponsor did not report the structure(s) of polyolprepolymer-2, although the formula is reported as $HO(C_3H_6O)_{12}[C_{15}H_{22}N_2O_2(C_3H_6O)_{12}]_mH$, where m = 1 to 4, predominately. The material is identified as 5 different peaks chromatographically with an average molecular weight of 4,000, although the range is approximately 1,000 to more than 5,000 daltons. Polyolprepolymer-2 is a new entity that has never been through the IND/NDA safety review process.

Pharmacokinetics: The sponsor performed no original pharmacokinetics preclinical studies. The sponsor submitted one journal article as a review of retinoid pharmacokinetics: Allen, JG, and Bloxham, DP, The Pharmacology and Pharmacokinetics of the Retinoids. *Pharmac. Ther.* 40:1-27, 1989. The article presents absorption, transport, distribution, metabolism, and pharmacokinetics associated with most retinoid compounds. Of specific concern to this NDA review is the section reviewing pharmacokinetics of tretinoin. The following section is taken from the article.

Pharmacokinetics

Studies in mammals have indicated that the relative amounts of the metabolites produced from all-*trans*-retinoic acid also depends upon the dose administered. Thus Roberts and Frolik (1979) reported that the ratio of 13-*cis*-isomer (isotretinoin) to 4-*oxo*-retinoic acid formed by tissues *in vitro* decreases as the concentration of tretinoin is increased. Similarly Swanson *et al.* (1981) and Zile *et al.* (1982) reported that, when tretinoin is given intravenously to rats, the proportion that is converted to the glucuronide metabolite increases with increasing dose. This suggests that some of the other metabolic pathways have been saturated. Such effects could explain why non-linear pharmacokinetics were seen when rats were given i.v. doses between 0.015 and 5 mg/kg (Swanson *et al.*, 1981). Thus, the initial rates of elimination reduced significantly with dose, but these deviations from first-order kinetics decreased with time, and all doses ultimately showed terminal half-lives of approximately 20 min. Similar non-linearities of pharmacokinetics were reported for mice given 10 mg/kg oral doses (Munsell *et al.*, 1987) but not in anaesthetised dogs dosed i.v. at 3 mg/kg (Patel *et al.*, 1982b).

Similar pharmacokinetic studies have not apparently been performed with tretinoin in humans (Verweij *et al.*, 1985). Chiang (1980) did administer a single 0.5 mg dose, intravenously to a male volunteer, as a control for a topical absorption study. Following the i.v. dose, plasma concentrations of 14.6 and 5.4 ng/ml were found after 5 min and 1 hr respectively. (Based on these concentrations Lucek and Colburn (1985) estimated that the volume of distribution for tretinoin in man was approximately 30 l.) Following topical application, tretinoin levels were reported to be non-measurable (<2 ng/ml) even after 28 days of continuous application of 0.025% cream to the arms and legs, and also following a single whole-body inunction with a 1% cream. These findings are consistent with data obtained following a single application of radioactive drug which showed that following seven days pretreatment with unlabelled tretinoin, only approximately 6% of the labelled dose could be recovered in urine and faeces (Lucek and Colburn, 1985).

Preclinal Studies

Note: The sponsor submitted studies for the cream and gel formulations together; often they were tested within a single study. Thus both gel and cream formulations are reviewed below. (In previous communications with the sponsor, we indicated that because the gel 0.025% formulation has greater uptake than the cream formulations, studies that tested only the gel would be considered sufficient.)

The following studies have not been reviewed previously.
All studies appear to have been done under GLP guidelines, except for the *in vitro* percutaneous absorption studies.

Percutaneous Absorption, *In Vitro*

Laboratory: The sponsor

Materials tested: Acticin 0.025% Gel (PDT 004-002), Retin-A® 0.025% Gel (PDT 004-003, both US and Foreign versions, although the sponsor has not explained how the two formulations differ)

Amount applied: 10 mg. to each 0.74 cm^2 diffusion cell

Time length of test: 48 hours

Method: Dermatomed human skin was placed on standard Bronaugh (Franz) flow-through percutaneous diffusion cells to evaluate the penetration potential of the test materials. The tretinoin formulations were spiked with tritiated tretinoin. The receptacle fluid beneath the skin was collected every 6 hours and counted for the absorbed amount of radio-labelled test material. At 48 hours, the skin surface was washed and the washes, epidermis, and dermis were also counted.

Results:

Percutaneous Absorption (% of Applied Dose; mean ± SD, n = 14)

Formulation	Receptor Fluid	Epidermis	Dermis	Total Recovery
Acticin Gel (PDT 004-002)	0.22 ± 0.04	0.58 ± 0.19 †	0.26 ± 0.10	93.5 ± 3.7
Retin-A® Gel-US (PDT 004-003)	0.28 ± 0.06 *	1.76 ± 0.82 *	0.28 ± 0.16	101.9 ± 5.6
Retin-A® Gel-Foreign (PDT 004-003)	0.22 ± 0.07	1.91 ± 0.70	0.21 ± 0.09	99.9 ± 3.0

* Statistically different from Acticin gel and "foreign" gel
† Statistically different from US and foreign Retin-A® gel

Under the conditions of this assay, Acticin Gel (0.025%) had less than 1% penetration into the epidermis, dermis, and receptor fluid. Penetration of Retin-A® gel (in both formulations) was only slightly greater.

Toxicity and Irritancy Tests

Acute Toxicity (LD_{50})

Laboratory:

Number of Animals: 10 (5/sex)

Animal Strain: Sprague Dawley rats

Formulations: Acticin 0.025% Gel (PDT 004-002)

Route: Oral

Results:

Material Tested	Route	LD_{50}
PDT 004-002	p.o.	> 5.0 g/kg

Results: No deaths occurred. Materials with an LD_{50} greater than 5.0 g/kg are considered to be of very low toxicity.

14-Day Dermal Toxicity Study in Mice

Laboratory:

Number of Animals/Group: 8/group (4/sex)

Animal Strain: Crl:CD®(ICR) BR mice

Materials Tested: Acticin 0.025% Gel (PDT 004-002), Acticin 0.05% Cream (PDT, 004-045), Acticin 0.10% Cream (PDT 004-046)

Dose levels/Study Design:

Group	Formulation	Dose level (mg/kg/day)	Concentration (% Tretinoin)	Dose Volume (ml/kg)
1	PDT 004-054 (cream vehicle)	0	0	5
2	PDT 004-045 (Acticin 0.05% cream)	2.28	0.05	5
3	PDT 004-046 (Acticin 0.10% cream)	4.55	0.10	5
4	PDT 004-006 (gel vehicle)	0	0	5
5	PDT 004-002 (Acticin 0.025% Gel)	0.52	0.025	5
6	PDT 004-002 (Acticin 0.025% Gel)	1.04	0.025	5

Route: Dermal

Methods: Test materials were administered to the clipped back every day for two weeks. Following six hours of exposure, residual test materials were wiped off. Animals were euthanized after 14 days of treatment.

Results:

Mortality: All animals survived to scheduled euthanasia.

Body Weights: Mean body weights and body weight gains were statistically comparable across all groups, although animals treated with the high-dose cream had somewhat lower body weights and body weight gains.

Clinical Observations: Males and females both exhibited test-article build up. Dermal findings were normal in the two control groups, except the cream vehicle mice (7/8) were noted to have stained exposure sites. The Acticin gel- and cream-treated animals exhibited a variety of findings at the exposure site, including slight-to-moderate erythema, slight-to-moderate atonia, slight-to-moderate desquamation, skin thickening, and whitening at the test site. Blanching was noted only in males treated with the high-dose gel. Eschar was noted in the males treated with the cream formulations and in the females in both the gel and cream formulations. No other clinical observations were made that were considered treatment related.

Necropsy: Animals treated with the low-dose gel formulation were noted at necropsy with a dilated kidney pelvis (one male) and ovarian cysts (two females); all other findings were unremarkable.

7-Day Dermal Irritation Study in Guinea Pigs

Laboratories: The Sponsor (report preparation),

Animals: 25 (13 males, 12 females)

Animal Strain: Hartley guinea pigs

Test Materials: All formulations contain 0.025% tretinoin: Acticin Gel (PDT 004-002), Retina-A® Gel (PDT 004-003), Acticin "Research" Cream (PD 46-1360-A), Retin-A® Cream (PDT 004-024)

Dose Levels: 50 or 100 mg twice/day

Study Design: This study was conducted under GLP conditions, although the design of the study is somewhat unusual. Six separate skin sites were designated on each animal. Each site was treated with the same compound, and thus every compound was tested with n=6 (where n = the number of skin sites tested). Each test material was tested on six different animals (but at single test sites). One animal served as an untreated control. Thus, the sponsor tested a large number of compounds while using a relatively small number of guinea pigs. The table on the following page summarizes the study design.

Formulation	PDT #	Dose (mg/animal/treatment)
Acticin 0.025% Gel	004-002	50
Retin-A® 0.025% Gel	004-003	50
Sham Treatment	none	50
Acticin 0.025% Gel	004-002	100
Retin-A® 0.025% Gel	004-003	100
Sham Treatment	none	100
Sham Treatment	none	50
Retin-A® 0.025% Cream	004-024	50
Acticin "Research" Cream Vehicle	46-1360-C	50
Acticin "Research" 0.025% Cream	46-1360-A	50

Methods: Test articles were administered to the clipped backs of guinea pigs, and the test skin sites were observed clinically for dermal erythema or edema. If sufficient erythema was noted, a guinea pig would skip one or more dosings. The skin was evaluated daily, and following euthanasia, skin samples were evaluated histopathologically.

Route and Duration: Dermal application twice per day for 7 days at unoccluded skin sites. Test materials were left on the animals for approximately 6 hours following each exposure.

Results:

Mortality: All animals survived to scheduled euthanasia.

Dermal Clinical Observations: The cream formulations (50 mg), which consisted of Retin-A®, the Acticin research vehicle, and the research cream, caused statistically significantly greater erythema and edema throughout the study (i.e. days 2 to 8). Retin-A® generally aused more severe effects than Acticin, although for all compounds the severity ranged from very slight to moderate with severity increasing over time.

Beginning one day post-treatment, animals treated with Acticin 0.025% Gel (50 and 100 mg) were noted to have greater erythema and edema than the sham controls. At 50 mg, differences were statistically significant on days 2, 6, 7, and 8 for erythema and days 5, 6,

7, and 8 for edema. At 100 mg, differences were statistically significant on days 3 through 8 for erythema and days 5, 6, 7, and 8 for edema. Retin-A® generally caused erythema more quickly and to a greater degree than Acticin. The sponsor statistically compared the Acticin-related effects to Retin-A® effects. Animals treated with 50 mg Acticin exhibited significantly less erythema than the Retin-A®-treated (50 mg) animals on days 3, 4, 5, 6, and 8; and significantly less edema on days 3 through 8. The severity for all of the observations ranged from very slight to moderate for both erythema and edema observations; severity tended to increase over time.

Histopathology: Histopathological evaluation of the skin revealed that treatment-related effects were more severe in the Retin-A®-treated than in the Acticin-treated animals. Animals treated with Acticin (50 and 100 mg) gel were noted to have numerous changes in the epidermis and dermis when compared to control. Changes of note include epidermal parakeratosis, hyperplasia, thickening, mitotic rate, hyperkeratosis, and inflammatory infiltrates in the dermis. Animals treated with Retin-A® presented with a similar histomorphology, although it tended to occur more rapidly and to a greater degree. The sponsor compared the Retin-A® and the Acticin groups statistically; the Retin-A® group had statistically greater severity of hyperplasia, thickening, and mitotic rate at 50 and 100 mg, and greater severity of epidermititis, crust formation, and vasodilation and inflammatory infiltrates of the dermis.

The Acticin cream (50 mg) effects were similar to the gel, although the effects were more severe in the cream and also caused epidermal hypergranulosis, epidermititis, crust formation, spongiosis, and slight vasodilation in the dermis. Once again, the Retin-A® product (in this case a cream) caused the same sort of effects, although they were somewhat more severe. (However, the only statistical difference between Retin-A® cream and Acticin cream was noted in vasodilation of the dermis.)

Acticin cream and gel are moderate irritants which cause classic tretinoin-related histomorphologic changes in guinea pig skin. Under the conditions of this test. it appears that the irritation and histomorphologic changes are less severe following treatments of Acticin gel than Acticin cream, and that both Acticin treatments cause less severe effects than Retin-A® products.

Primary Skin Irritation Study in Rabbits

Laboratory:

Number of Animals: 6 (3/sex)

Animal Strain: New Zealand White

Formulation: Acticin 0.025% Gel (PDT 004-002)

Dose Level: 0.05 ml

Administration: Dermal

Duration: 24 hours

Methods: The test material was applied to 1 X 1" gauze squares on intact and abraded skin on each animal. Sites were occluded and animals were restrained to protect the application sites. At 24 hours, the sites were cleaned and skin irritation was evaluated at 24 hours and 72 hours. The animals were scored by the method of Draize.

Dermal Evaluation: The primary irritation index, based on scores of edema and erythema, was 4.0, and thus Acticin 0.025% Gel was found not to be a primary irritant. No corrosion of the skin was noted.

Primary Eye Irritation Study

Laboratory:

Number of Animals: 12 (3/sex/group)

Animal Strain: New Zealand White Rabbits

Formulation: Acticin 0.025% Gel (PDT 004-002)

Dose Level: 0.1 ml to one eye/animal

Duration: 6 animal eyes were not rinsed, 6 animal eyes were rinsed with lukewarm tap water for 1 minute following 30 seconds of sample contact.

Method: Rabbit eyes were administered Acticin 0.025% Gel, and then rinsed (6 animals) or not rinsed (6 animals). At 24 hours, all rabbit eyes were rinsed with physiological saline. Eyes were examined and graded by the Draize method for ocular reactions at 24, 48, and 72 hours following dose administration.

Ophthalmic Evaluation Results: Acticin 0.025% Gel produced corneal opacity (maximum score 2) in rinsed and unrinsed eyes that persisted up to day 10 in unrinsed eyes and up to day 7 in rinsed eyes. In the conjunctiva, erythema, swelling, and discharge were noted up to day 7 in rinsed and unrinsed eyes, although the findings were generally longer lasting and more severe (maximum score 2) in unrinsed eyes. No corrosion was seen in rinsed or non-rinsed eyes. The material was considered an irritant in unrinsed eyes.

13-Week Dermal Irritation and Toxicity Study

Laboratory:

Animal Strain: New Zealand White rabbits, approximately 15 weeks old, 2.2 to 2.6 kg.

Animals: 7/sex/group (42 total)

Test Materials: Polyolprepolymer-2 (PDT 002-002)

Route: Dermal

Duration: at least 13 weeks, dosing 5 days/week

Study Design & Dose Levels:

Group	Treatment	Dose level (mg/kg)	Dose Level (ml/kg)
1	Vehicle Control	125	0.125
2	polyolprepolymer-2 (PDT 002-002)	200	0.200
3	polyolprepolymer-2 (PDT 002-002)	500	0.500

Methods: The appropriate test material was applied to two application sites clipped of fur on each animal: an abraded or a non-abraded site. Test materials were applied over the skin site and occluded. Animals were collared; after approximately 6 hours of exposure, occlusions were removed, remaining test material was wiped off, and the collars were removed.

Results:

Mortality: All animals survived to scheduled euthanasia.

Clinical Observations: No compound-related changes were noted, except for changes in the skin (discussed below).

Body Weights and Food Consumption: Body weights and body weight gains were slightly and sporadically depressed in the treated groups, but none of the differences were statistically significant. Food consumption was similarly decreased; the decrease was statistically significant during week 7 for males in both treated groups.

Dermal Irritation Results: Occasional desquamation and slight erythema was noted in males and females in the low and high dose groups (1-3 males per day, 1-5 females per day). High dose animals were noted with slight erythema earlier and in more animals compared to low dose incidence. One male in the high dose was noted with pustules/papules throughout most of the study. Based on these findings, polyolprepolymer-2 appears to be a slight dermal irritant.

Ophthalmic Observations: No visible lesions were noted at the end of the study.

Hematology (16 parameters): High-dose males had statistically significantly increased red blood cell count (RBC) and hematocrit percentile (HCT%) as compared to control males following 13 weeks of treatment. Other hematology values for high-dose males and females varied slightly from controls, but the difference did not appear to be related to the treatment.

Clinical Chemistry (16 parameters): No significant differences were noted between control and treated groups. As with hematology, some variances were noted between high and control groups, but the changes were not clearly related to treatment.

Organ and Organ-to-Body Weights: No significant differences were noted between groups, except for high-dose females. This group had significantly greater ovary, ovary-to-body, and ovary-to-brain weights.

Gross Necropsy Observations: One high-dose male had a mottled lung; all ovaries appeared normal. No other findings were noted.

Histopathology: Only the control and high-dose animals were examined histopathologically. In the lungs, one control male and one control female had acute alveolar/bronchiolar inflammation; one high-dose male had congestion and three high-dose females had chronic inflammation. Liver infiltrate was noted once each in high-dose male, high-dose female, and control female. One high-dose female was noted to have chronic inflammation (papillary dermis) on abraded skin, and one high-dose female had chronic inflammation (papillary dermis), epidermal hyperplasia, and hyperkaretenosis. In the urinary bladder, calcereous material was noted in two animals in all groups, except for the high-dose females noted with three incidence. One high dose male had an atrophied/degenerated testis. None of the findings appear to be treatment-related. All other findings were not remarkable.

91-Day Dermal Irritation and Toxicity Study

Laboratory:

Animal Strain: Crl:CD-1®(ICR) BR Mice

No. of Animals: 20/sex/group

Test Materials: Acticin 0.025% Gel (PDT 004-002)

Route: Dermal

Duration: At least 91 days

Study Design & Dose Levels:

Group	Formulation	Dose of Tretinoin (mg/kg/day)	Dose Conc. (% of Tretinoin)	Dose Volume (ml/kg)
1 (control)	Gel Vehicle (PDT 004-006)	0	0	3.33
2 (low dose)	Acticin 0.025% Gel (PDT 004-002)	0.07	0.025	0.33
3 (mid dose)	Acticin 0.025% Gel (PDT 004-002)	0.25	0.025	1.17
4 (high dose)	Acticin 0.025% Gel (PDT 004-002)	0.70	0.025	3.33

Methods: The appropriate test material was applied to the back (clipped of fur) on each animal every day for 13 weeks. The exposure area constituted at least 10% of the animal body surface area. After approximately 6 hours of exposure all remaining test material was wiped off.

Results:

Mortality: One mid-dose male was found dead; all other mice survived to scheduled euthanasia.

Clinical Observations: In male mice (all groups) and one mid-dose female, palpable masses in the urogenital area were noted. All other findings were in the range of normal for mice, except for findings in the skin (detailed below).

Body Weights: Low dose male body weights were significantly below control on days 71 and 91 and generally lagged below control values following 1 week of treatment. High-dose male

body weight gains were significantly less than control in week 8. All differences, however, were minimal (less than 10%). All other body weights and all body weight gains in male mice were similar. Female body weights were similar for all groups. Female body weight gains were significantly below control for the low-dose during week 3; for the mid-dose during weeks 2 and 6, and for the high dose in weeks 3 and 6.

Food Consumption: Food consumption was significantly below control values for mid-dose males in weeks 7 and 10, and in high-dose males for weeks 7, 10, 11, 12, and 13. High dose female values were significantly below control in weeks 2, 4, 6, 9, 10, 11, 12, and 13.

Dermal Irritation Results: Compound-related findings were noted in both the males and the females. Observations included erythema, edema, atonia, desquamation, fissuring (males only), eschar areas, thickened skin, and skin whitening (males only). These findings increased in quantity and severity with increasing dose-level.

Ophthalmic Observations: Ophthalmological examination revealed corneal crystals in the week 13 examination. The reviewing ophthalmologist (David A. Wilkie DVM, MS, Diplomate ACVO; Ohio State University) did not consider the changes to be related to compound treatment.

Hematology (16 parameters): In low-dose males, leukocytes and segmented neutrophils were significantly decreased when compared to control values. In low-dose females, reticulocytes were significantly decreased compared to control values. All other values were comparable; no findings were considered treatment related.

Clinical Chemistry (6 parameters): In all treated animals (low-, mid-, and high dose males and females), mean aspartate transferase (AST) values were significantly greater than control values. Glucose was significantly decreased in mid-dose males, and urea nitrogen was significantly increased in low and high-dose females in comparison to control values. (Mid-dose females were also increased, although the difference was not statistically significant.)

Organ, Organ-to-Body, and Organ-to-Brain Weights: Differences between control mean values and mean values from the Acticin-treated animals are summarized on the following page.

Organ	MALES			FEMALES		
	Low Dose	Mid Dose	High Dose	Low Dose	Mid Dose	High Dose
Kidney Wt.	↓*	↓*	↓			
Kidney:Brain	↓*	↓*	↓			
Heart Wt.	↓*	↓ (slt)	↓ (slt)			
Heart:Body	↓*	↓	↓	↓		
Heart:Brain	↓*	↓*	↓*			
Liver Wt.	↓*	↓	↓ (slt)	↓	↓*	
Liver:Body	↓*	↓	↑	↓*	↓*	↓ (slt)
Liver:Brain	↓*	↓*	↓			
Brain Wt.						
Brain:Body	↑	↑	↑*			

↓ or ↑ indicate a decrease or increase, respectively, from mean control values; * indicates change was statistically significant; slt is the abbreviation for a slight change; dose levels with no entries were virtually equal to control values

Although numerous changes are noted, particularly in the kidney, heart and liver, consideration should be given to the fact that in both males and females the changes decrease or even disappear in the high dose (except in male heart:brain weight).

Gross Necropsy Observations: At necropsy, three high-dose males had enlarged mandibular lymph nodes. Male mice also had enlarged inguinal lymph nodes in low- (1 observation), mid- (2) and high-dose (10) animals; and enlarged axillary lymph nodes in the mid- (3) and high-dose (10) mice. Female mice had enlarged inguinal lymph nodes in the low (10) and high (3) doses; and enlarged axillary lymph nodes in the mid- (1) and high- (3) dose groups. Other findings did not appear to be treatment related.

Histopathology: Only low- and high-dose tissues were evaluated from the brain, heart, kidneys, liver, lungs, skin, thymus, and gross lesions. The reviewing pathologist (Robert G. Geil, DVM, Diplomate) considered treatment-related findings in the skin to include acanthosis, hyperkeratosis, and chronic dermatitis. The changes did not increase with dose level. Outside of the skin area, the only other possibly treatment related effect was in the thymus where a diffuse necrosis of individual lymphocytes was noted. The pathologist, however, noted that the condition could be stress related. All other microscopic findings were consistent with normal background lesions for this age and strain of mice.

Reproduction Parameters: No statistically significant differences were noted between groups. The high-dose group had fewer total mean implantation sites and a greater pre-implantation loss than the control and low-dose groups. The low-dose group had a greater number of early resorptions and post-implantation loss.

Fetal Malformations and Variations: All fetuses appeared normal; no differences were noted.

Segment II Teratology Study

Laboratory:

Number of Animals/Group: 18/group

Animal Strain: New Zealand White female rabbits

Animal Age & Weight: Approximately 6 months old, from 3.1 to 4.5 kg

Dose levels/Study Design:

Group	Compound	Tretinoin Dose (mg/ kg/day)	Dosage Conc. - % Active	Dosage Volume (ml/kg)
1	PDT 004-006 (gel vehicle)	0	0	2
2	Sham control	0	0	0
3	PDT 004-002 (Acticin gel)	0.42	0.025	2
4	PDT 004-003 (Retin-A® gel)	0.40	0.025	2
5	PDT 004-031 (Retin-A® cream)	1.82	0.100	2
6	PDT 004-046 (Acticin cream)	1.82	0.100	2

Route of Administration: Dermal

Methods: Test materials were applied dermally beginning on gestation day 5 on the clipped backs in three areas that were rotated for treatment every 3 days. Collars were placed on the rabbits immediately prior to dosing, and were left on the females for 6 hours. At 6 hours,

any remaining test material was wiped off, the area was washed, and the collars were removed. Animals that aborted were euthanized. All surviving females were euthanized on gestation day 29 and fetuses were evaluated for visceral and morphologic abnormalities. Does were grossly evaluated at necropsy; uterine contents were evaluated and implantation sites were counted.

Results:

Mortality: The Acticin gel-treated group had four unscheduled deaths: three females that aborted and 1 moribund animal were euthanized. The other treated groups had one unscheduled death each. Groups treated with Retin-A® gel or the Acticin cream formulation each lost a female due to abortion; the group 5 treated with the Retin-A® cream product had one unscheduled death due to an accidental injury.

Pregnancy Rate: Pregnancy rates ranged from 100% in the gel vehicle treated group to 89% in the Acticin Cream group; all other groups had a 94% pregnancy rate. The pregnancy rate did not appear to be decreased by tretinoin treatment.

Clinical Observations: Several clinical observations were noted that indicated the animals were discomforted by the tretinoin-containing treatments. Observations included vocalization and animals struggling during dosing or rinsing; these observations were particularly high in the Retin-A® cream-treated group. Other observations were considered within the range of normal.

Dermal Evaluation: Clinical observations at the exposure sites included slight to moderate erythema, slight desquamation, and multiple red areas in the gel control group; the sham controls had no abnormal dermal observations. Animals in the treated groups had a large number of observations indicating severe irritation at the treatment sites; observations included slight to severe erythema, slight edema, atonia, desquamation, fissuring, eschar areas, thickened skin, bleeding, and red raised areas. Additionally, despite washing, residual test material was often noted at or around the treated site.

Body Weight Gain and Food Consumption: Body weights were similar for all groups throughout gestation. However,the Retin-A® and Acticin Cream-treated groups had significantly lower body weight gains during days 9-12 and 6-19, and all treated animals had decreased body weight gains to some extent. Food consumption was also lower for the two cream-treated groups and it was significantly less than control during days 9-12.

Maternal Necropsy: Observations at necropsy were not considered out of the ordinary for this size and sex of animal undergoing dermal dosing.

Reproduction Parameters: All tretinoin-treated animals (except for the commercial gel formulation, Retin-A® gel group) had an increase in the mean number of late resorptions. Retin-A® cream-treated had a slightly greater pre-implantation loss, fewer viable fetuses, and

larger fetal weights; none of these findings, however, were statistically significant. Statistically significant findings consisted of greater post-implantation loss in the Acticin gel group and significantly fewer male fetuses in the Retin-A® cream group. All other gravid females generally were comparable across groups for reproduction parameters.

Fetal Malformations: Fetal malformations are summarized in the table on the following two pages. Several findings in the treated fetuses appear to be drug related. All of the tretinoin-treated groups had a higher incidence of domed head; this difference was statistically greater than controls for the Retin-A® Gel-treated group only. Treated groups also had a higher incidence of cleft palate, flexed paw, and omphalocele, although these differences were not statistically significant. In the visceral examination, groups treated with Acticin 0.025% Gel and the Retin-A® products had a statistically significant greater incidence of hydrocephaly; The Acticin 0.1% Cream-treated group also had a higher incidence of hydrocephaly, although it was not statistically significant. Other visceral findings did not appear to be drug related. In the skeletal examination, the Retin-A® cream group had a significantly greater number of skull anomalies when compared to control. Total malformations consisted of a significantly greater number of soft tissue malformation for the Acticin gel-treated group, greater number of external tissue malformations for the Retin-A® gel group , and a greater number of external, skeletal, and total malformations for the Retin-A® cream group. Acticin 0.1% Cream group also was noted to have a greater number of malformations, although the findings were not statistically significant.

SLS STUDY NO.: 3313.3
CLIENT: PENEDERM INC.
CLIENT NO.: TOX 004-026

TABLE 10
DERMAL TERATOLOGY STUDY IN RABBITS WITH PDT 004 COMPOUNDS
SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

	FETUSES/LITTERS					
GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	0	0.42*	0.40	1.82	1.82
	GEL VEHICLE (PDT 004-006)	SHAM CONTROL	GEL PRODUCT FORMULATION (PDT 004-002)	COMMERCIAL GEL PRODUCT (PDT 004-003)	COMMERCIAL CREAM PRODUCT (PDT 004-031)	CREAM PRODUCT FORMULATION (PDT 004-046)
NUMBER EXAMINED EXTERNALLY	109/ 18	121/ 17	78/ 13	105/ 16	67/ 15	95/ 15
DOMED HEAD	1/ 1	1/ 1	9/ 5	14/ 6*	9/ 5	8/ 4
CLEFT PALATE	1/ 1	0/ 0	3/ 2	1/ 1	6/ 3	3/ 2
FLEXED PAW	1/ 1	0/ 0	1/ 1	3/ 1	5/ 4	4/ 3
OMPHALOCELE	0/ 0	0/ 0	0/ 0	1/ 1	1/ 1	0/ 0
HIGH-ARCHED PALATE	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
OPEN EYELID(S)	0/ 0	0/ 0	1/ 1	0/ 0	1/ 1	0/ 0
MICROGNATHIA (MAXILLARY OR MANDIBULAR)	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
GASTROSCHISIS	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
KINKED TAIL	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
NUMBER EXAMINED VISCERALLY	109/ 18	121/ 17	78/ 13	105/ 16	67/ 15	95/ 15
HYDROCEPHALY	1/ 1	2/ 1	12/ 6*	15/ 7*	10/ 6*	9/ 4
HEART AND/OR GREAT VESSEL ANOMALY	1/ 1	1/ 1	1/ 1	0/ 0	0/ 0	0/ 0
ADRENAL(S) ANOMALY	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
TRANSPOSITION OF THE GREAT VESSELS	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0
NUMBER EXAMINED SKELETALLY	109/ 18	121/ 17	78/ 13	105/ 16	67/ 15	95/ 15
APPENDICULAR SKELETAL DEFECT	0/ 0	0/ 0	2/ 2	1/ 1	3/ 3	0/ 0
EXTRA SITE OF OSSIFICATION ANTERIOR TO STERNEBRA #1	2/ 2	1/ 1	0/ 0	1/ 1	5/ 3	1/ 1
SKULL ANOMALY	0/ 0	0/ 0	0/ 0	0/ 0	12/ 4*	4/ 2
RIB ANOMALY	0/ 0	1/ 1	0/ 0	0/ 0	2/ 2	0/ 0
COSTAL CARTILAGE ANOMALY	0/ 0	0/ 0	2/ 2	1/ 1	2/ 2	1/ 1
STERNEBRA(E) MALALIGNED (SEVERE)	0/ 0	1/ 1	0/ 0	0/ 0	1/ 1	0/ 0
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	0/ 0	0/ 0	2/ 2	1/ 1	3/ 2	1/ 1

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05

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TABLE 10
DERMAL TERATOLOGY STUDY IN RABBITS WITH PDT 004 COMPOUNDS
SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

	FETUSES / LITTERS					
GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	0	0.42	0.40	1.82	1.82
	GEL VEHICLE (PDT 004-006)	SHAM CONTROL	GEL PRODUCT FORMULATION (PDT 004-002)	COMMERCIAL GEL PRODUCT (PDT 004-003)	COMMERCIAL CREAM PRODUCT (PDT 004-031)	CREAM PRODUCT FORMULATION (PDT 004-046)
TOTAL MALFORMATIONS						
NUMBER WITH EXTERNAL MALFORMATIONS	2/ 1	1/ 1	9/ 5	14/ 6*	11/ 7*	9/ 4
NUMBER WITH SOFT TISSUE MALFORMATIONS	2/ 2	3/ 2	13/ 7*	15/ 7	10/ 6	9/ 4
NUMBER WITH SKELETAL MALFORMATIONS	2/ 2	3/ 3	4/ 4	3/ 2	23/ 9*	6/ 3
TOTAL NUMBER WITH MALFORMATIONS	5/ 4	6/ 5	15/ 9*	16/ 8	29/ 10*	16/ 6

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05

SLS STUDY NO.: 3313.3
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TABLE 11
DERMAL TERATOLOGY STUDY IN RABBITS WITH PDT 004 COMPOUNDS
SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

	FETUSES / LITTERS					
GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	0	0.42	0.40	1.82	1.82
	GEL VEHICLE (PDT 004-006)	SHAM CONTROL	GEL PRODUCT FORMULATION (PDT 004-002)	COMMERCIAL GEL PRODUCT (PDT 004-003)	COMMERCIAL CREAM PRODUCT (PDT 004-031)	CREAM PRODUCT FORMULATION (PDT 004-046)
NUMBER EXAMINED EXTERNALLY	109/ 18	121/ 17	78/ 13	105/ 16	67/ 15	95/ 15
NUMBER WITH FINDINGS	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
NUMBER EXAMINED VISCERALLY	109/ 18	121/ 17	78/ 13	105/ 16	67/ 15	95/ 15
HEMORRHAGIC RING AROUND THE IRIS	2/ 2	1/ 1	1/ 1	1/ 1	1/ 1	0/ 0
RETROCAVAL URETER	1/ 1	4/ 4	4/ 3	4/ 3	0/ 0	1/ 1
MAJOR BLOOD VESSEL VARIATION	8/ 5	2/ 2	4/ 2	2/ 2	6/ 2	5/ 4
TRACHEA ANOMALY	1/ 1	0/ 0	2/ 2	0/ 0	3/ 2	2/ 1
NUMBER EXAMINED SKELETALLY	109/ 18	121/ 17	78/ 13	105/ 16	67/ 15	95/ 15
STERNEBRA(E) MALALIGNED(SLIGHT OR MODERATE	32/ 14	43/ 11	19/ 8	41/ 15	16/ 8	25/ 10
13TH RUDIMENTARY RIB(S)	31/ 14	26/ 15	16/ 8	16/ 10	9/ 5*	13/ 11
7TH CERVICAL RIB(S)	3/ 3	2/ 2	0/ 0	0/ 0	10/ 5	1/ 1
HYOID ARCH(ES) BENT	9/ 7	9/ 4	5/ 3	14/ 8	8/ 5	5/ 4
13TH FULL RIB(S)	41/ 13	42/ 14	24/ 9	57/ 15	33/ 12	44/ 14
27 PRESACRAL VERTEBRAE	16/ 8	23/ 14*	18/ 8	22/ 10	20/ 7	29/ 11
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	4/ 3	5/ 2	0/ 0	3/ 3	0/ 0	1/ 1
ACCESSORY SKULL BONE(S)	1/ 1	0/ 0	0/ 0	3/ 3	1/ 1	2/ 2
SPHERICAL ENLARGEMENT OF THE RIB(S)	1/ 1	1/ 1	1/ 1	1/ 1	0/ 0	1/ 1
STERNEBRAE WITH THREAD-LIKE ATTACHMENT	0/ 0	0/ 0	3/ 3	2/ 1	1/ 1	1/ 1
25 PRESACRAL VERTEBRAE	0/ 0	0/ 0	1/ 1	0/ 0	1/ 1	0/ 0
REDUCED OSSIFICATION OF THE SKULL	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
STERNEBRA(E) #1,#2,#3 AND/OR #4 UNOSSIFIED	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05

Mutagenicity Studies

Ames (Bacteria) Mutagenicity Assay *(In Vitro)*

This assay was performed at . PDT 002-002 was tested using the Salmonella/mammalian-microsome plate incorporation assay at concentrations of 667, 1000, 3333, 6667, and 10,000 μg/plate. Generally, this assay evaluates the mutagenicity potential of the test article for its ability to induce back mutations at selected loci in several strains of Salmonella.The tester strains used in the study consist of TA-98, TA-100, TA1535, TA1537, and TA1538. The assay was performed in triplicate and DMSO was used as the vehicle. A positive control was included to verify all tests.

All concentrations of PDT 002-002 were negative for mutagenicity in this assay.

Mouse Lymphoma Mutagenicity Assay *(In Vitro)*

This assay was performed at PDT 002-002 was tested using in the L5178Y TK+/- mouse lymphoma mutagenicity assay with and without S-9 (which adds some metabolizing capabilities). This assay tests for specific locus mutations in a mouse lymphoma cell line. Without S-9 activation, PDT 002-002 was tested at 0.05, 0.1, 0.5, 1.0 , and 5.0 μl/ml. With activation, tests were performed at 0.1, 0.8 1.4, 2.1, and 2.9 μl/ml. (In an initial toxicity test, PDT 002-002 was found to be toxic at 50 μl/ml for all cultures.) DMSO served as the solvent for all materials tested. Three counts per plate were made and the median value was reported. A positive control was included to verify all tests. A substance is considered a positive mutagen in this test if there is a positive dose response and the mutant frequency is double the background growth.

Assays performed at the described dose levels were negative for mutagenicity.

Mouse Micronucleus Bone Marrow Erythrocyte Assay *(In Vivo)*

This assay was performed at PDT 002-002 was tested in the micronucleus bone marrow erythrocyte assay for chromosome-breaks or mitotic spindle damage. The test is evaluated through erythroblasts undergoing final DNA replication and mitosis before the main nucleus is expelled. When chromosome breaks or spindle abnormalities occur during erythrocyte division, abnormal chromosomes and their fragments are left in the daughter cells. These are counted as micronuclei. The assay of PDT 002-002 first included a dose range-finding study dose levels of 313, 625, 1250, 2500, and 5000 mg/kg for two days (3/sex/group). This was followed by a sponsor-described "definitive" assay at 1250, 2500, and 5000 mg/kg/day (10/sex/group). Both the range-finding and the definitive test included control mice dosed with corn oil; the definitive test also included a positive control group dosed with benzene. Mice were evaluated by clinical observations, cytotoxicity, and micronucleus formation in bone marrow erythrocytes. A maximum tolerated dose level (MTD) should be reached in the mice, and the data should be

expressed as a ration of polychromatic erythrocytes (PCEs) to total erythrocytes (RBCs). A compound would be considered positive for genotoxicity if they have a larger number of micronuclei than noted in the negative controls and if the number increases with increasing dose level.

In the pilot study, male mice were noted to have fight wounds, scabs, and rough fur. The PCEs were comparable to controls at all dose levels. In the definitive assay, male mice were again noted to have fight wounds, scabs, and rough fir. One male mouse dosed with benzene was found dead on day 2, although its death was thought to be fight related. At both the 24 and 48 hour harvest no significant differences were noted between the negative control animals and the PDT 002-002 animals in evaluation of PCEs. The benzene-treated group had significantly increased PCEs, approximately 5 to 10 times greater than negative controls. PDT 002-002 may be considered negative for genotoxicity in mice based on the time and conditions of this test.

The following studies were previously reviewed by Dr. Syed Alam. The studies are summarized below.

***In Vitro* Percutaneous Absorption Studies in Human Cadaver Skin**

The table on the following page summarizes the findings of nine studies using the Franz assay system to test several formulations. In brief, the studies demonstrate that Acticin seems to be absorbed somewhat less than Retin-A®, although less than 5% of both compounds penetrated to the receptor fluid under all conditions of the assays.

Primary Eye Irritation in Rabbits

The sponsor performed nine primary eye irritation studies in rabbits. The studies are summarized on the table below. For all studies, gross observations were performed under white light and longwave UV light subsequent to fluoresceine staining. Eyes were scored by the method of Draize. In brief, none of the materials were corrosive and all signs of conjunctivitis cleared with 48 hours.

Primary Skin Irritation Potential in Rabbits

New Zealand White rabbits (6) were given 0.5 ml Acticin 0.25% gel (PDT 004-002) or Retin-A® Gel (PDT 004-003). Materials were applied to the clipped and abraded skin under occlusion for 24 hour.Observations for erythema and edema were performed at 24 and 72 hours after application. PDT 004-002 and Retin-A® produced a skin irritation score of 3.1 and 3.8, respectively, and therefore are not considered primary skin irritants.

Material Tested	Dose (mg/cm^2)	Duration (hours)	Method of Quantification	Results
PDT 002-001 45% w/w in 95% ETOH	225	24	UV Spec.	No compound was detectable in the receptor fluid; minimum sensitivity level was 50μg.
PDT 002-002 neat in ETOH	45-140	48	Radio-label with ^{14}C; scintillation count and gel permeation chromatography	Highest penetration was in the 25% petrolatum based ointment; epidermal levels reached approximately 7%, dermal levels were 1.2%. Lowest penetration used 100% PDT 002-002 with 1.1% in the epidermis and 0.2 % in the dermis. All receptor levels were < 1%.
Retin-A®, PDT 004-002, PDT 004-007 (no polyolprepolymer-2)	3.18	40	same as above	Retin-A® penetrated at 18.3%, 0.2% and 0.4% ; PDT 004-002 at 27.4%, 0.4%, and 0.4%; and PDT 004-007 (no polyolprepolymer-2) at 65%, 1.3%, and 0.3% into the SC/epidermis, dermis, and receptor fluid, respectively.
Retin-A® Cream, PDT-004,044, 045, and 046 (Acticin creams)	10/0.64	48	same as above	For all test materials, 99.1 ± 1.3% of the applied radioactivity was removed from the skin surface by ethanol wash. The absorption of the 0.025% formulation was comparable between Acticin and Retin-A® formulations. The absorption of the 0.05% Acticin was somewhat greater than the control formulation. But at 0.1%, absorption from Retin-A® was significantly greater than the Acticin formulation.
Tretinoin Ointment (0.1%, 0.3%, 0.5%) , 0.1% Retin-A® cream, and two "Frost & Weinstein" formulations	3.2/0.64	24	same as above, but used ^{3}H-tracer	The percent of applied dose for high-dose PDT 004-070 was 1.86 ± 0.54, 1.08 ± 0.68, and 0.79 ± 0.31 for the epidermis, dermis, and receptor fluid, respectively. No statistical differences were noted between 0.5% tretinoin test formulation and the 0.3% Frost and Weinstein preparation.

Material Tested	Dose (ml)	No. of Animals	Duration	Method	Results
PDT 004-002	0.1	9	1 exposure	6 eye unrinsed, 3 rinsed following 30 second exposure	The material was considered a severe irritant in both rinsed and non-rinsed eyes. No corrosion was noted.
Retin-A® 0.025% Gel	0.1	9	1 exposure	6 eye unrinsed, 3 rinsed following 30 second exposure	The material was considered a severe irritant in both rinsed and non-rinsed eyes. No corrosion was noted.
in petrolatum: PDT 002-001 (10%) and PDT 002-002 (10%, 20%)	0.1	6	1 exposure	6 eyes with and without rinsing	The materials produced no corneal opacity, iritis, or significant conjunctivitis. No corrosion was observed. The materials were "practically non-irritating."
in petrolatum: PDT 002-001 (10%) and PDT 002-002 (10 & 20%)	0.1	6	1 exposure	6 eyes without rinsing, evaluations to 3 days	The 10% formulations produced conjunctival irritation clearing in 24 hours; 25% formulation required 3 days to clear.
Acticin 0.1% Cream (PDT 004-046)	0.1	6	1 exposure	6 eyes rinsed after 30 seconds, 6 eyes unrinsed	All eyes cleared by 48 hours; no corneal involvement was noted, the compound was considered "practically non-irritating."
Retin-A® 0.1% Cream	0.1	6	1 exposure	6 eyes rinsed after 30 seconds, 6 eyes unrinsed	All eyes cleared by 48 hours; no corneal involvement was noted, the compound was considered "practically non-irritating."
0.2% retinoic acid solution	0.1	6	1 exposure	all eyes (6) rinsed 24 hours post exposure	Irritation cleared by 48 hours. No corrosion was noted. The material was considered a "mild irritant."
tretinoin ointment (0.1, 0.3, 0.5%; PDT 004-068, 069, and 070)	0.1	6	1 exposure	all eyes (6) rinsed 24 hours post exposure	All formulations were "virtually non-irritating" to the eye. There was no evidence of irritation to either the iris or cornea in any animal in any formation.

Repeat Skin Irritation Test in Guinea Pigs

This study was performed at the

NOTE: This laboratory was found to be out of regulatory compliance (profoundly) on 11/26/91 and thus this study is considered unacceptable. Penederm was informed by letter that the studies performed by this laboratory will not be considered in support of an application for research or marketing.

Acute Toxicity (LD_{50})

Acticin 0.025% Gel (PDT 004-002) and Retin-A® 0.025% Gel (PDT 004-003) was given to 10/group Sprague Dawley rats orally. The LD_{50} was greater than 5.0 g/kg, and is thus considered to be of very low toxicity.

An LD_{50} was performed in BALB/C mice using polyolprepolymer-2 (PDT 002-001) in 2% ethanol. It is not clear whether this study was performed at and is therefore not acceptable. It is included here for completeness. Deaths occurred within 15 minutes of injection; observations included quivering and convulsions followed by death. LD_{50} was estimated to be "approximately" 3.7 g/kg.

Polyolprepolymer-2 (PDT 002-002) was given to 10 Sprague Dawley rats by gavage. Two rats died on the day of dosing. At necropsy, no gross pathology was reported in any rat. The LD_{50} was estimated at 5.0 g/kg, and is thus considered to be of very low toxicity.

Hypersensitivity Test in Guinea Pigs

Ten Hartley guinea pigs were given a 10% concentration of polyolprepolymer-2 (PDT 002-002) in a GLP hypersensitivity study (Maguire, 1973, modified, J. Soc. Cosm. Chem., 24, 151-162. Prince and Prince, 1977, Cosmetic Toiletries, 92, 53-58). No allergic contact dermatitis was noted in the guinea pigs.

Comedogenicity Study in Rabbits

New Zealand White rabbits (6) had applied 0.2 ml of polyolprepolymer-2 (25% w/v) on the inner surface at the basal portion of the right ear once daily, five days per week, for three weeks. The test materials were found to be non-comedogenic; evaluation included histopathology of the ear skin.

28-Day Percutaneous Toxicity Study in Rabbits

New Zealand Albino rabbits [20/group (10/sex)] were given Polyolprepolymer-2 (100, 25, or 10%) on the clipped dorsal skin under occlusion once daily for a total of 28 doses. The test material was left on the skin for 6-8 hours. Smaller adrenal glands were noted in males dosed at 25%; no other significant group differences were reported. In the histopathological

exam, chronic inflammation was noted in the low-dose animals. All other findings were considered incidental and not related to treatment.

Summary and Conclusion

Penederm Inc., Foster City, CA has filed this NDA for approval of Acticin 0.025, 0.05 and 0.1% Cream, retinoid formulations (tretinoin, all-*trans*-retinoic acid) to be applied dermally for the treatment of acne vulgaris. A second ingredient in the formulations is polyolprepolymer-2, which according to the sponsor adds qualities to their formulation that makes them superior to the already-marketed Retin-A® products. Polyolprepolymer-2 is the only difference in formulation between Retin-A® and Acticin. Polyolprepolymer-2 is a new entity that has never been through the IND/NDA safety review process.

The sponsor presented results from an assortment of formulations in the IND and NDA: studies of Acticin cream and gel products, Retin-A® creams and/or gels, along with an array of other formulations. The only data summarized below, however, is what directly supports this NDA for Acticin creams, and includes solely (1) Acticin creams and gel, (2) Retin-A® products, (3) polyolprepolymer-2 (PDT 002-002), and (4) appropriate controls. All else is considered background.

For clarity the summary is divided into two sections: data from polyolprepolymer-2 studies, and data from the Acticin/Retin-A® studies.

Polyolprepolymer-2 Summary:

In the non-GLP *in vitro* **percutaneous absorption studies** in human cadaver skin (the Franz system), polyolprepolymer-2 (PDT 002-002) in ethanol had receptor rates up to 1.2% with 7% epidermal levels at the high concentration (25%). This appears to be a relatively low level of absorption, however, no standard positive control was tested in this assay. According to Dr. Thomas Franz (personal communication) percutaneous assays usually include the positive control tritiated water. But the sponsor did include Retin-A® 0.025% Gel as a positive control, which as expected exhibited low levels of absorption. Thus, the assay appears to at least be qualitatively acceptable, and supportive of the sponsor's claim that polyolprepolymer-2 has low absorption potential into human skin.

In **primary eye irritation studies** in rabbits, polyolprepolymer-2 (0.1 ml, 25% concentration in petrolatum) applied without rinsing caused conjunctival irritation that cleared within 3 days; a similar experiment involving rinsed eyes was graded at "practically nonirritating." In acute toxicity tests, polyolprepolymer-2 (PDT 002-002) had an LD_{50} greater than 5.0 g/kg, which indicates very low toxicity. Polyolprepolymer-2 also was tested for **hypersensitivity in guinea pigs; and codedogencity and 28-day percutaneous toxicity in rabbits.** Polyolprepolymer-2 was found to be negative for allergic dermatitis and comedogenicity. In

the toxicity study, no findings were clearly dose-related. These irritation, acute, and subacute toxicity studies submitted by the sponsor support the claim that polyolprepolymer-2 is a slight irritant of low toxicity.

The longest study done for polyolprepolymer-2 alone was a **13-week dermal irritation and toxicity study** in New Zealand White rabbits. No compound-related changes were noted, except for changes in the skin. Occasional desquamation and slight erythema were noted in males and females in the low and high dose groups (1-3 males per day, 1-5 females per day). High dose animals were noted with slight erythema earlier and in more animals compared to low dose incidence. One high-dose male was noted with pustules/papules throughout most of the study. Based on these findings, polyolprepolymer-2 appears to be a slight dermal irritant. No other visible lesions were noted at necropsy. In hematology and clinical chemistry tests, some variances were noted between high-dose and control groups, but the changes were not clearly related to treatment. High-dose females had significantly greater ovary, ovary-to-body, and ovary-to-brain weight. The finding, however, appears to be unimportant because no ovarian lesions were noted in the gross necropsy and the histopathology. (Only the control and high-dose animals were examined histopathologically.) One high-dose female was noted to have chronic inflammation (papillary dermis) on abraded skin, and one high-dose female had chronic inflammation (papillary dermis), epidermal hyperplasia, and hyperkaretenosis. Several lesions were noted in the lung, liver, and bladder, but they did not appear in a dose-related manner, and thus none of the findings appear to be treatment-related. All other findings were not remarkable. In conclusion, under the conditions of this study, polyolprepolymer-2 was not systemically toxic and caused slight skin irritation.

The sponsor performed a **dermal teratology pilot study** in New Zealand White female rabbits using polyolprepolymer-2 (1000, 2000 mg/kg/day). Fetal evaluation of malformations and variations was done by external evaluation only. Slight desquamation was noted at a slightly higher rate in the treated females when compared to controls. The high dose group was noted to have a high incidence of unkempt appearance, possibly because the formulation was extremely sticky. Other findings were considered within the range of normal. No statistically significant differences were noted between groups for pregnancy parameters. The high-dose group had fewer total mean implantation sites and a greater pre-implantation loss than the control and low-dose groups. The low-dose group had a greater number of early resorptions and post-implantation loss. These findings may indicate that the compound is feto-toxic, especially because no maternal toxicity was noted. This data is from a pilot study with no follow-up study. As such, the findings are equivocal. All fetuses appeared normal; no differences were noted. Under the conditions of this pilot study, polyolprepolymer-2 is not teratogenic.

The sponsor submitted three mutagenicity assays. In the ***in vitro*** **Ames assay,** polyolprepolymer-2 was negative for mutagenicity. In an ***in vitro*** **mouse lymphoma assay,** polyolprepolymer-2 was tested using in the L5178Y TK+/- mouse lymphoma mutagenicity assay (without S-9 activation at 0.05, 0.1, 0.5, 1.0 , and 5.0 μl/ml and with activation at

0.1, 0.8 1.4, 2.1, and 2.9 μl/ml) Assays performed at the described dose levels were negative for mutagenicity. This assay, however, would have been more meaningful if the sponsor had tested one or two dose levels between 5.0 μl/ml and 50μl/ml. As the test was performed, the dose levels have simply portrayed the no-effect level and the toxic level; the value of the assay (as performed by the sponsor) to test the mutagenicity potential of PDT 002-002 is an unknown.

Polyolprepolymer-2 was evaluated in an ***in vivo*** **mouse micronucleus bone marrow erythrocyte assay** for chromosome-breaks or mitotic spindle damage (1250, 2500, and 5000 mg/kg/day, 10/sex/group). Both the range-finding and the definitive test included control mice dosed with corn oil; the definitive test also included a positive control group dosed with benzene. Mice were evaluated by clinical observations, cytotoxicity, and micronucleus formation in bone marrow erythrocytes. A maximum tolerated dose level (MTD) generally should be reached, and although the sponsor did not reach the MTD in dose levels for this test, the high dose level of 5,000 mg/kg/day is considerable; testing beyond that level often is beyond the volume capacity of the mouse. Thus, polyolprepolymer-2 may be considered negative for genotoxicity in mice based on the time and conditions of this test.

Acticin Summary:

The following studies were reviewed previously in the original IND and supplements. These studies are separately summarized because they included results from a different Acticin formulation (presented in Appendix A) from what has been submitted for NDA approval.

In the non-GLP ***in vitro*** **percutaneous absorption** studies in human cadaver skin (the Franz system) Retin-A® 0.025% Gel and Acticin 0.025% Gel penetrated less than 1% into the receptor fluid and 18 and 27%, respectively into the epidermis. In another formulation of Acticin Gel made up without polyolprepolymer-2, less than 1% reached the receptor fluid and 65% was found in the epidermis. As noted above for polyolprepolymer-2, this assay serves as qualitative evidence that Acticin 0.025% Gel has a relatively low absorption rate.

In **primary eye irritation studies** in rabbits, Acticin 0.025% Gel and Retin-A® 0.025% Gel were graded severe irritants; no corneal corrosion was noted (0.1 ml dose, rinsed and unrinsed eyes). In a **primary skin irritation study** in rabbits with Acticin 0.025% Gel and Retin-A® 0.025% Gel applied to clipped and abraded skin, both compounds were not considered primary irritants. In acute toxicity tests for LD_{50}, Acticin 0.025% Gel and Retin-A® 0.025% Gel both had LD_{50} greater than 5.0 g/kg, which indicates very low toxicity.

The following studies had not been previously reviewed.

These studies were done with the formulations of Acticin that are proposed for NDA approval. Except for the *in vitro* percutaneous absorption assay, all of the following studies appear to have been completed under GLP guidelines.

In a non-GLP *in vitro* **percutaneous absorption study** of Acticin 0.025% Gel and Retin-A® 0.025% Gel (10 mg. to each 0.74 cm^2 diffusion cell), Acticin Gel (0.025%) had less than 1% penetration into the epidermis, dermis, and receptor fluid. Penetration of Retin-A® Gel (in both formulations) was only slightly greater. As noted above, this assay serves as qualitative evidence that Acticin 0.025% Gel has a relatively low absorption rate.

For acute/subacute toxicity testing, the sponsor submitted an **oral acute toxicity** test in Sprague Dawley rats. Acticin 0.025% Gel (PDT 004-002) was found to have an LD_{50} of approximately 5.0 g/kg, i.e. a substance of low acute toxicity. In a **14-day dermal toxicity study** with Acticin 0.05 and 0.1% creams 0.025% gel, mice were evaluated for body weights, clinical observations, dermal evaluation, and gross necropsy observations. Acticin was found to be an irritant with no systemic toxic effects.

In a **7-day dermal irritation study** in Hartley guinea pigs, Acticin 0.025% "Research Cream" or Retin-A® 0.025% cream (50 mg) was administered twice/day to the clipped backs of guinea pigs, and the test skin sites were observed clinically for dermal erythema or edema. Following euthanasia, skin samples were evaluated histopathologically. The cream formulations caused statistically more erythema and edema that control values throughout the study (Days 2-8) Acticin cream in general caused more severe dermal irritation effects than the gel. Retin-A® generally caused more severe effects than Acticin products, although for all compounds the severity ranged from very slight to moderate with severity increasing over time. Acticin tested as a moderate irritant that caused classic tretinoin-related histomorphologic changes in guinea pig skin.

Rabbits exposed dermally to Acticin 0.025% Gel (0.05 ml) under occlusion for 24 hours in a **primary skin irritation study**. The primary irritation index, based on scores of edema and erythema, was 4.0, and thus Acticin 0.025% Gel was not found to be a primary irritant. No corrosion of the skin was noted. (Cream products were not tested.)

In a **primary eye irritation study** in New Zealand White rabbits, Acticin 0.025% Gel (0.1 ml to one eye/animal), Acticin 0.025% Gel produced corneal opacity (maximum score 2) in rinsed and unrinsed eyes that persisted up to day 10 in unrinsed eyes and up to day 7 in rinsed eyes. In the conjunctiva, erythema, swelling, and discharge were noted up to day 7 in rinsed and unrinsed eyes, although the findings were generally longer lasting and more severe (maximum score 2) in unrinsed eyes. No corrosion was seen in rinsed or non-rinsed eyes. The material was considered an irritant in rabbit eyes. (Cream products were not tested.)

The longest study performed for Acticin 0.025% Gel was a **91-day dermal irritation and toxicity study** in mice. The creams were not included in this assay. Acticin (0.07, 0.25, and 0.70 mg/kg/day) was applied to the clipped back (10% of body surface area) for 6 hours every day for 13 weeks. One mid-dose male was found dead; all other mice survived to scheduled euthanasia. In male mice (all groups) and one mid-dose female, palpable masses in the urogenital area were noted. All other findings were in the range of normal for mice,

except for findings in the skin (detailed below). Body weights (total or as ratios) and/or food consumption occasionally were significantly below control for treated males and females. Compound -related skin observations included erythema, edema, atonia, desquamation, fissuring (males only), eschar areas, thickened skin, and skin whitening (males only). These findings increased in quantity and severity with increasing dose-level. The ophthalmological examination was negative for compound-related changes. In the hematology evaluation, no findings were considered treatment related. In all treated animals (low-, mid-, and high dose males and females), mean aspartate transferase (AST) values were significantly greater than control values. Glucose was significantly decreased in mid-dose males, and urea nitrogen was significantly increased in low and high-dose females in comparison to control values. (Mid-dose females were also increased, although the difference was not statistically significant.) Numerous changes were noted in organ weights, particularly in the kidney, heart and liver, although consideration should be given to the fact that in both males and females the changes decrease or even disappear in the high dose (except in male heart:brain weight). At necropsy, the only possibly treatment-related finding was increased lymph node weights in treated males and females. Only low- and high-dose tissues were evaluated from the brain, heart, kidneys, liver, lungs, skin, thymus, and gross lesions. The reviewing pathologist considered treatment-related findings in the skin to include acanthosis, hyperkeratosis, and chronic dermatitis. The changes did not increase with dose level. Outside of the skin area, the only other possibly treatment related effect was in the thymus where a diffuse necrosis of individual lymphocytes was noted. The pathologist, however, noted that the condition could be stress related. All other microscopic findings were consistent with normal background lesions for this age and strain of mice.

The dermal application of all levels of Acticin 0.025% Gel resulted in skin irritation with the expected accompanying histomorphological changes in the skin. A confounding factor throughout this study is the lack of restraint during the period the compound was on the mice skin. (The sponsor was not acting irresponsibly; it is a weakness in the study design despite the fact that this is a commonly performed study.) The amount of Acticin ingested by the animals is unknown. In support of this compound, and despite possible oral ingestion, few findings in any observation outside of the skin can be clearly labelled compound related. The changes in liver and kidney enzymes and body weights are of concern, although the observations are not supported by histopathological findings. (A lifetime chronic study would allow us to fully evaluate the effect of the drug to liver and kidney.) Thus under the conditions of this study, Acticin is considered not systemically toxic, although it is clearly a skin irritant.

Of great concern are the findings in the **Segment II teratology study** in New Zealand White female rabbits. The sponsor tested just one dose level of Acticin Cream (0.1%) as well as one dose level of Retin-A® cream (also 0.1%). This dose is approximately 7 times the dose expected to be applied to humans, assuming a 1 cc dose to a 70 kg individual. Test materials were applied dermally for 6 hours to collared rabbits beginning on gestation day 5. The Acticin cream-treated group had one unscheduled death due to abortion. The Retin-A® cream-treated group had one unscheduled death due to an accident. Pregnancy rates were 100% in

the control group and, 94% in the Acticin cream and 89% in Retin-A® cream group.

Several clinical observations were noted that indicated the animals were discomforted by the tretinoin-containing treatments, in particular vocalization and animals struggling during dosing or rinsing. Clinical observations at the exposure sites included slight to moderate erythema, slight desquamation, and multiple red areas in the gel control. Animals in the treated groups had a large number of observations indicating severe irritation at the treatment sites (slight to severe erythema, slight edema, atonia, desquamation, fissuring, eschar areas, thickened skin, bleeding, and red raised areas.) Additionally, despite washing, residual test material was often noted at or around the treated site. Body weights and food consumption were similar for all groups throughout gestation. Observations at necropsy were not considered out of the ordinary for this size and sex of animal undergoing dermal dosing.

Females treated with Acticin and Retin-A® creams had occasional significantly decreased body weight gains and food consumption. Acticin-treated animals had an increase in pre-implantation loss and fewer viable fetuses, although the differences were not statistically significant.

Several findings in the treated fetuses appear to be drug related. Acticin and Retin-A®-treated groups had a higher incidence of domed head; this difference was statistically greater than controls for the Retin-A® group only. Treated groups also had a higher incidence of cleft palate, flexed paw, and omphalocele, although these differences were not statistically significant. In the visceral examination, Acticin and Retin-A®-treated groups had a statistically significant greater incidence of hydrocephaly. Other visceral findings did not appear to be drug related. Total malformations consisted of a significantly greater number of soft tissue malformations for the Acticin group and a greater number of external tissue malformations for the Retin-A® group. For the sake of comparison, the following table presents the abnormal findings as percents and includes historical control data from MARTA (Middle Atlantic Reproduction and Teratology Association) published in September, 1993. The percentage of hydrocephaly and domed head in the Acticin and Retin-A® groups is almost 10 times higher than that seen in the control values in this NDA.

Comparison of Teratogenicity Findings (Fetus/Litter)
(percent of mean)[1]

	External Anomaly: Domed Head (%)	Visceral Anomaly: Hydrocephalus (%)
MARTA Control Values (Summary of all Studies)	Avg: 0.06/0.32	Avg: 0.05/0.24 Max: 3.03/16.67
NDA 20-400 Vehicle Control	0.9/.6	0.9/5.6
Acticin 0.1% Cream	8.4/26.7	9.5/26.7
Retin-A® 0.1% Cream	13.4/33.3	14.9/40.0

In addition, this study is of an unusual design: the sponsor tested several different compounds rather than several doses of Acticin gel. The study design prevents us from investigating an expected attribute of teratogens: increasing severity with increasing dose. A further confounding factor is that animals may have received a higher dose than intended through oral ingestion of dosing material left on the animals fur and through the tretinoin-irritated skin. Also of concern is feto-toxicity: the statistically significant increases in late resorptions and post-implantations in the Acticin-gel treated group combine with the changes seen in the polyolprepolymer-2 pilot teratogenicity study to suggest fetal viability effects. (Polyolprepolymer-2 treated animals in the high dose had fewer mean implantation sites and an increased number of pre-implantation loss; the low-dose had an increased number of early resorptions and post-implantation losses.)

As this study stands, Acticin 0.1% Cream is considered a teratogen and a possible feto-toxicant in rabbits.

Recommendations:

Approval, with the following caveats:

1. The sponsor must complete a one-species carcinogenicity test because of the addition of polyolprepolymer-2, a previously untested compound. This test will also better clarify the findings in increased liver and kidney enzymes and increased lymph node size found in the 91-day dermal study. (The sponsor has sent a letter dated 6/9/94 agreeing to a carcinogenicity study for the gel to begin within four months of final approval of the gel and

[1] Percent of mean = total occurrences of malformations in fetuses or litters / total number of fetuses or litters * 100

cream formulations.)

2. Acticin 0.1% gel must be given at minimum a pregnancy category C.

3. Product labelling has not been submitted and thus cannot be reviewed. Labelling must be submitted and reviewed prior to approval.

4. Establish that the name "Acticin" is acceptable, given its similarity to "Actinex", an already-approved dermatologic drug for actinic keratosis.

Hilary V. Sheevers, Ph.D.

cc:
HFD-340
HFD-540
HFD-540/PHARM/HSHEEVERS
HFD-540/MO/SLIFMAN
HFD-540/CHEM/REJALI
HFD-540/PMS/CHAPMAN

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Concurrence Only:
HFD-540/DD/JWilkin 8/22/94
HFD-540/SPHARM/SALAM 8/24/94

Appendix A

PDT 004-002 - 0.025% Retinoic Acid Gel (from jacket Volume 1.1)
This formulation was utilized in the studies reviewed by Dr. Alam.

Component	Grams/100 g
All-trans-retinoic acid	
PDT 002-002	
Butylated hydroxytoluene	

PDT 004-006 - Gel Vehicle (Vol. 1.1)

Component	Grams/100 g
PDT 002-002	
Butylated hydroxytoluene	

(also used g in some formulations)

Tretinoin Ointment Formulations

Component	PDT 004-068	PDT 004-069	PDT 004-070
Tretinoin, USP			
Butylated hydroxytoluene, NF (BHT)			
Polyolprepolymer-2			

Formulations of Acticin Creams

Component	PDT 004-046	PDT 004-044	PDT 004-055	PDT 004-054
Tretinoin				
✓Purified Water				
✓Stearic Acid NF				
✓Polyolprepolymer-2 (PDT 002-002)				
✓Isopropyl myristate NF				
✓Polyoxyethylene 40 stearate NF				
✓Propylene glycol USP				
✓Stearyl alcohol NF				
✓Xanthan gum, Food Grade				
✓Sorbic acid NF				
Butylated ✓hydroxytoluene				

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-404 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 12-18-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-24-93	9-24-93	
RESUBMISSION	3-28-94	3-29-94	
AMENDMENT/NC	12-11-96	12-12-96	
AMENDMENT/NC	12-13-96	12-16-96	

DEC 20 1996

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME

Proprietary: Avita Cream

Nonproprietary/USAN: Retinoic acid/all-trans
Retinoid acid/Vitamin A

Code Names/#'s:

Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Cream
STRENGTHS: 0.025%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

$C_{20}H_{28}O_2$ Mol.weight:344.44
CAS# [302-79-4]

PATENT STATUS:

3,729,568; expired April 24, 1990
4,247,547; expired January 27, 1998; no exclusivity exists.

SUPPORTING DOCUMENTS:

IND
DMF

DMF

DMF

DMF

DMF

NDA 17-340 Retin A Cream, 0.1%
NDA 17-522 Retin A Cream, 0.05%
NDA 19-049 Retin A Cream, 0.025%

AMENDMENTS:

Dated: December 11, 1996, withdrawal of Avita Cream 0.05% and 0.01%
Received: December 12, 1996.

Dated: December 13, 1996, commitment to add "avoid freezing" to storage condition, see MEMO OF TELECONFERENCE
Received: December 16, 1996.

Dated: December 18, 1996, E-mail from Rita Hassal regarding signed Fonsi by Nancy Sager on December 12, 1996.
Recevied: December 18, 1996.

CONSULTS:

The updated environmental assessment package suitable for release under FOI found to be acceptable. The prepared FONSI was sent to Nancy Sager (HFD-357) on November 25, 1996. The Fonsi was issued on December 12, 1996 by Nancy Segar. The trade name "Avita" was found acceptable by the Labeling and Nomenclature Committee on May 28, 1996.

REMARKS/COMMENTS:

This is the final chemistry review for Avita 0.025% Cream. The only pending issues on this application were EA and final labeling information. The information regarding signed Fonsi by Nancy Sager dated December 12, 1996 is included (Attachment 1). The following comments address our concerns regarding labeling issues:

1. The withdrawal of two strengths of Avita Cream on December 11, 1996. Avita Cream, 0.025% is the only strenght to be marketed. ✓

2. The applicant's commitment to modify the storage condition by including the statement " Avoid freezing " on the labeling. For more information, please see Attachment I, the MEMO TELECONFERENCE between the Review Chemist, Nahid Mokhtari-Rejali, Ph.D., Robin Anderson, Project Manager and Bhaskar Chaudhuri, Ph.D., of Penederm dated December 12, 1996. This information was requested based on chemistry review #2. The applicant had indicated in this review that they have no plan to freeze the product for storage; therefore, no data was submitted for storage under freezing temperature. ✓

3. A draft copy of the container label and the box for shelf use is provided.

4. In the package insert all the requirement for DESCRIPTION Section and HOW SUPPLIED Section are satisfactory. The applicant has committed to add the statement "Avoid freezing" as mentinoed

above. However, it should be noted that although the other strengths of Avita Cream (0.05% &0.1%) have been withdrawn from the application (item #1), nevertheless, the package insert still includes the three strengths, 0.025%. This was brough to Dr. Blatt's attention, Project Manger, on December 18, 1996. Per Dr. Blatt, this has been an oversight from Penderm and would be corrected Immediately.

The applicant has responded adequately to our labeling concern except for the deletion of the two strengths in the package insert and addition of
From a manufacturing and control standpoint, this application is currently adequate to recommend for approval.

Satisfactory EER (#9999) has been received from the Office of Compliance on 5/20/96.

Method validation remains pending, see Chem. Review #3.

CONCLUSIONS:

This application is APPROVABLE from a manufacturing and control standpoint.

Nahid Mokhtari-Rejali

Nahid Mokhtari-Rejali, Ph.D.,
Review Chemist, HFD-540

cc: Orig. NDA 20-404
HFD-540/Division File
HFD-540/Rejali/12/18/96
HFD-540/Labib
HFD-540/Jacobs
HFD-540/Blay
HFD-540/WHDeCamp
HFD-830/Eric Sheinin
HFD-354/Yana Mille
R/D Init by: SUPERVISOR

4. In the package insert all the requirement for DESCRIPTION Section and HOW SUPPLIED Section are satisfactory. The applicant has committed to add the statement "Avoid freezing" as mentinoed

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-404 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 11-29-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-24-93	9-24-93	
RESUBMISSION	3-28-94	3-29-94	
AMENDMENT/AC	7-12-96	7-15-96	
AMENDMENT/BC	6-13-96	6-14-96	
AMENDMENT/BC	11-20-96	11-21-96	DEC 3 · 1996

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME

Proprietary: Avita Cream
Nonproprietary/USAN: Retinoic acid/all-trans Retinoid acid/Vitamin A
Code Names/#'s:
Chemical Type/ Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Cream
STRENGTHS: 0.025%, 0.05% & 0.1%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

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CAS# [302-79-4]

PATENT STATUS:

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SUPPORTING DOCUMENTS:

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DMF

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DMF

DMF

DMF

NDA 17-340 Retin A Cream, 0.1%
NDA 17-522 Retin A Cream, 0.05%
NDA 19-049 Retin A Cream, 0.025%

AMENDMENTS:

Dated: June 3, 1996, the official copy of information faxed on May 31, 1996, regarding specifications for degradants.
Received: June 4, 1996, this information was reviewed in chemistry review #2.

Dated: June 13, 1996, upon my request, three copies of updated method validation including modified HPLC method with revised specifications to be forwarded to LA District.
Received: June 14, 1996, this information was reviewed in chemistry review #2.

Dated: November 20, 1996, Updated EA was submitted upon my request.
Received: November 21, 1996.

CONSULTS:

The updated environmental assessment package suitable for release under FOI found to be acceptable. The prepared FONSI was sent to Nancy Sager (HFD-357) on November 25, 1996. The trade name "Avita" was found acceptable by the Labeling and Nomenclature Committee on May 28, 1996.

REMARKS/COMMENTS:

The applicant has responded to our nonapprovable letter of

June 26, 1996 regarding the deficiencies found in chemistry review #2. It should be noted that Avita cream is a line extension to the Avita gel.

From a manufacturing and control standpoint, the data and information submitted to Avita gel as well as this application are currently adequate to recommend that this application is approvable. The major concerns in two applications were the impurity profiles for the degradants. There is no new information regarding the degradation products since previous review. However, as we suggested, Penederm has committed to further develop the analytical method (PDM 29) to cover all the tretinoin degradation products in the finished drug products and aged products. This should include specifications for all the photo-isomerization, autoxidation, and photo-oxidation products in tretinoin cream.

It should also be noted that the current in-process Revision in the First Supplement, USP 23, NF 18, July-August 1995, page 2511 proposes limit of 90-120% label claim for tretinoin cream. The proposal HPLC method and assay limit for tretinoin in official monograph, USP 23 is different from this application. Penederm may choose to request that their own procedure be adopted. The Compendial Operation Branch has been notified of the different specification (90-115%) and procedure (HPLC) for tretinoin assay and method than USP. When the method is found acceptable by FDA Laboratory, this issue should be pursed.

The applicant has submitted the additional 18 months stability data for other two strengths, tretinoin cream
The data indicates that all the batches are within limit for all specifications. The 18 months stability data support the two-year expiry date for tretinoin cream 0.025%

Method validation remains pending. Updated method validation package including modified HPLC method (variable wavelength) and revised specifications for isotretinoin and other degradants was sent to the LA District on November 26, 1996.

An FUR was sent to the office of compliance on April 17, 1996 (Cirts, EER #9999). The satisfactory response was received from the Office of Compliance on May 20, 1996. Another update will be requested in future if is appropriate.

The updated environmental assessment package was amended on November 20, 1996. The EA is acceptable. The prepared FONSI was sent to Nancy Sager (HFD-357) on November 29, 1996. No response

has been received as of today.

CONCLUSIONS:

This application is APPROVABLE from a manufacturing and control standpoint pending acceptable EA .

Nahid Mokhtari-Rejali

Nahid Mokhtari-Rejali, Ph.D.,
Review Chemist, HFD-540

cc: Orig. NDA 20-404
HFD-540/Division File
HFD-540/Mokhtari-Rejali/11/29/96
HFD-540/MO
HFD-540/Jacobs
HFD-540/Blay
HFD-540/WHDeCamp
HFD-830/Eric Sheinin
HFD-354/Yana Mille
R/D Init by: SUPERVISOR 12/31/96

filename: **NDA20400.rv3**

12/30/96

MEMO OF TELECONFERENCE

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

Sponsor: Penederm, Inc.

NDA: 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

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUN 11 1996

NDA #: 20-404 CHEM.REVIEW #: 2 REVIEW DATE: 6-2-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-24-93	09-24-93	
RESUBMISSION	3-28-94	03-29-94	
AMENDMENT/AC	12-20-95	12-26-96	
AMENDMENT/BC	5-24-96	05-26-96	

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME

Proprietary: Acticin Gel

Nonproprietary/USAN: Retinoic acid/all-trans
Retinoic acid/Vitamin A

Code Names/#'s:

Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Gel
STRENGTHS: 0.025%,
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

$C_{20}H_{28}O_2$ Mol.weight:344.44
CAS# [302-79-4]

PATENT STATUS:

3,729,568; expired April 24, 1990
4,247,547; expired January 27, 1998; no exclusivity exists.

SUPPORTING DOCUMENTS:

IND
DMF

DMF

DMF

DMF

DMF

NDA 17-340 Retin A Cream, 0.1%
NDA 17-522 Retin A Cream, 0.05%
NDA 19-049 Retin A Cream, 0.025%
NDA 20-404 Acticin (tretinoin) Cream 0.025%,

AMENDMENTS:

Dated: May 24, 1996, response to my request, see MEMORANDUM of TELEPHONE CONVERSATION on May 23, 1996, regarding the EA, (Appendix D).
Received: May 24, 1996, received By fax.

Dated: May 31, 1996, response to telephone conversation, see MEMORANDUM of TELEPHONE CONVERSATION on May 31, 1996, regarding specifications for degradants, (Appendix E).
Received: May 31, 1996, received By fax.

CONSULTS:

The environmental assessment package suitable for release under FOI found to be acceptable (Appendix A). The prepared FONSI was sent to Nancy Sager (HFD-357) on May 24, 1996. The consult on the drug product was sent to Rita Hassal (HFD-350) on 5/27/96. A Request for Trademark Review of "Avita" was sent to the Labeling and Nomenclature Committee on April 16, 1996 (Appendix B).

REMARKS/COMMENTS:

The applicant has responded to the not APPROVABLE letter of March 29, 1995 regarding the deficiencies found in chemistry review #1. This amendment contains the following new information: The impurity profile for the drug substance and the drug product, report of degradation pathways for the tretinoin, six months stability at 40°C and 12 months stability at 27°C for batches made at DPT laboratories. Additional six months stability data at 27°C was received by fax on May 31, 1996.

as the original contract facility for the manufacture and testing of Tretinoin Cream 0.025%, , has been withdrawn from the application. is the only manufacturing site for this product. It should be noted that the current procedure at is to collect the representative samples of the product for in process, release and stability testing. The representative samples then will be shipped overnight to Penederm (California), where they are analyzed and the results returned to Due to the instability of tretinoin considerable attention should be given to the handling and storage during the manufacturing process. It is advisable to perform the assay as soon as possible and samples should not stand longer than overnight. The in-process and release testing should be performed by

From a manufacturing and control standpoint, the data and information submitted to this application are currently adequate to recommend that this application is approvable pending of resolving additional concerns. The major manufacturing and control issues were the inadequacy of stability data from the new

manufacturing site and impurity profile for the tretinoin cream.

The overage of *trans* retinoic acid had been lowered to % (from % in Retin-A). The proposed assay for tretinoin %) is according to the monograph, first Supplement, USP 23/NF 18, July-august 1195, page 2511. The assay specification is acceptable. However, it is recommended that both finished release and finished stability be revised to % of label amount of tretinoin. The stability data support the proposed specifications.

Penederm has done an extensive literature research on tretinoin. The revised HPLC method, with photodiode array UV detection at multiple wavelengths, ranging from nm and LC/MS was capable of detecting other impurities besides isotretinoin. These studies confirm that not all degradants of tretinoin (and isotretinoin) will be detected at a single wavelength during HPLC analysis, whether the Penederm or USP methods are used. The proposal HPLC method in official monograph, USP 23 is different from this application. Penederm may choose to request that their own specification and procedure be adopted. When specifications for all the impurities are established and the method is found acceptable by our laboratory, this issue will be perused. The compendial Operation Branch, Yana Mille, has been notified of these differences.

Based on degradation study of tretinoin raw material by and tretinoin cream products by applicant, three key degradation products, in addition to isotretinoin, have been identified as occurring at low levels on stability storage. These are: 5,6-dihydroretinoic acid (5,6-epoxide), 5,8-epoxy-5,8-dihydroretinoic acid (5,8-epoxide or 5,8 furanoid), and the double bond isomeric retinoid, 9,13-di-*cis*-retinoic acid. The proposed tretinoin degradation pathways (photo-oxidative and autoxidative) are also provided.

The stability data for the lots manufactured at are provided. These data include six months stability data at 40°C and 12 months stability data at room temperature, 27°C. Limits for isotretinoin and total degradation are not according to values obtained in the stability studies.

These limits do not comply with the USP 23/NF 18 monograph. According to USP monograph, the isotretinoin specifications for finished drug product and stability specification cannot exceed 5% of the tretinoin. The total degradation product cannot exceed 10% of the amount of tretinoin based on 10% overage in the formulation.

On May 31, 1996, the applicant has submitted [received by fax on May 31, 1996, (Appendix E)] a new limit for degradation products including 18 months supporting stability data for tretinoin 0.05% tretinoin cream, (see MEMORANDUM OF TELEPHONE CONVERSATION dated May 31, 1996). The new limits have been established based on the modification of the HPLC method, PDM 29. The LOQ of isotretinoin was originally found to be %wt, and has now been revised to %wt, page 187. The new specifications are in accordance with USP monograph. The 18 months stability data at 27°C for lots SP-94-32 & SP-94-33 support the new specifications for Tretinoin Cream, 0.05%. The new specifications for isotretinoin and other degradants are acceptable. However, the individual specification for other degradants should be provided. Identical specifications for finished product stability and finished product release should be submitted. In addition, additional 18 months stability data at room temperature for other batches and strengths should also be included.

The 18 months stability data support the two-year expiry date for tretinoin cream 0.05%. It is recommended that as a post-approval commitment the applicant attempt to develop a new analytical methodology to identify all the impurities. This should include specifications for all the photo-isomerization, autoxidation, and photo-oxidation product in tretinoin cream.

Method validation remains pending. The method validation package for revised HPLC method has been requested. Upon the receipt of this package, the method will be forwarded to the LA District for evaluation.

A Request for Trademark Review of "Avita" was sent to the Labeling and Nomenclature Committee (LNC) April 16, 1996. An acceptable response was received on May 28, 1996. Therefore, the tradename "Avita" is acceptable. However, the statement "PROTECT

FROM FREEZING" should be added to the "HOW SUPPLIED" Section of the labeling.

A joint pre-approval inspection was conducted by Review Chemist (myself) and Wilson DeCamp, Ph.D., Supervisory Chemist with participation of Jim Robinson (San Antonio Residents Post CSO) and Jerome Elkins (Dal-Do Chemist) at on April 10-11, 1995 (Appendix C). During this inspection, we found that Penederm is currently engaged in the process of qualifying for QC testing. It was found that the facilities were not currently performing all operations identified in the NDA, and initial QC testing and stability tests were being performed only at Penederm facility. A limited GMP inspection of the manufacturing, packaging and analytical laboratory at did not reveal any GMP deficiencies and no 483 was issued. An FUR was sent to the office of compliance on April 17, 1996 (Cirts, EER #9999). The satisfactory response was received from the Office of Compliance on May 20, 1996.

The environmental assessment package suitable for release under FOI found to be acceptable. The prepared FONSI was sent to Nancy Sager (HFD-357) on May 29, 1996. The response with the following comments was received on 6/10/96 (Appendix A).

CONCLUSIONS:

This application is APPROVABLE from a manufacturing and control standpoint pending acceptable EA report. However, before final approval the applicant is to provide the following information:

1. Revise the assay limit to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of tretinoin.

2. Modify all the specification of degradants to the percent of labeled amount of tretinoin.

3. Provide identical specifications for finished product stability and finished product release.

4. Provide individual specification for 5,6-dihydroretinoic acid, 5,8-dihydroretinoic acid, and 9,13-di-*cis*-retinoic acid.

5. Provide additional 18 months stability data at room temperature for other batches and strengths of tretinoin cream to support 24 months expiry date. It is recommended that the future stability studies be performed at either C/ambient humidity or %RH.

6. States which tests (in-process and/or regulatory) are performed by as compare to Penederm. Please include time frames for testing and release.

7. In addition, it is recommended that as a post-approval commitment, the applicant attempt to develop a new analytical methodology to identify all the impurities. This should include specifications for all the in tretinoin cream.

8. regarding the environmental assessment: (a) information has to be provided for the drug substance site (format item 6), since it is a foreign manufacturer, a certification of compliance is sufficient (see Industry Guidance for appropriate certification language); (b) on page 8 of the EA (last sentence) a compliance statement for is referenced but the compliance statement is not included; (c) there are no format items 12, 13 or 14 which are required for the abbreviated EA format for topical drugs [25.31a(b)(3)].

Nahid Mokhtari-Rejali,
Ph.D., Review Chemist

cc: Orig. NDA 20-404
HFD-540/Division File
HFD-540/Mokhtari-Rejali/6/10/96
HFD-540/Slifman
HFD-540/Jacobs
HFD-520/Utrup
HFD-540/Blay
HFD-540/WHDeCamp
HFD-830/Eric Sheinin
R/D Init by: SUPERVISOR
filename:
NDA20404.rv2

Dir. Div. comments

1. Formal submission of the material submitted by FAX on 5-24 + 5-31-96 should be made by Penederm if this has not yet been done.

2. Based on MaPP 7211-1, I do not believe we can ask the applicant to have a tighter assay limit than is currently in the USP.

EBSheinin
6-11-96

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.

D Boring 5/23/96, Chair
CDER Labeling and Nomenclature Committee

Appendix (A

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)

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 20-404

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: April 13, 1995

To:
NDA 20-404, Acticin (tretinoin) Cream, 0.025 %

From: Nahid Mokhtari-Rejali, Ph.D
Review Chemist

Wilson H. De Camp, Ph.D.
Supervisory Chemist, HFD-540

Subject: Inspection travel to

We traveled to San Antonio to provide technical support for the inspection of as requested under an EER (#7510) submitted January 18, 1995, for the above products.

On Monday morning, April 10, we met with James H. Robinson (San Antonio Resident Post) and Jerome S. Elkins (DAL-DO) and provided them with a detailed technical briefing of the application. We developed a general plan for the inspection, in which Mr. Elkins would focus on the results of analytical testing, and we would support Mr. Robinson in the areas of manufacturing procedures and record-keeping.

After lunch, we went to where we all met with John Feik, President, and Michael Bordovsky, Vice-President, Manufacturing, of We presented credentials and a notice of inspection, and then initiated a general discussion of our plan of inspection. We were advised that they did no testing at the facility, either at the manufacturing site at 307 E. Josephine St. or at their research and development laboratories at another site in We also learned that there are several other tretinoin products manufactured there, apparently ANDA products that are pending approval.

Two representatives from Penederm then joined us, Bhaskar Chaudhuri, Ph.D., Director, Pharmaceutical Sciences, and Subru Bhat, Manager, Quality Assurance. In the ensuing discussions, we were made aware that all quality control testing was done at Penederm's Foster City, CA, facility, and that they were currently engaged in efforts to qualify for QC testing in the future. The current

procedure is that samples of the product are taken for in-process testing and shipped overnight to Foster City, where they are analyzed and the results returned to All original analytical records are kept in California.

At the request of the Penederm representatives, we met privately with them on Monday evening. We discussed the manufacturing issues raised in the action letters of March 29, and their plan for responding to them. They also explained their testing procedures to us in detail. We also discussed with them the need for clarifying the exact role of each facility in their response, and pointed out that the statements in the NDA amendments of 12/16/94 were not, in fact, correct. These statements clearly said that analytical testing had been done at Another point of discussion was their future intentions to reduce the assay limits below the current 90-120% of label.

On Tuesday, April 12, we took a tour of the facility. No manufacturing operation were ongoing. We were told that a GMP course was scheduled for that day. We reviewed the manufacturing records for 9 lots of Acticin products (all the ones used for the stability studies). The records were consistent with a delay of approximately five days for in-process testing. No observations resulted in potential GMP violations, and no FD 483 was issued.

During the course of our review and discussion of the manufacturing records, the Penederm representatives provided us with a copy of a letter from Penederm to DAL-DO, dated January 24 (copy attached), in which the fact was stated that would be doing analytical testing of the product at a later date. We commented that such submissions should also have been sent to the NDA files as general correspondence.

We were also provided with copies of internal protocols for the assay qualification, cleaning validation, process validation and packaging validation for the cream and gel products. These documents are not attached to this report. Copies were retained by Mr. Robinson for inclusion in his EIR.

A few informal observations were communicated to regarding potential improvements to their general procedures. These included:

1. retaining copies of supplement submission letters and FDA actions in their change procedure files;
2. obtaining full copies of analytical test results from Penederm, not just a tabulation of results (the current practice);
3. adding diode array detector capability to their HPLC instrumentation (this capability currently exists only in their laboratory;
4. revising the manufacturing batch record to state limitations on time and

temperature on the in-process storage of the bulk product prior to packaging; and

5. validating such times and conditions as part of their process validation studies.

In our discussions after the inspection with Mr. Robinson, we agreed that a recommendation of approval of the NDAs would be appropriate.

cc: HFD-540/Chapman
HFD-540/Cook
HFD-540/Chambers
HFD-540/Slifman
HFD-540/Labib
HFD-540/Jacobsn
HFD-540/Sheevers
HFD-324
HFR-SW1540/Robinson
HFR-SW160/Elkins

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-404 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 10-25-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	09-29-93	09-29-93	9-29-93
RESUBMISSION	03-28-94	03-29-94	
AMENDMENT/AC	12-16-95	12-16-94	12-20-94
AMENDMENT/BC	1-17-95	12-19-95	1-25-95

NAME & ADDRESS OF APPLICANT: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
Tel: (415)-378-6479

DRUG PRODUCT NAME

Proprietary: Acticin Cream

Nonproprietary/USAN: Retinoic acid/all-trans Retinoic acid/Vitamin A

Code Names/#'s:

Chemical Type/
Therapeutic Class: 5 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Retinoid/Topical treatment of acne vulgaris

DOSAGE FORM: Cream
STRENGTHS: 0.025%,
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

$C_{20}H_{28}O_2$ Mol.weight:344.44
CAS# [302-79-4]

PATENT STATUS:

3,729,568; expired April 24, 1990
3,906,108; expired September 16, 1992; no exclusivity exists.

SUPPORTING DOCUMENTS:

IND
DMF

DMF

DMF

DMF

DMF

NDA 17-340 Retin-A Cream, 0.1%
NDA 17-522 Retin-A Cream, 0.05%
NDA 19-049 Retin-A Cream, 0.025%

AMENDMENTS:

Dated: March 28, 1994, response to our deficiencies found at the time of fileability of the application.

Dated: December 16, 1994, CMC information on new manufacturing site, including one month accelerated stability data.

Dated: January 17, 1995, addresses the information on the changes in amendment of December 16 from the original application.

CONSULTS:

Environmental Impact Assessment consult for tretinoin, drug substance, was requested from HFD-102 on 1/27/95 (Appendix A, NDA . The consult has not been received as of today. Trade name consult is deferred; the applicant intends to propose a new trade name.

REMARKS/COMMENTS:

This application was first submitted as ANDA (generic equivalent to Retin-A) on July 1992.

The entire application was submitted as a line extension for all three strengths to the Acticin gel NDA on September 29, 1993. The deficiencies found at the time of fileability of the NDA were responded on March 28, 1994.

The synthesis of drug substance is not a concern because tretinoin is a compendial item, and the source of new drug substance (NDS) are being used for the Retin-A and Renova products and the synthesis has been reviewed.

All manufacturing operations for this product are performed at
Penederm, conducts confirmatory QC lot release testing. Penederm also conducts the stability program. However, the current contract manufacturer for both NDAs, gel and cream was found not to be in GMP compliance as stated below, and was found to file for Chapter 11. Thus, Penederm has selected a new manufacturing site, and amended their application on December 16, 1994. This amendment includes the similar CMC information on new manufacturing site with [redacted]% overage of tretinoin and one months accelerated stability data.

The EER was requested from the Office of Compliance on May 17, 1994 (CIRTS, EER #6383). A product specific pre-approval inspection was conducted by Gregory Bobrowicz, SAN-DO Inspector, with participation of Ruth Johnson, the analyst Chemist from Seattle-DO, on July 11-15, 1994 (Appendix B, NDA 20-400, Tretinoin Gel). A 483 was issued by SAN-DO for , contract manufacturer of Acticin cream on July 15, 1994. A copy of recommendation from SAN-DO to withhold approval of this NDA was issued on July 21, 1994. Several deficiencies and inconsistencies have been observed by the inspector and participant chemist. According to the inspectors, " The biobatch was manufactured using a rework process for which no documentation is available. In addition, the product will need to be reformulated because the USP limits on tretinoin cream assay are narrowing from)% %, effective August 1994. The firm has manufactured their clinical and stability lots above % potency." The applicant has responded to the 483 items on August 22, 1994. The firm's response was reviewed by the inspector, and found to be inadequate. A copy of Penederm EIR FD-483, Penederm's response to the FD 483, and inspector's evaluation are attached

The applicant has requested a pre-approval inspection for in the amendment of December 16, 1994. A Final Update Request was sent to the Office of Compliance for Penederm on February 23, 1995 (CIRTS, EER #7510).

Method validation packages were sent to Los Angeles District Laboratories on January 30, 1995 (Appendix C, NDA 20-400, Tretinoin Gel). The report will be reviewed when is found acceptable by our laboratory.

CONCLUSIONS:

This application is NOT APPROVABLE from a manufacturing and control standpoint and GMP compliance. The major manufacturing and control concerns are the inadequacy of stability data from the new manufacturing site and impurity profile for the tretinoin cream.

The one months accelerated stability data at cannot justify the proposed two years expiry date. Therefore, the evaluation of the stability data will be deferred until the receipt of three months accelerated stability data at and satisfactory GMP inspection.

In addition, a chromatographic impurity specification should be added to the finished drug products and stability specifications. The new regulatory specification for the total degradant is not adequate. The applicant should attempt to develop an impurity profile for the drug substance and drug product. This should include specifications for all the products in tretinoin cream.

Deficiencies are outlined in the Review Notes and the Draft Letter to the applicant. The CSO is to convey these deficiencies to the applicant.

Nahid Mokhtari-Rejali,
Ph.D., Review Chemist

cc: Orig. NDA 20-404
HFD-540/Division File
HFD-540/Mokhtari-Rejali/1/26/95
HFD-540/Slifman
HFD-540/Sheevers
HFD-520/King
HFD-540/Chapman
HFD-540/WHDeCamp
R/D Init by: SUPERVISOR 2/29/95
filename:N20404.rv1

3/7/95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

MICROBIOLOGY REVIEW(S)

OCT 21 1994

CONSULTATIVE REVIEW FOR TOPICAL DRUG PRODUCTS (HFD-540)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Microbiological Review of Manufacturing and Controls

Requestor: Kennerly Chapman

Reason for Request: Microbiology Review of Manufacturing and Controls

NDA #: 20-404 **MICRO.REVIEW #:** 1 **REVIEW DATE:** 5-AUG-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT/AC	28-MAR-94	29-MAR-94	5-JUL-94

NAME & ADDRESS OF APPLICANT: PENEDERM INCORPORATED
320 Lakeside Drive, Suite A
Foster City, CA 94404

DRUG PRODUCT NAME

Proprietary:	ACTICIN Cream
Nonproprietary/USAN:	Tretinoin
Code Names/#'s:	CAS-302-79-4
Chemical Type/ Therapeutic Class:	5 S

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Keratolytic agent in a cream base for the topical treatment of acne vulgaris.

DOSAGE FORM:	CREAM
STRENGTHS:	0.025%
ROUTE OF ADMINISTRATION:	TOPICAL
DISPENSED:	__X__ Rx _____ OTC

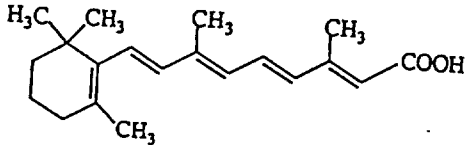
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name:

Tretinoin, also known as retinoic acid, all-trans-retinoic acid, and vitamin A acid, in a cream vehicle of stearic acid, polyolprepolymer-2, isopropyl myristate, polyoxyl 40 stearate, propylene glycol, stearyl alcohol, xanthan gum,

sorbic acid, butylated hydroxytoluene and purified water.

Structural Formula:



Molecular Formula: $C_{20}H_{28}O_2$

Molecular Weight: 300.44

SUPPORTING DOCUMENTS:

Initial submission: NDA 20-404
Received by CDER: September 29, 1993
Not acceptable for filing: November 23, 1993

Abbreviated New Drug Application:

Investigational New Drug Application:

Drug Master File: DMF , for Penederm, Inc.; reference authorized by letter dated June 11, 1993, signed by Paula S. Kirk, Product Regulations Specialist,

DMF for Penederm, Inc.; reference authorized by letter dated June 4, 1993, signed by Anne Z. Martin, Director of Quality Assurance, Packaging Corporation of America.

DMF and addendums, for Penederm, Inc,; reference authorized by letter dated June 7, 1993, signed by D. Bailey, Quality Control Manager, Montebello Packaging.

RELATED DOCUMENTS: None

CONSULTS: None

REMARKS/COMMENTS:

Tretinoin, also known as vitamin A acid, is a derivative of retinol (vitamin A) and is an endogenous

substance in humans. Tretinoin and retinol are necessary for the growth and differentiation of epithelial tissue and skin. Topical tretinoin acts through a reduction in keratinization, an increase in basal cell proliferation, and an increase in the desquamation of the epidermis.

An application, submitted by another sponsor, for the drug substance tretinoin in a different vehicle was approved and is marketed as Retin-A. Penederm Incorporated submitted an abbreviated application for tretinoin in a different cream vehicle containing polyolprepolymer-2, stearic acid, isopropyl myristate, polyoxyl 40 stearate, propylene glycol, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene and purified water, which was determined to be

The subsequent new drug application was found to be incomplete and not acceptable for filing. This amended submission is for tretinoin for use as a topical agent in the treatment of acne vulgaris with no microbiological indications.

In the Manufacturing and Controls section, the Certificates of Analysis (volume 1.2.2, pages 2-0249, 2-0250, 2-0251) state that the microbial testing specifications are $\leq$100 cfu/g total aerobic count and $\leq$100 cfu/g total yeast and mold count. This value is inconsistent with the Quality Standard Finished Product Stability specifications (volume 1.2.2, page 2-0261). The Certificates of Analysis should be changed to total aerobic counts of $\leq$100 cfu per gram and total yeast and mold counts of $\leq$10 cfu per gram. The following table summarizes the results of the microbial limits test on tubes stored the recommended temperature of below 27°C. The sponsor states that these lots passed the microbial limits specification, but did not include the actual data. The actual data and the protocol for the microbial limits test should be submitted.

MICROBIAL LIMITS TEST				
Concentration (%)	Lot number	Tube size (g)	Temperature (°C)	Time (months)
0.025	73509	2	30	3,6,9,12,18
0.025	73509	20	30	3,6,9,12,18
0.025	73509	45	30	3,6,9,12,18
0.05	73510	2	30	3,6,9,12,18

0.05	73510	20	30	3,6,9,12,18
0.05	73510	45	30	3,6,9,12,18
0.1	73511	2	30	3,6,9,12,18
0.1	73511	20	30	3,6,9,12,18
0.1	73511	45	30	3,6,9,12,18
0.025	73509	45	30	3,6
0.1	73511	45	30	3,6
Vehicle	73471	45	30	3,6

The preservative effectiveness test was used to test the effectiveness of the sorbic acid. The protocol submitted was similar to that recommended by USP and the following table indicates the lots tested. The bacterial results were equal to the initial concentration at 7 days and $\leq$0.1% of the initial concentration at 14, 21, and 28 days and the yeast and mold counts were less than or equal to the initial concentration at 7,14,21 and 28 days, which are within acceptable range.

PRESERVATIVE EFFECTIVENESS TEST			
Concentration (%)	**Lot number**	**Tube size (grams)**	**Time (months)**
0.025	73509	45	3,6,12,18
0.05	73510	45	3,6,12,18
0.1	73511	20	6
0.1	73511	45	3,6,12,18
Vehicle	73471	45	3,6

The microbiology portion of the chemistry, manufacturing and controls review is approvable with four deficiencies to be corrected by the sponsor.

CONCLUSIONS & RECOMMENDATIONS:

From a microbiological perspective, this application is approvable with the following four deficiencies to be corrected by the sponsor. 1) The microbial limits specification on the Certificates of Analysis should be consistent with the Quality Standard Finished Product Stability specifications which are total aerobic counts of ≤100 cfu per gram and total yeast and mold counts of ≤10 cfu per gram. 2) The microbial limits protocol should be submitted. 3) Actual microbial limits test results on the following three lots should be submitted: Lot # 73509, 2 gram tube; Lot #73510, 20 gram tube; Lot # 73511, 45 gram tube. 4). Since there will be a change in the manufacturing facility, stability data including microbial limits and preservative effectiveness testing on the first three lots will need to be submitted (Please refer to the chemistry review).

Linda J. Utrup

LINDA J. UTRUP, PH.D.
Review Microbiologist

cc: Orig. NDA 20-404
HFD-540/Division File
HFD-520/Micro/LUtrup/8-5-94
HFD-540/MO/RLabib
HFD-540/Pharm/HSheevers
HFD-540/Chem/M-Rejali
HFD-540/CSO/KChapman
HFD-520/SMicro/ATSheldon
R/D Init by: SUPERVISOR 9/20/94 10/13/94ATS 10.13.94
filename:20-404.FIN

10/21/94.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Avita (Tretinoin) Cream, 0.025%

NDA 20-404

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-540

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-404

Avita (Tretinoin) Cream, 0.025%

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application, Penederm Incorporated has prepared an abbreviated environmental assessment 21 CFR 25.31a which evaluates the potential environmental impacts of the manufacture and use of Avita, Tretinoin Cream, 0.025%. The drug is indicated for topical treatment of acne vulgaris. The point sources of manufacture of the drug substance is at the signed certification of compliance is provided. The finished product is manufactured at the the compliance statement is included.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

11/29/96 Nahid Mokhtari-Rejali
DATE PREPARED BY
Nahid Mokhtari-Rejali, Ph.D.
Chemist, HFD-830

12/2/96 Wilson De Camp, Ph.D.
DATE DIVISION CONCURRENCE
Wilson De Camp, Ph.D.
Team Leader, Chemistry
HFD-830

12/2/96 Nancy B. Sager
DATE Approved
Environmental Assessment Officer
Office of the Center Director
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet for tretinoin
Revised DRAFT Package Insert

CC: Original NDA 20-404/HFD-540/NRejali
Division File(s)

FONSI File 20-404/HFD-540
N. Sager/HFD-102
Docket File 20-404/HFD-540
FOIA Copy HFD-019 (HOLD UNTIL APPROVED)

NDA #20-404: AVITA™ (TRETINOIN) CREAM 0.025%
ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)
TABLE OF CONTENTS

NDA #20-404: AVITA™ (TRETINOIN) CREAM 0.025%
ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)
TABLE OF CONTENTS (CONTINUED)

NONCONFIDENTIAL

NDA #20-404: AVITA™ (TRETINOIN) CREAM 0.025%
ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)

1. DATE

Revised November 20, 1996

2. NAME OF APPLICANT

Penederm Incorporated

3. ADDRESS

320 Lakeside Drive
Suite A
Foster City, CA 94404

4. DESCRIPTION OF PROPOSED ACTION

A. REQUESTED APPROVAL

Penederm requests the approval of Avita (tretinoin) Cream 0.025%, topical formulation for the treatment of acne vulgaris. The proposed action encompasses the manufacture of the drug substance, tretinoin, and the finished product manufacturing, testing, packaging, and use of the topical product.

The product is packaged in 2-gram, 20-gram, and 45-gram , epoxy/phenolic-lined aluminum tubes with a blinded end and a polypropylene screw cap. All tubes are then packaged in cartons.

B. NEED FOR ACTION

Tretinoin is a keratolytic agent known to be effective topically in the treatment of acne vulgaris. According to 25.31a(b)(3), the information is arranged in the abbreviated format.

In the course of evaluating the efficacy of retinoic acid and the emolliency of potential formulation excipients, the sponsor identified the cream formulation presented here, Avita Cream 0.025%, which has subsequently been evaluated and found to be therapeutically equivalent to the marketed Retin-A® cream product, and superior to vehicle control in the treatment of acne vulgaris. The formulation is intended to be used for the topical treatment of acne vulgaris. In addition, the formulation appears to cause less irritation than the currently marketed Retin-A formulation.

Tretinoin, also known as vitamin A acid, is a derivative of retinol (vitamin A) and is an endogenous substance in humans. Tretinoin and retinol are necessary for the growth and differentiation of epithelial tissue and skin. After dietary consumption, retinol and retinol esters are stored in the liver and other tissues, and are released to maintain endogenous plasma levels of tretinoin and retinol. Conditions associated with tretinoin and retinol deficiencies can present as keratinization and drying of the epidermis, increased incidence of respiratory infections, diarrhea, degeneration of the testes, night blindness, nerve lesions, and thick, cancellous bone.

The indication proposed is the treatment of acne vulgaris with topical tretinoin. Kligman first demonstrated that topically applied tretinoin is clinically effective in the treatment of acne vulgaris. Tretinoin acts through a reduction in keratinization, an increase in basal cell proliferation, and an increase in the desquamation of the epidermis.

Acne is a dermal disease. It has many causes and manifestations, but its primary presentations are papules, pustules, and nodules. The initial presentation of acne is as a noninflammatory hyperkeratinization in the follicular duct also known as comedo formation. Comedones result from failure to exfoliate normally the keratinized epidermal cells lining the follicular canal. Tretinoin is a highly effective chemical commonly used in acne treatment because it serves many physiological functions at both cellular and tissue levels.

Although tretinoin and retinol do not circulate similarly, they do enter cells by related receptors. Tretinoin and retinol appear to exert their biological effects intracellularly through binding to cytosol receptors. Three of the most commonly recognized cytosolic retinoid-binding proteins are: cellular retinol binding protein (CRBP), cellular retinoic-acid binding protein (CRABP), and retinoic-acid receptor (RAR).

The net effect of dermal application of tretinoin is the normalization of altered epithelial structures, produced in part by a marked increase in epithelial proliferation and desquamation. The return to a more organized tissue is initiated at both a cellular and ultrastructural level. At the cellular level, hyperproliferation of keratinizing cells in the basal layer leads to a thickening of the granular layer. The rapid increase in epithelial tissue also leads to a thinning or compaction of the stratum corneum in which the horny cells become flatter and more uniform. Coupled with the physical changes of the stratum corneum are intercellular changes.

Increased vasculature in the epidermis generally accompanies topical tretinoin treatments as does intercellular edema and spongiosis. The increase in intercellular fluid increases the distance between cells causing cell membranes to push apart. In the edemic tissue surrounding the follicle, polymorphonuclear leukocytes collect, invade the follicular lining, and form pools between the horny kernel and the encapsulating membrane. The massing of polymorphonuclear leukocytes around the horn-filled follicle brings about a discharging of the comedone through the weakening of its anchorage. Tretinoin not only has the effect of expulsing open comedones, but of changing closed comedones to open ones that are subsequently discharged.

The cells of the stratum corneum treated with tretinoin do not reach terminal differentiation. Treated cells generally contain substantial lipid droplets of large numbers. A marked diminution of tonofilaments is thought to lead to the decrease in cellular cohesion. Also, it has been shown that tretinoin suppresses proteolysis of certain keratins critical in cornification of cells in the horny layer. There are reports of the inhibition of the keratin-binding substance, filaggrin *in vitro* by tretinoin. All of these factors combine to make a stratum corneum with poor cohesion that is easily sloughed.

Topical treatment with tretinoin produces a reorganized epidermis, intercellular edema, and a compacted but unstable stratum corneum. The fragility of the stratum corneum created by tretinoin application allows for sloughing off of this epithelium, the expulsion of both open and closed comedones, and the prevention of microcomedone formation.

C. LOCATION OF PRODUCTION

The drug substance is manufactured by:

The drug substance is supplied by:

Complete manufacturing, processing, and packaging of Avita Cream 0.025% is done by:

is responsible for component receipt testing, compounding, in-process testing, packaging, and bulk and finished product release testing.

Raw material vendor qualification testing, finished product release to market, and stability evaluations are the responsibility of:

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

D. LOCATION OF USE AND DISPOSAL OF DRUG PRODUCT

Avita Cream 0.025% will be used by individuals throughout the United States. Other than the trace metabolites that result from topical application of the product, the small amount of material remaining unused by the patient is anticipated to be disposed of nationally as solid wastes and handled in accordance with local conventions (landfill, incineration).

Waste generated from the production of Avita Cream 0.025% will be disposed of in accordance with local, state, and federal requirements. utilizes the resources of licensed, bonded, and certified waste disposal firms for both hazardous and nonhazardous disposal.

Rejected, returned, or expired drug product, rejected raw materials, and scrap from packaging lines will be disposed of by incineration by the hazardous waste disposal contractor identified in Attachment 1 of the Confidential Environmental Assessment.

General nonhazardous plant refuse including waste paper and corrugated will be disposed of by landfill by the nonhazardous waste disposal contractor identified in Attachment 1 of the Confidential Environmental Assessment.

Water for cleaning and cooling used in the manufacturing of the drug product are discharged into the sewage treatment system. The permits for this purpose are identified in Attachment 2 of the Confidential Environmental Assessment.

E. ENVIRONMENTAL SETTING OF DPT LABORATORIES

is located approximately two miles from the center of the City of San Antonio in a light manufacturing/ industrial area at has been at this location since 1953 and has conscientiously observed all environmental conditions for this type of facility. Additional information about the facility is provided in Section 6., Introduction of Substances to the Environment.

5. LIST OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION

All relevant chemical information on the drug substance is summarized on the following page. As mentioned previously in this document, tretinoin drug substance has been available on the market for over ten years. The MSDS for tretinoin is provided as Attachment 1.

A. DRUG SUBSTANCE:

Names:

Established Chemical Name: (Generic Name) Tretinoin

Alternative Names: (Synonyms) Retinoic acid
All-*trans*-retinoic acid
Vitamin A acid

Code Designation: CAS Registry #302-79-4

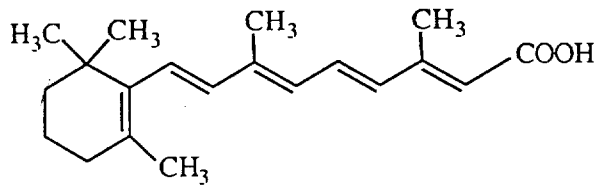
Physical and Chemical Characteristics:

Appearance and Physical Form: Yellow powder

Empirical Formula: $C_{20}H_{28}O_2$

Molecular Weight: 300.44

Structural Formula:



For complete information regarding the physical and chemical characteristics of the drug substance, reference is made to Drug Master File, DMF A letter of authorization to reference this DMF is provided in Volume 1.1.1 of NDA #20-404.

Manufacturer:

The drug substance is manufactured by:

The drug substance is supplied by:

B. DRUG PRODUCT:

Avita Cream 0.025% is an oil-in-water emulsion that is opaque yellow with a smooth texture.

A list of the other ingredients used in this dosage form is provided below. These ingredients are commonly used in the pharmaceutical and/or cosmetic industry.

- Purified water, USP
- Stearic acid, NF
- Polyolprepolymer-2
- Isopropyl myristate, NF
- Polyoxyl 40 stearate, NF
- Propylene glycol, USP
- Stearyl alcohol, NF
- Xanthan gum, NF, Cosmetic Grade
- Sorbic acid, NF
- Butylated hydroxytoluene, NF or FCC

6. INTRODUCTION OF SUBSTANCES TO THE ENVIRONMENT

Solid waste accumulated during cleaning and rejected goods at the manufacturing site are disposed of via government-permitted techniques. Returned goods received by Penederm are disposed of via government-permitted techniques.

A. MANUFACTURING

Drug Substance:

The drug substance, tretinoin, is manufactured by:

The drug substance is supplied by:

is in compliance with all applicable environmental regulations in Germany.

Drug Product:

Complete manufacturing, processing, and packaging of Avita Cream 0.025% is done by:

is responsible for component receipt testing, compounding, in-process testing, packaging, and bulk and finished product release testing.

is registered with the EPA and the local Emergency Planning Commission regarding the storage of chemicals located at this site. location is listed as: Latitude 20°, 26 minutes, 45 seconds; Longitude 98°, 28 minutes, 43 seconds.

Since effective controls are utilized in the receipt, storage, and use of these substances, probable impact on the environment would be minimal. Controls exercised in the handling of these substances are as follows:

- Covered loading dock for receipt of substances
- Environmentally-controlled and covered warehouse storage areas
- Localized dust collection units for sampling, weighing, and dispersing ingredients
- Handling of ingredients is conducted in appropriately controlled manufacturing areas.
- Preparation of batch is conducted in environmentally-controlled and GMP-controlled areas.

Waste generated from the production of Avita Cream 0.025% will be disposed of in accordance with local, state, and federal requirements. utilizes the resources of licensed, bonded, and certified waste disposal firms for both hazardous and nonhazardous disposal.

It is anticipated that preparation of Avita Cream 0.025% will have no significant impact on any existing waste streams.

Wastewater Permit:

The San Antonio Water System, Wastewater Quality Division is responsible for assuring that San Antonio complies with EPA and state requirements for wastewater discharge, stormwater runoff, and other applicable functions. They conduct quarterly, random wastewater sampling to monitor plant discharge as well as semi-annual inspections of the facility for compliance. In order to continue to discharge into the wastewater system, the agency also requires self-monitoring, semi-annual tests to assure effluent meets requirements. This permit does not have a fixed expiration date but is continually monitored for compliance. Permit information is reviewed and updated by city personnel on a semi-annual basis. The current permit was issued in 1992.

Texas Natural Resource Conservation Commission (TNRCC):

This agency is responsible for enforcing EPA regulations, both state and federal, regarding the generation, storage, and disposition of both nonhazardous and hazardous waste. Under the regulation of this authority, generates, stores, and disposes of various categories of liquid and solid waste, manifests shipments when required, and submits annual summary reports on waste generated. is currently registered as a small quantity generator and meets all the provisions for this category. This permit does not expire as long as the generator's conduct does not significantly change. When wastewater streams are added or modified, the authority issues a revised permit to cover those activities. The current permit was issued in 1993.

EPA and RCRA ID Number:

This particular identification number is issued by the TNRCC and is used in all pertinent state and federal reporting activities regarding various generation, storage, and disposition of both hazardous and nonhazardous waste. This number remains the same unless there is a change in ownership, location, or other significant reason.

Air Quality:

has been exempted from requiring an air pollution license by the City of San Antonio, San Antonio Metropolitan Health District. This agency is charged with maintaining air quality standards in the city limits of San Antonio. This exemption will be in effect as long as continues at their current low level of emissions.

Safety:

Operating procedures are established to minimize exposure to chemicals. Health and environmental monitoring is performed as required. manufacturing employees participate in group and individual health and safety training programs. Training regarding the proper operation of both manufacturing equipment and material-handling equipment is conducted. Monthly reviews of employee safety records are conducted and recorded in a formalized report. Routine blood profile monitoring is conducted for manufacturing, technical, and other personnel who might come in contact with products manufactured at the facility. Annual blood profiles are compared to baselines previously established by qualified medical personnel.

Appropriate particulate monitoring of environmental air is conducted by in-house personnel for evaluation of bioburden and by a contract industrial hygienist for determination of airborne exposure levels. Additionally, determination of decibel ratings of different pieces of the manufacturing equipment is made to identify any potential areas where hearing protection is required.

Employees routinely receive documented training in the safe and proper handling of all chemicals used in the department and have Material Safety Data Sheets available for timely reference. Prior to manufacturing Avita Cream 0.025%, compounders review the safety precautions outlined in the section provided in the Compounding Module. Personal safety protective equipment available includes surgical latex gloves when handling chemical components of the drug product; safety glasses/goggles worn during the entire manufacturing process; and personal respirators when handling chemicals which are prone to generation of dust and/or exposure to organic vapors. Tyvek disposable coveralls, shoe coverings, and head protection are also available when required.

is currently operating in compliance with all applicable emission requirements (including operational) at local, state, and federal levels and the additional production of Avita Cream 0.025% should not have any appreciable effect on ability to continue to comply with environmental emission/discharge requirements. Attached is General Compliance Statement which attests to this.

Emergency Response Plan:

In the event of a minor release, the Emergency Response Team is activated and the area is evacuated. Plant personnel who are trained in emergency response will re-enter the area wearing proper protective clothing and respiratory protection to take remedial action. Emergency equipment immediately available includes: Hazmat carts, spill control kits, personal protective equipment, respirators, rescue and escape air, and first aid supplies.

In the event of a serious release or an escalation of an existing situation, the external emergency plan will take effect with plant evacuation and mobilization of the Regional Hazmat Team, Fire Department, and Hospital/Emergency Services.

All material generated during a clean-up will be treated as hazardous and dealt with according to federal, state, and local regulations.

The maximum possible amounts of tretinoin from manufacturing that could possibly end up in wastewater are provided in Attachment 4 of the Confidential Environmental Assessment.

Raw material vendor qualification testing, finished product release to market, and stability evaluations are the responsibility of:

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

Penederm is located on flat terrain in an urban area.

B. COMPLIANCE STATEMENTS

Compliance statements for each of the three facilities and Penederm Incorporated) are provided on the following pages.

PENEDERM INC.
attn. Bhaskar Chaudhuri, Ph. D.
320 Lakeside Drive
Foster City, CA 94404

USA

04.07.1996/sk SWZ0003.DOC
ME/DZ - D 205
Dr. W. Schwarz
☎ 0621/60-93674
🖷 0621/60-92930

Letter of Compliance

Dear Dr. Chaudhuri,

we hereby certify that the facilities in for the manufacturing of TRETINOIN are

1. in compliance with all local and national environmental laws;
2. in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
3. that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Sincerly

Preiskorn Schwarz

September 20, 1994

GENERAL COMPLIANCE STATEMENT

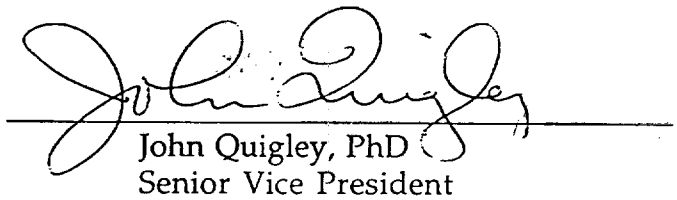
states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of TRETINOIN CREAM at its facilities at as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of TRETINOIN CREAM at its facilities located at

Michael J. Bordovsky
Vice President
Manufacturing Operations

Terrance Clifford
Manufacturing Manager

COMPLIANCE STATEMENT

Penederm Incorporated states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees, and administrative orders applicable to the storage, handling, and disposition of Avita Cream 0.025% at its facilities in Foster City, California as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Avita Cream 0.025% at its facilities in Foster City, California.



John Quigley, PhD
Senior Vice President
Research and Development

11/20/96
Date

7. FATE OF EMITTED SUBSTANCES

These items are ordinarily not required according to 25.31a(b)(3). The toxicologic and pharmacologic properties of the drug substance indicates that the amount entering the environment is considerably lower than the amount required to elicit adverse effects in microorganisms or any other species.

*8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

*9. USE OF RESOURCES AND ENERGY

*10. MITIGATION MEASURES

*11. ALTERNATIVES TO THE PROPOSED ACTION

* These items are ordinarily not required according to 25.31a(b)(3), as indicated in the "Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplements," CDER, November 1995, CMC 6, pages 7 and A-1.

12. LIST OF PREPARERS

This document was prepared by:

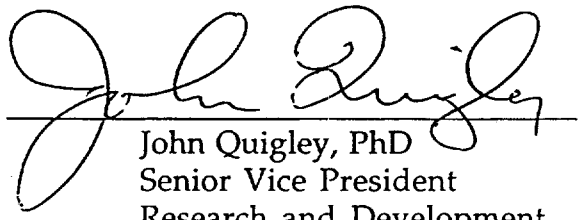
Sui Yuen Eddie Hou, PhD
Research Scientist, Formulations and Product Development

Bhaskar Chaudhuri, PhD
Executive Director, Pharmaceutical Sciences

Barry Calvarese, MS
Executive Director, Clinical/Regulatory Affairs

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of his knowledge.



John Quigley, PhD
Senior Vice President
Research and Development

11/20/96
Date

ATTACHMENT 1

Material Safety Data Sheet

BASF CORPORATION
1609 BIDDLE AVENUE
WYANDOTTE, MI 48192
(313) 246-6526

Original Date: 01/04/1994
Revision Date: 03/12/1996

Emergency Telephone: (800) 424-9300 (CHEMTREC)
(800) 832-HELP (BASF Hotline)
BOTH NUMBERS ARE AVAILABLE DAYS, NIGHTS, WEEKENDS, & HOLIDAYS.

SECTION 1 - PRODUCT INFORMATION

TRETINOIN, USP
Product ID: NVN 684821
Common Chemical Name:
RETINOIC ACID
Synonyms:
ALL-TRANS-RETINOIC ACID, VITAMIN A ACID
Molecular Formula:
C(20)H(28)O(2)

Chemical Family: Vitamin
Molecular Wt.: 300.4

SECTION 2 - INGREDIENTS

Chemical Name:	CAS	Amount
RETINOIC ACID	302-79-4	~ 100.0 %
PEL/TLV NOT ESTABLISHED		

SECTION 3 - PHYSICAL PROPERTIES

Color: Yellow
Form/Appearance: Crystalline Powder
Odor: Odorless

	Typical	Low/High	U.O.M.
Specific Gravity:	NOT AVAILABLE		
Bulk Density:	~ 0.48		G/CC
pH:		6 - 7	SU

	Typical	Low/High	Deg.	@	Pressure
Boiling Pt:	NOT AVAILABLE				
Freezing Pt:		176 - 182	C	1	ATMOSPHERES
Decomp. Tmp:	~ 60		C	1	ATMOSPHERES

Solubility in Water, Description: Insoluble
SOLUBLE IN MANY ORGANIC SOLVENTS

SECTION 4 - FIRE AND EXPLOSION DATA

	Typical	Low/High	Deg.	Method
Flash Point:	NOT AVAILABLE			

ATTACHMENT 1 (CONTINUED)

SECTION 4 - FIRE AND EXPLOSION DATA (cont) -

	Typical	Low/High	Deg.	Method
Autoignition:	265		C	DIN 51794

Extinguishing Media:
Use water fog, foam or dry chemical extinguishing media.
Fire Fighting Procedures:
Firefighters should be equipped with self-contained breathing apparatus and turn out gear.
Unusual Hazards:
Adequate ventilation and cleanup must be maintained to minimize dust accumulation. May form explosive dust-air mixture.

SECTION 5 - HEALTH EFFECTS

Routes of entry for solids and liquids include eye and skin contact, ingestion and inhalation. Routes of entry for gases include inhalation and eye contact. Skin contact may be a route of entry for liquified gases.

Toxicology Test Data:
Rat, Oral LD50 - < 2 G/KG
Moderately Toxic
Health Effects Testing -
Irritating
Mouse, Oral LD50 - 5,500 (30%)
Slightly Toxic
Rabbit, Dermal LD50 - > 2500(50%) MG/KG
Slightly Toxic
Rabbit, Primary Skin Irritation - 50 % AQ.SOL.
Nonirritating
Rabbit, Primary Skin Irritation - 50 % AQ.SOL.
Nonirritating
Rabbit, Eye Irritation -
Nonirritating
Mouse, IP Dominant Lethal Assay - @104 MG/KG
Not mutagenic
Mouse, Acute Intraperitoneal LD50 - 550 (APPROX) MG/KG
Moderately Toxic
Rat, Acute Intraperitoneal LD50 - 350 (APPROX) MG/KG
Very Toxic
Rat, Dermal LD50 - > 2000 MG/KG
Slightly Toxic
Acute Overexposure Effects:
Contact can cause irritation to the eyes, skin, and mucous membranes. Prolonged skin contact may result in dermatitis or blistering. Material can be skin absorbed.
Ingestion of excessive amounts of vitamin A may result in headaches, nausea, blurred vision, and decreased appetite.
Chronic Overexposure Effects:
Chronic overexposure to vitamin A is associated with low red blood count, low leukocyte count, joint/bone pain, fatigue, depression, skin rash, and liver & spleen abnormalities. Some cases of hypervitaminosis A, have resulted in bone changes and CNS effects. Animal

ATTACHMENT 1 (CONTINUED)

SECTION 5 - HEALTH EFFECTS (cont)

studies have shown that vitamin A is teratogenic in several species.

First Aid Procedures - Skin:
Wash affected areas with soap and water. Remove and launder contaminated clothing before reuse. If irritation develops, get medical attention.

First Aid Procedures - Eyes:
Immediately rinse eyes with running water for 15 minutes. Get immediate medical attention.

First Aid Procedures - Ingestion:
If swallowed, dilute with water and immediately induce vomiting. Never give fluids or induce vomiting if the victim is unconscious or having convulsions. Get immediate medical attention.

First Aid Procedures - Inhalation:
Move to fresh air. Aid in breathing, if necessary, and get immediate medical attention.

First Aid Procedures - Notes to Physicians:
None known.

First Aid Procedures - Aggravated Medical Conditions:
No data is available which addresses medical conditions that are generally recognized as being aggravated by exposure to this product. Please refer to Section 5 (Effects of Overexposure) for effects observed in animals.

First Aid Procedures - Special Precautions:
None

Special Precautions: Under no circumstances should the product come in contact with the skin of pregnant women or be inhaled by them.

SECTION 6 - REACTIVITY DATA

Stability Data:
Stable

Incompatability:
Acids.
Oxidizers

Conditions/Hazards to Avoid:
Avoid dust cloud formation.

Hazardous Decomposition/Polymerization:
Hazardous decomposition products: None known.
Polymerization: Does not occur.

Corrosive Properties:
Not Corrosive.

Oxidizer Properties:
Not an oxidizer

SECTION 7 - PERSONAL PROTECTION

Clothing:
Gloves, coveralls, apron, boots as necessary to minimize contact.

Eyes:
Chemical Goggles

vitaminosis A, have resulted in bone changes and CNS effects. Animal

ATTACHMENT 1 (CONTINUED)

SECTION 7 - PERSONAL PROTECTION (cont)

Ventilation:
Use local exhaust to control dusts.
Explosion Proofing:
None required.
Other Personal Protection Data:
Eyewash fountains and safety showers must be easily accessible.

SECTION 8 - SPILL-LEAK/ENVIRONMENTAL

General:
Spills should be contained, solidified and placed in suitable containers for disposal in a licensed facility. This material is not regulated by RCRA or CERCLA ("Superfund"). Wear appropriate respiratory protection and protective clothing and provide adequate ventilation during clean-up.
Waste Disposal:
Incinerate or bury in a licensed facility. Do not discharge into waterways or sewer systems without proper authority.
Container Disposal:
Dispose of in a licensed facility. Recommend crushing or other means to prevent unauthorized reuse.
Environmental Toxicity Test Data:
Ready Biodegradability: Modified MITI - > 70 PERCENT
Readily Biodegradable
Inhibition of activated sludge; LC20 - 300 MG/L
No Inhibition

SECTION 9 - STORAGE AND HANDLING

General:
Store at moderate temperatures in tight, light-resistant containers.

SECTION 10 - REGULATORY INFORMATION

TSCA Inventory Status
Listed on Inventory: YES
Product Grades: USP: Y NF: FCC:

This product is hazardous or contains components which are hazardous according to the OSHA Hazard Communication Standard.

SECTION 11 - TRANSPORTATION INFORMATION

DOT Proper Shipping Name:
NONE
DOT Technical Name:
NONE
DOT Primary Hazard Class:
NONE
DOT Secondary Hazard Class:
NONE
DOT Label Required:
NONE
DOT Placard Required:
NONE

ATTACHMENT 1 (CONTINUED)

SECTION 11 - TRANSPORTATION INFORMATION (cont)

DOT Poison Constituent:
NONE
BASF Commodity Codes: 453 453 UN/NA Code: N/A .. E/R Guide:

Bill of Lading Description:
FOOD, DRUGS OR MEDICINE, NOIBN

	CLASS:	P. G.	SHIPPING NAME:
IATA:	NONE	N/A	NONE
IMO:	NONE	N/A	NONE
TDG:	NONE	N/A	NONE

"IMPORTANT: WHILE THE DESCRIPTIONS, DESIGNS, DATA AND INFORMATION CONTAINED HEREIN ARE PRESENTED IN GOOD FAITH AND BELIEVED TO BE ACCURATE, IT IS PROVIDED FOR YOUR GUIDANCE ONLY. BECAUSE MANY FACTORS MAY AFFECT PROCESSING OR APPLICATION/USE, WE RECOMMEND THAT YOU MAKE TESTS TO DETERMINE THE SUITABILITY OF A PRODUCT FOR YOUR PARTICULAR PURPOSE PRIOR TO USE. NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, ARE MADE REGARDING PRODUCTS DESCRIBED OR DESIGNS, DATA OR INFORMATION SET FORTH, OR THAT THE PRODUCTS, DESIGNS, DATA OR INFORMATION MAY BE USED WITHOUT INFRINGING THE INTELLECTUAL

END OF DATA SHEET

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

STATISTICAL REVIEW(S)

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

Division of Biometrics
HFD-713, Room 18B-45
5600 Fisher's Lane
Rockville, Maryland 20857
Telephone: (301) 443-4594

DATE: August 17, 1994

FROM: Elizabeth A. Turney, M.S., Mathematical Statistician

TO: Barry M. Calvarese, M.S., Executive Director Clinical/Regulatory Affairs
Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, California 94494

SUBJECT: Additional data analyses and electronic submission for NDAs 20-404, Acticin™ (tretinoin) gel and cream

Dear Mr. Calvarese,

The following is a detailed description of the data analyses and electronic submission requested in our telephone conversation on August 16, 1994:

- Studies to be analyzed: Studies 003, 015, and 011. Each study should be analyzed separately. The analyses should include all treatment arms and all investigators.

- Primary parameter of interest: Percent change in lesion count from baseline to each visit. Separate analyses should be performed for non-inflammatory lesions, inflammatory lesions, and total (non-inflammatory plus inflammatory) lesions.

- Patient populations: Separate analyses should be performed for all patients who were randomized and treated, and for the subset of these patients who were evaluable per protocol.

- Statistical methods: The analysis should be performed using the last observation carried forward (LOCF) approach. A patient should not be included in this analysis until the first post-baseline visit. If a patient does not have any post-baseline visits, he/she should be excluded from this analysis. The effects of treatment, investigator, and the treatment by investigator interaction should be evaluated at each visit using a two way analysis of variance.

- Electronic submission of LOCF datasets: The datasets used in the LOCF analyses of studies 003, 015, and 011 should be provided. The datasets should be provided on 3.5 inch diskettes. The preferred software format is PC SAS version 6.08. The

preferred dataset layout is one record per patient per visit. At a minimum, these datasets should include variables for patient id, investigator, treatment, visit, evaluability status (yes/no), sex, age, race (if possible), baseline non-inflammatory lesion count, baseline inflammatory lesion count, baseline total lesion count, non-inflammatory lesion count, inflammatory lesion count, and total lesion count.

- *Electronic submission of study reports:* The study reports (including tables) from studies 003, 015, and 011 of the original NDA should be provided. The files should be provided on 3.5 inch diskettes. The preferred software format is WordPerfect version 5.1.

Please forward all pertinent information to your colleagues at Pharmaco. If you have any questions, do not hesitate to call me.

Sincerely,

Elizabeth A. Turney

Elizabeth A. Turney

cc:
HFD-540
HFD-540/Chapman
HFD-540/Slifman
HFD-540/Labib
HFD-713/Harkins
HFD-713/Turney

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020404

CORRESPONDENCE

21

CRT

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 20-404

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 carcinogenicity 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 20-404
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

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
5-358-0100
X 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 #20-404, Avita™ Cream 0.025%,
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.

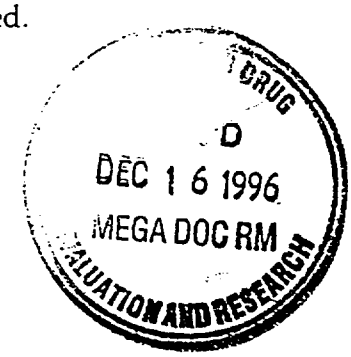
As mentioned in the conversation, Penederm agrees to modify the storage statement in the labeling by including the words, "AVOID FREEZING". The modified labeling for both products will read as follows:

Storage Conditions: Store below C °F). Avoid freezing.

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

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

PENEDERM

December 11, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic 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 #20-404, Avita™ Cream 0.025%

Dear Dr. Wilkin:

As discussed previously with Dr. Roy Blay and Ms. Mary Jean Fornaro, Penederm Incorporated requests the withdrawal of the drug products from the above-referenced NDA.

Please continue the current regulatory review cycle for the Avita Cream 0.025% drug product.

We look forward to your timely response on this matter.

Sincerely,

John Quigley, PhD
Senior Vice President
Research and Development

copy: Mr. Hal Blatt (for Dr. Roy Blay)
Ms. Mary Jean Fornaro
Mr. Lloyd Malchow, President and CEO, Penederm

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

PENEDERM

December 19, 1996

Fax Message
(1-301-827-2075)

Mr. Harold J. Blatt
Dept. of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
9200 Corporate Boulevard
Rockville, MD 20850

Subject: NDA # 20-404, Avita™ Cream 0.025%

Dear Mr. Blatt:

In our telephone conversation yesterday on NDA 20-404, Avita™ Cream 0.025%, we have confirmed the % strengths from the NDA 20-404.

We sent the letter withdrawing the strengths from the NDA 20-404 on December 11, 1996. On December 12, 1996, we sent an electronic copy of the Patient Instructions for Avita™ Cream 0.025% in WordPerfect® 6.1 for Windows '95 format. However, we did not delete these two strengths from the text because we were of the understanding that the request was to send the information as originally submitted. We are committed to the withdrawal of the % strengths from the NDA.

We hope that this letter clarifies the situation. Please let us know if you need additional information or have any questions.

Sincerely,

Subru Y. Bhat, M. S., R. Ph.
Senior Group Leader, Quality Assurance
(415)-638-3019
Fax (415)-358-0101

CC: John Quigley, Ph. D.
Senior Vice President, R & D, Penederm

DUPLICATE

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 # 20-404, Avita™ Cream 0.025%

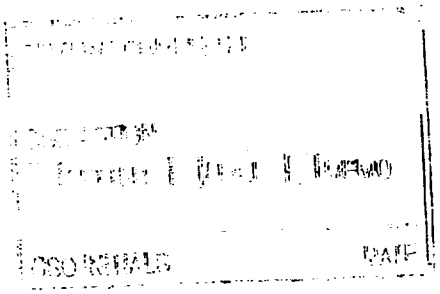
Dear Dr. Wilkin:

Based on our initial review, Penederm agrees with the Labeling and the Patient Instructions, as supplied to us,
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



DUPLICATE

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
-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 # 20-404, Avita™ Cream 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 PDM 29 to cover the tretinoin degradation products as part of a Phase IV study. This will encompass
products in the tretinoin cream.

Results from the study will be submitted as part of the Annual Report to 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

PENEDERM INCORPORATED
[illegible] LAKESIDE DRIVE, SUITE A
[illegible]TER CITY, CA 94404
[illegible]-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 #20-404, 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 dermal carcinogenicity study after final approval of Avita Cream and Gel.

Upon completion of the carcinogenicity study, Penederm commits to submit the final report to 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, PhD
Executive Director
Pharmaceutical Sciences

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

PENEDERM

December 19, 1996

Fax Message
(1-301-827-2075)

Mr. Harold J. Blatt
Dept. of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
9200 Corporate Boulevard
Rockville, MD 20850

Subject: NDA # 20-404, Avita™ Cream 0.025%

Dear Mr. Blatt:

In our telephone conversation yesterday on NDA 20-404, Avita™ Cream 0.025%, we have confirmed the withdrawal of the strengths from the NDA 20-404.

We sent the letter withdrawing the strengths from the NDA 20-404 on December 11, 1996. On December 12, 1996, we sent an electronic copy of the Patient Instructions for Avita™ Cream 0.025% in WordPerfect® 6.1 for Windows '95 format. However, we did not delete these two strengths from the text because we were of the understanding that the request was to send the information as originally submitted. We are committed to the withdrawal of the strengths from the NDA.

We hope that this letter clarifies the situation. Please let us know if you need additional information or have any questions.

Sincerely,

Subru Y. Bhat, M. S., R. Ph.
Senior Group Leader, Quality Assurance
(415)-638-3019
Fax (415)-358-0101

CC: John Quigley, Ph. D.
Senior Vice President, R & D, Penederm

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

PENEDERM

December 16, 1996

BO
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 #20-404, Avita™ (tretinoin) Cream 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 #20-404. These modifications do not change the essence of the environmental assessment in any way.

Please note that NDA #20-404 is now for the 0.025% concentration only. Therefore, no claims are being made for the

Also enclosed is a legible copy of page 27 of the Confidential Environmental Assessment for Avita Cream 0.025%.

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 17 1996
HFD

ORIGINAL

NEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
-358-0100
415-378-6488

PENEDERM

December 12, 1996 NEW CORRESPONDENCE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 13 1996
MEGA DOC RM

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 #20-404, Avita™ Cream 0.025%
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™ Cream 0.025% 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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

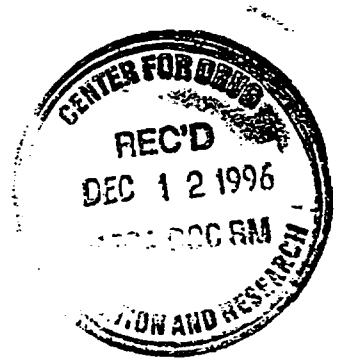
DUPLICATE

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

PENEDERM

December 11, 1996

Bm
NDA ORIG AMENDMENT



Jonathan Wilkin, MD, Director
Division of Dermatologic 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 #20-404, Avita™ Cream 0.025%

Dear Dr. Wilkin:

As discussed previously with Dr. Roy Blay and Ms. Mary Jean Fornaro, Penederm Incorporated requests the withdrawal of the Avita Cream drug products from the above-referenced NDA.

Please continue the current regulatory review cycle for the Avita Cream 0.025% drug product.

We look forward to your timely response on this matter.

Sincerely,

John Quigley, PhD
Senior Vice President
Research and Development

copy: Mr. Hal Blatt (for Dr. Roy Blay)
Ms. Mary Jean Fornaro
Mr. Lloyd Malchow, President and CEO, Penederm

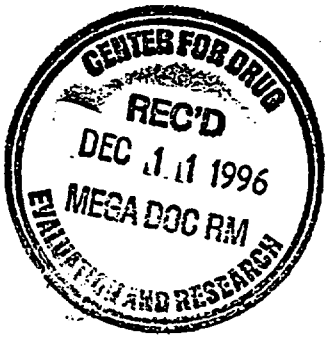
[redacted] 12/96 [redacted]

ORIGINAL

DERM INCORPORATED
AKESIDE DRIVE, SUITE A
ER CITY, CA 94404
58-0100
115-358-0101

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 #20-404, Avita™ Cream 0.025%
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 and the Package Insert for Avita™ Cream 0.025% 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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

LA 12/13/96
CSO INITIALS DATE

ORIGINAL

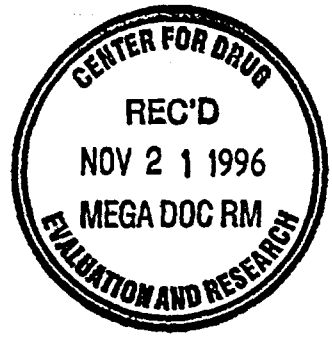
PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
15-358-0100
AX 415-358-0101

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 #20-404, Avita™ (tretinoin) Cream 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 #20-404. 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

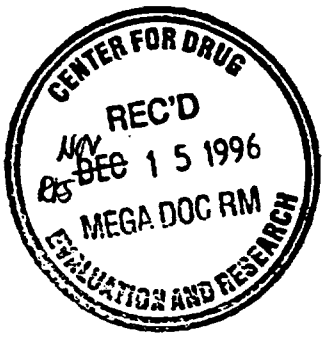
ORIGINAL

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

PENEDERM

November 14, 1996

NDA ORIG AMENDMENT BM



Jonathan Wilkin, MD
Director
Division of Dermatological and Dental Drug Products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation And Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-404, Avita Cream 0.025%

Dear Dr. Wilkin:

Penederm Incorporated requests the withdrawal of the Avita cream drug products from the above referenced NDA. This withdrawal is contingent upon your confirmation, in writing, that the withdrawal of the two higher strengths will not adversely affect the review of the above application as it pertains to the 0.025% Avita cream drug product. In particular, please confirm that the withdrawal will not result in the resetting of the current regulatory review cycle for the 0.025% Avita cream product.

We look forward to your timely response on this matter.

Sincerely,

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
11/22/96
CSO INITIALS DATE

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

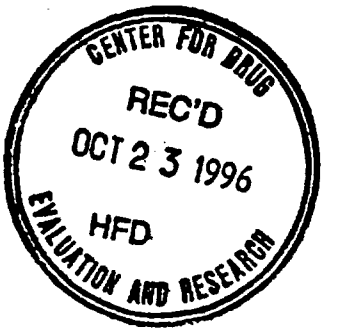
ORIGINAL

Receipt Note RS Lab 11/4/9

PENEDERM

NEW CORRESPONDENCE

October 22, 1996



Jonathan Wilkin, MD
Director
Division of Dermatological and Dental Drug Products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation And Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850

10/25/96

DR. LABIB,

PLEASE NOTE THAT DR. WILKE SAYS THAT THEY WILL RECEIVE A STANDARD ACKNOWLEDGEMENT LETTER ONLY.

RB

RE: NDA 20-404, Avita Cream 0.025%

Dear Dr. Wilkin:

Penederm Incorporated intends to withdraw the Avita cream drug products from the above referenced NDA, so that the Division of Dermatological and Dental Drug Products can allocate its resources to the review and approval process of the 0.025% cream strength, which is expected to conclude over the next 3 months. Please confirm, in writing, that the withdrawal of the two higher strengths will not adversely affect or otherwise prejudice the review of the above application, so that we may officially request this withdrawal.

Upon receipt of your confirmation, Penederm will immediately submit a written request to officially withdraw the creams from the application, with the understanding that we will continue to work with the agency to satisfy the requirements for the approval of these higher strengths. We look forward to your timely response on this matter.

Sincerely,

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
15-358-0100
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ORIG AMENDMENT

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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 #20-404, Tretinoin Cream 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 Cream 0.025%, Penederm has responded to all of the comments pertaining to Chemistry, Manufacturing, and Controls and the Carcinogenicity Advisory Committee Recommendations.

Avita Cream is being considered as a line extension to the Avita Gel.

With the resolution of the nonapprovability issues associated with Avita Gel, Penederm has the understanding that one clinical study, previously submitted (PDC 004-011), will be acceptable as the clinical basis for approval of Avita Cream.

The Agency had previously issued a nonapprovable letter for NDA #20-404, dated March 29, 1995. In that letter you stated the following:

> The analysis of PDC 004-011 failed to demonstrate a statistically significant difference between Acticin Cream 0.025% and 0.1%. A justification for the multiple concentrations is therefore needed for the development of each of these concentrations.

Penederm addressed this comment in a letter to you dated November 14, 1995, and in our Avita Cream NDA amendment dated December 22, 1995. The nonapprovable letter of June 26, 1996 from the Agency did not address clinical issues associated with the cream, so we have not received your input on the dose justification. Under separate cover we have requested a meeting to discuss the cream clinical issues.

As previously described in a June 9, 1994 letter to Dr. Lumpkin, Penederm is committed to the initiation of a Phase 4 dermal carcinogenicity 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

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

DUPLICATE

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

PENEDERM

July 8, 1996

NEW CORRESPONDENCE

Jonathan Wilkin, MD
Director
Division of Dermatological and Dental Drug Products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-404
Avita Cream 0.025%

Dear Dr. Wilkin:

Penederm Incorporated would like to schedule a face-to-face meeting to discuss issues related to the approvability of Avita Cream 0.025% Previously, we sent you a letter dated 11/14/95 requesting input on the justification of the multiple Avita Cream formulations and the approvability of the clinical data package. We never received a reply to our request for a teleconference to discuss these very important issues.

This justification information was submitted in our Avita Cream amendment dated 12/22/95. Your nonapprovable letter dated 6/26/96 does not address any deficiencies within the clinical section of the letter, so we still do not have your input on the clinical issues related to the approvability of all Avita Cream formulations. We feel that it would be useful to confirm this in a face-to-face meeting scheduled at your earliest convenience.

Sincerely,

John W Quigley

For

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

T-CON HELD ON 8/28/96 TO DISCUSS ABOVE ISSUES WITH SPONSOR.

AUG 30 1996

Enc. 11/14/95 letter Dr. Wilkin

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☒ N.A.I. ☐ MEMO	
RB	8/29/96
CSO INITIALS	DATE

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

ORIGINAL

NEW CORRESP

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PENEDERM

June 28, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
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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 #20-404, Tretinoin Cream 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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

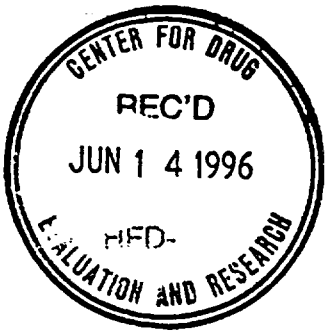
NEW CORRESP

AC

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

PENEDERM

June 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 #20-404, Tretinoin Cream 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. HPLC Methods for Tretinoin Drug Substance and Finished Product, BHT, and Sorbic Acid
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
STER CITY, CA 94404
358-0100
AX 415-358-0101

PENEDERM

June 3, 1996

BC

NDA CDIC 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 #20-404, Tretinoin Cream 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 HKEA and HKEB (0.05%) 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
'STER CITY, CA 94404
-358-0100
AX 415-358-0101

ORIGINAL
NEW CORRESP
NC

PENEDERM

May 31, 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 #20-404, Tretinoin Cream 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 9/29/93 (page 2-0257). A copy is also included in this package.

2. Description of Crimps

   This information was provided in the amendment dated 12/16/94 (page 0-0128). 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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

PENEDERM

May 14, 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 #20-404, Tretinoin Cream 0.025%,
(Avita™)

Dear Dr. Wilkin:

At the request of Mr. Peter Cooney (reviewing Microbiologist), please find enclosed the Microbial Limits test results for Tretinoin Cream 0.025%
, Lot Numbers 73509, 73510, and 73511, respectively.

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

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

Noted.
RSLabels
6/6/96

PENEDERM
ORIGINAL
NEW CORRESP
NC

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: [redacted]
NDA #20-404 Avita™ (Tretinoin) Cream 0.025%

Dear Dr. Wilkin:

The purpose of this letter is to address the approvability of 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 Cream NDAs.

Penederm was recently informed that a meeting will be held within the Dermatologic Division on February 26th to discuss the Avita 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 cream strength would be approvable as a bracketed strength between 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 establishmenf 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 % 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
STER CITY, CA 94404
358-0100
.X 415-358-0101

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PENEDERM

20 December 1995

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 #20-404, Tretinoin Cream 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 Cream 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 as manufacturer of Avita Cream 0.025%, from this NDA. Therefore, which has been qualified as a GMP facility will be the only manufacturer of Avita Cream 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 three new study reports. These reports have been submitted to IND

Penederm Incorporated acknowledges our correspondence dated May 19, 1995, August 24, 1995, November 14, 1995, and December 6, 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 Cream 0.025%, . Penederm Incorporated has agreed with CDER that the Acticin Cream formulations are line extensions of the formulation and require one pivotal study that demonstrates superiority to vehicle. This concept is based on Penederm's agreement with CDER that approval of Acticin Cream 0.025%, is related to the approval of Penederm has submitted an amendment to NDA that addresses all deficiencies cited in the March 29, 1995 nonapprovable letter, and therefore, has clearly established the route of approval for Acticin Cream 0.025% Additionally, as originally suggested by the Anti-Infective Division, Penederm agrees that the middle concentration of Acticin Cream will be bracketed by the low (0.025%) strength cream formulations. Therefore, based on the results of PDC 004-011 and the agreements referenced above, Penederm believes that Acticin 0.025% Cream formulations should be approved.

Sincerely,

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

ORIGINAL

Noted. Not in attendance at the referenced meeting. N.Bilstad

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

PENEDERM

December 6, 1995

NEW CORRESPONDENCE

CENTER FOR DRUG REC'D DEC 07 1995 HFD EVALUATION AND RESEARCH

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 20-404, Acticin Cream 0.025%,

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.

Not true! Neither Ralph or I Stated This

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

K.K.C 12/28/95

Additionally, Penederm confirms the agreement with the Topical Drug Product Division regarding the clinical trial requirements for Acticin Cream 0.025%, 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 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

NDA KSLabels 12/7/95

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

PENEDERM

ORIGINAL

BM

November 14, 1995

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 #20-404
Acticin Cream 0.025%

Dear Dr. Wilkin:

Thank you for this opportunity to respond to your letter dated March 29, 1995 in which you stated the following:

"The analysis of PDC 004-011 failed to demonstrate a statistically significant difference between Acticin Cream 0.025% A justification for the multiple concentrations is therefore needed for the development of each of these concentrations."

In this report we will directly address your comments regarding the analytical support and clinical rationale for approval of three concentrations of Acticin® Cream: the 0.025%,

The report is divided into three sections:

- Statistical Report: a re-analysis of the clinical data from Penederm's study PDC 004-011 focusing on the differences between the Acticin 0.025% Creams;

- Practice Patterns in the Use of Topical Tretinoin: a clinical section that demonstrates the medical need for several concentrations and formulations of topical tretinoin; and

- Examples of Other Multiple Strength Therapies: examples of drug therapies previously approved in the absence of specific studies addressing differences between strengths.

The Statistical Report provides numerical and statistical evidence from 004-011 supporting the assertion that Acticin 0.1% Cream is superior to the 0.025% cream, while at the same time providing an acceptable safety profile.

The key points from the Statistical Report are the following:

- In a well designed and controlled, parallel clinical study, both Acticin 0.025% Creams were shown to be safe and efficacious relative to a vehicle control.

- The data show clear and consistent numerical superiority of the Acticin Cream over the 0.025% concentration in all relevant endpoints at nearly every assessment. Ten of 20 key paired comparisons between strengths (see Tables 2 and 3 in the Statistical Report) are statistically significant, and most are nearly significant, despite the fact that this study was only powered to detect statistical differences between the active comparator and the vehicle control.

- The statistical analysis suggests that the Acticin Cream acts more quickly than the 0.025% cream, and that the activity of the 0.025% cream begins to approach that of the higher strength only at the end of the study.

- The study skin safety parameter assessments (erythema, peeling, dryness, burning/stinging, itching & tightness) also demonstrated higher activity in the patient group treated with the higher concentration of the Acticin Cream. Both concentrations were generally significantly different (i.e., showed more activity) from vehicle early in the study and through to study end. The magnitude of the activity tended to decrease throughout the study, suggesting that both Acticin concentrations were well tolerated.

- Both concentrations of Acticin were safe. No patients withdrew from the study because of an adverse event. Similar proportions of patients reported at least one adverse event across all study groups, including vehicle alone. A slight numerical difference between the Acticin , and 0.025% Creams was seen in the "Skin and Appendages" adverse event category, again without reaching statistical significance in comparison to the vehicle group.

The Clinical Section presents conclusive data from the published literature and from interviews with practicing dermatologists in support of the following key points:

- To achieve successful management of acne with tretinoin, treatment must be individualized to meet each patient's therapeutic needs.

- It is essential for the optimal control of acne that physicians have a range of concentrations and formulations of tretinoin available in order to achieve the delicate balance between control of acne lesions, and undue local irritation that could lead to noncompliance with this most effective acne medication.

- The preponderance of published recommendations by experts, as well as commonly followed practice patterns by community dermatologists, confirm that the availability of tretinoin in a range of concentrations is essential to achieve the therapeutic balance as stated in the previous point.

Additionally, in the final section we present for your consideration examples of other therapies that have been made available to the medical community in multiple strengths or concentrations to meet a clinical need, without clear evidence of strength differences from clinical trials designed specifically for that purpose. Two key points from this section are the following:

- As with tretinoin, clinical trials with benzoyl peroxide at a variety of concentrations did not to show clear cut differences in efficacy.

- There are abundant examples of approved drug product labeling providing prescribers with the latitude to use clinical judgment in selecting medication strength for treatment of dermatological and systemic diseases when the results of controlled clinical trails designed to show differences based on strength are equivocal. We believe that the evidence supporting trends of greater efficacy with higher strengths of Acticin far exceeds the standard of evidence cited in the examples provided.

In summary, we believe that the attached statistical support demonstrates superior efficacy versus vehicle for both cream strengths and a pattern of superior efficacy with the higher strength cream compared to the low strength cream. Further, practicing dermatologists have observed differences between strengths of tretinoin in clinical practice and strongly believe that numerous dosage strengths must be made available to individualize therapy even in the

absence of clinical data that confirms their experience. Finally, there are numerous examples of approved drugs that clearly have not shown differences in efficacy between strengths as seen with Acticin. These drugs have labeling that allows physicians to make their own dose selection based on individualization of benefits and risks observed in a given patient. Penederm believes that a similar approach for higher strengths of Acticin Cream in the "Dosage and Administration" section of the label is appropriate. Based on the examples cited, the tretinoin higher strength justification exceeds the standards deemed appropriate for other approved drug products.

Reference is made to our April 20, 1995 meeting when the Topical Drug Product Division confirmed its earlier commitment to bracketing the Acticin cream formulation by the 0.025% formulations.

Penederm is prepared to teleconference with you at your earliest convenience to solicit your input on the justification of the multiple Acticin Cream formulations and the approvability of the clinical data package.

Sincerely,

Barry Calvarese
Executive Director
Regulatory & Clinical Affairs

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

ORIGINAL

RSLabs 10/26/95

PENEDERM

NEW CORRESPONDENCE

October 13, 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

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

Dear Dr. Wilkin:

In your letter dated March 29, 1995, you identified an issue that served as a basis for issuing a non-approval for the above referenced Acticin NDA. According to the agency the analysis of the pivotal Acticin Cream study PDC 004-011 failed to demonstrate a statistical difference between Acticin Cream 0.025% and Acticin Cream 0.1%. A justification for the multiple concentrations is therefore needed for the development of each of the concentrations.

Penederm will complete the justification for multiple concentrations of Acticin Cream and provide it to you by November 10, 1995. Therefore, Penederm would like to schedule a meeting with you before December 1, 1995 to solicit your input on the justification of the multiple Acticin Cream concentrations.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese
Executive Director
Clinical/Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 17 1995
HFD-520

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

Noted
RSLabib
7/10/95

PENEDERM

19 May 1995

ORIGINAL

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 20-404, Acticin Cream 0.025%

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:

<u>Issues Related to Acticin Gel - Common Investigator</u>

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.

<u>Issues Related to Acticin Gel Equivalence</u>

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 ± 8.2 lesions, based on an expected decrease of approximately 38 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
STER CITY, CA 94404
358-0100
415-358-0101

Noted
RSLabels
5/1/95

PENEDERM

17 April 1995

NC

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 #20-404 (Tretinoin Cream, 0.025%, 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

APR 20 1995

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

Noted
RSLabels
4/24/95

PENEDERM

[redacted]
NC

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 20-404
All-trans-retinoic acid, Acticin Cream 0.025% topical formulations

Dear Dr. Wilkin:

Penederm Incorporated acknowledges the receipt of your March 29, 1995 nonapprovable letter regarding the above referenced drug products. 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 face-to-face conference 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 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

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

RSLab6
1/30/95

PENEDERM

ORIGINAL

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 20-404, Acticin (tretinoin) Cream 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 formulations for all three concentrations were changed to reflect a [redacted]% overage of the active (instead of a [redacted]% overage as stated in the original submission) - shown on page 0011 of the 12/16/94

  - The differences in the manufacturing processes used at (discussed on pages 0037 and 0038 of the Amendment) versus the processes used originally at are further clarified in Table I of this letter

  - A description of the facilities of is provided page 0030 of the CMC Amendment

- Updated stability tables for batches manufactured at both manufacturing sites

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

- 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 0082 through 0127 of the amendment

- Updated specifications and analytical methods for raw materials and finished product

  - Updated specifications for raw materials

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

    Xanthan gum - Grade changed to NF or Cosmetic and added

    Purified water - Bacteriological purity requirements clarified and section on eliminated

  - Updated specifications (Quality Standard) for product

    All specifications for Bulk Product Release (page 0131), Finished Product Release (page 0135) and Finished Product Stability (page 0397) were updated to reflect the following, as applicable:

    i) decreased overage
    ii) addition of specification for content
    iii) clarification of specification for total degradant
    iv)Tretinoin content changed from % Label Strength to % as required by USP 23
    v) Changed BHT content from wt. % to % wt.%
    vi) Changed Storage from between °F(1°C) - °F °C) to °C· °C.
    vii) Changed crimp code to package code.
    viii) Changed label and package appearance to product appearance.
    ix) Deleted Part II. Contract Manufacturer.
    x) Revised Sampling Requirements

  - Updated analytical methods

    PDM 36 - Addition of correction factor (page 0142)
    PDM 59 - New method for sorbic acid (page 0145)

- 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

Receipt noted
RSLabib 12/21/94

NEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
TER CITY, CA 94404
8-0100
15-358-0101

ORIGINAL PENEDERM

AC

December 16, 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

RE: NDA 20-404, Acticin (tretinoin) Cream 0.025%,
CMC Amendment

Dear Dr. Wilkin:

Please find enclosed an NDA amendment addressing the addition of another manufacturing site for the above referenced drug products and the following items:

- Updated stability tables for batches manufactured at both manufacturing sites
- Special *in-vitro* studies performed to compare the products manufactured at the two sites
- Updated specifications for both raw material and finished products
- Environmental assessment for the new manufacturing site

Penederm Inc. requests that the additional manufacturing site, undergo a pre-approval inspection as soon as possible.

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
358-0100
415-358-0101

PENEDERM

ORIGINAL

A2

October 28, 1994

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 20-404, Acticin Cream 0.025%

Dear Ms. Chapman:

Enclosed, please find the statistical analysis requested by Beth Turney, Division of Biometrics, on August 17, 1994. A copy of Ms. Turney's 8/17/94 Memo is attached for reference. Two 3.5 inch disks containing WordPerfect DOS format versions of the statistical reports for Penederm clinical studies PDC 004-003, PDC 004-011 and PDC 004-015 and zipped ASCII files of the tables are provided. An additional copy of the disk has been sent to Ms. Turney under separate cover.

Additionally, tabulations of skin safety data by race from Penederm clinical studies PDC 004-003, PDC 004-011 and PDC 004-015 are provided in response to a request by Dr. Nancy Slifman and Dr. Ramzy Labib.

Please call if you have any questions regarding this submission.

Sincerely,

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

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

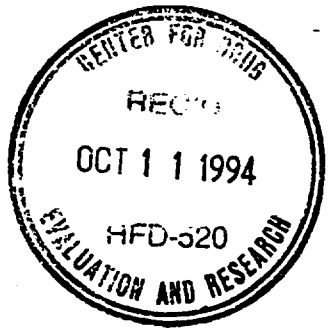
PENEDERM

[redacted]

Bm

ORIGINAL

October 7, 1994



Kennerly Chapman
Consumer Safety Officer
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 20-404, Acticin (tretinoin) Cream 0.025%,

Dear Ms. Chapman:

The following information is being provided in response to a recent request from Dr. Ramzy Labib regarding racial demographic information for Penederm clinical study PDC 004-011.

- Updated summary tables of race information for PDC 004-011
- Listings of adverse events by treatment and race
- Listings of adverse events by race and treatment

Please call me if you have any further questions.

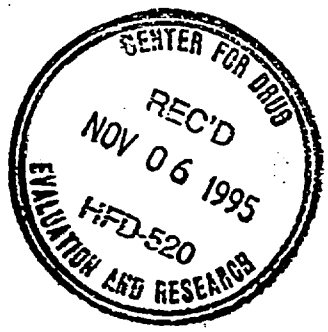
Sincerely,

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

ORIGINAL

PENEDERM



NEW CORRESPONDENCE
REPORTS

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

MHF 6/4/96
FB

RE: New Drug Application 20-404
For:
Acticin™ (tretinoin) Cream, 0.025%,

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

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

ORIGINAL

NEW CORRESPONDENCE

PENEDERM

Noted
RS Labib
9/28/94

September 13, 1994

Kennerly Chapman
Consumer Safety Officer
Division of Topical Drug Products
HFD 540, Room 17B-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 20-404, Acticin Cream 0.025%
Clinical Study PDC 004-011, Subject

Dear Ms. Chapman:

I spoke to Dr. Labib today about subject , who became pregnant during Clinical Study PDC 004-011 and was subsequently dropped from the study after the day 56 visit. A review of this subject's case report forms did not reveal any information that would support noncompliance. This subject was categorized as noncompliant, although the protocol violation category would have been more appropriate in this case, since pregnancy is an exclusion criteria.

Please call me if you have any questions or comments.

Sincerely,

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

Noted
RS Labib
12/7/

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

PENEDERM

ORIGINAL

September 12, 1994

BZ

Kennerly Chapman
Consumer Safety Officer
Division of Topical Drug Products
HFD 540, Room 17B-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 20-404, Acticin Cream 0.025%
Errata for Protocol PDC 004-011 Statistical Report

Dear Ms. Chapman:

Enclosed is a list of errata along with corrected tables for the statistical report for Protocol PDC 004-011. These errata include corrections to selected p values for mean and mean percent change for total, total non-inflammatory and inflammatory lesion counts for the intent-to-treat patient population. These are presented in nine tables in Appendix F. Also enclosed is a correction to a typographical error in table 4.3.2.1.

The errors in the appendix tables occurred during manual transcription of the p-values from the statistical output to WordPerfect p-values for presentation in the statistical report. The statistical output supporting these tables is correct. Except for the typographical error noted in Table 4.3.2.1, the main tables used to support the conclusions drawn in the report are correct, and thus the conclusions are correct. The intent-to-treat results presented in Appendix F were not used to draw any conclusions in the statistical report. The typographical error in Table 4.3.2.1 did not affect any results or conclusions.

Please call me if you have any questions or comments.

Sincerely,

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

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

Noted RSLabib 11/9/94

PENEDERM

ORIGINAL

June 24, 1994

Ramzy S. Labib, M.D.
Topical Drug Product Division
HFD-540 , Room 17B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fischers Lane
Rockville, MD 20857-1706

RE: NDA 20-404, Acticin Cream 0.025%,

Dear Dr. Labib:

It was a pleasure talking to you on Tuesday June 21st regarding WordPerfect files for the clinical/statistical sections of the Acticin Cream NDA. The following files on the enclosed disk should be accessible but some formatting may have been lost in the translation:

- CRMNDAC& - Clinical Technical Section
- CRMSECT& - Statistical Technical Section
- CRMNDAI& - List of PDC 004-011 Investigators
- S16CREA& - Response to question 16 of 11/23/93 nonfilable letter "With regard to the statistical methodology, a longitudinal data analysis which evaluates the treatment effect over time should be conducted"
- Clin App Sum - Application Summary Clinical Section

Please contact me if you have any questions or comments regarding this information. 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
415-358-0100
FAX 415-358-0101

June 9, 1994

Approved 3/23/95 ltr 3/22/95
Call Barry Calvarese

Carcinogenicity studies are not new requirements on a formulation regardless of new drug or generic, otherwise we would also need a carc study for the cream W.Ie

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) Cream NDA 20-404, 0.025%,

Dear Doctor Lumpkin:

Recently, a request was made by the Anti-Infective Division to confirm, in writing, Penederm's commitment to conduct a post-approval, phase 4 dermal carcinogenicity 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 dermal carcinogenicity study within four months after final approval of both the gel and cream formulations. We understand that the requirement for a dermal carcinogenicity 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 dermal carcinogenicity study.

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

Noted.
RS Lubin
6/13/94

PENEDERM

ORIGINAL

June 2, 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 20404
For: Acticin™ (tretinoin) Cream, 0.025%,

Dear Dr. Lumpkin:

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

Sincerely,

Barry M. Calvarese
Executive Director
Clinical/Regulatory Affairs

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

PENEDERM

ORIGINAL

March 28, 1994

ORIG AMENDMENT
RS

CENTER FOR DRUG
HFD
MAR 29 1994
HFD-520
AND RESEARCH

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 20-404
For: Acticin™ (tretinoin) Cream, 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 concentrations of 0.025%, in an cream vehicle. Previous information concerning this formulation has been submitted to the Agency under New Drug Application #20-404, Investigational New Drug Application (IND)

Eight copies of this six-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

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

Received noted
RSLab 11/29/93

NEW CORRESP

ORIGINAL

October 28, 1993

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 Fishers Lane
Rockville, MD 20857-1706

RE: **General Correspondence, Human Pharmacokinetic and Toxicology Sections**

NDA 20404, Acticin™ (tretinoin) Cream, 0.025%,

Dear Doctor Lumpkin:

In response to Rosemary Cook's request of October 27, 1993, Penederm is submitting information regarding two ongoing studies that are near completion.

The in-life phase of a 91 day dermal toxicity study in mice exposed to daily doses of Acticin Gel 0.025% and vehicle has been completed. The final report will be available December 15, 1993. Four copies of the protocol are provided for review (attachment 1).

A single-center, double-blind, parallel study to determine the effect of multiple applications of tretinoin-containing formulations on plasma levels of tretinoin in normal volunteers is scheduled to be completed on October 31, 1993. The design of this study was discussed with Dr. Frank Pelsor of the Division of Biopharmaceutics. Dr. Pelsor indicated that the design of this study was sufficient to answer the Division of Anti-Infective's issue regarding absorption of Acticin Gel. This protocol, which was submitted as an IND amendment on October 6, 1993, is also provided in quadruplicate (attachment 2).

Finally, a copy of our August 3, 1993 letter submitted to IND requesting a waiver of a carcinogenicity study is enclosed (attachment 3).

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
415-358-0100
FAX 415-358-0101

PENEDERM

ORIGINAL

N

20-404

September 29, 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) Cream, 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) Cream, 0.025%, The new drug product contains the active drug substance, tretinoin, at concentrations of 0.025% in a cream 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 cream formulations to the Innovator products, Retin-A® creams, Abbreviated New Drug Applications (ANDAs) were submitted for these products in July of 1992. Subsequently, 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 these submissions were not acceptable for filing as ANDAs due to the inclusion of two excipients in the Acticin formulations which are not present in the innovator products. The two excipients are propylene glycol, which is a well-known pharmaceutical ingredient, and the Sponsor's proprietary excipient, polyolprepolymer-2, which has not been previously approved for use in a new drug. Although the Sponsor did not at that time agree, and continues to disagree with that interpretation, the ANDAs were 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. Based on conversations with the Agency subsequent to the February 11, 1993 communication, Penederm is submitting this NDA as a line extension to the Acticin Gel NDA (submitted September 24, 1993). It was additionally confirmed by the Agency in May of 1993 that one NDA for all 3 strengths would be acceptable for submission.

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) Cream, 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	1.3.1-6	1.1.1 & 1.3.1-6
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	///
Total No. of Volumes	23	25

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 Calvarese

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
29 Sep 93	30 Sep 93
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
520	20-404

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 29 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)*

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 29 1993
CDR

DRUG PRODUCT

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

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

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Cream	Topical	0.025% 0.05% 0.1%

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#

OCT 1 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 ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

PROPOSED MARKETING STATUS *(Check one)*

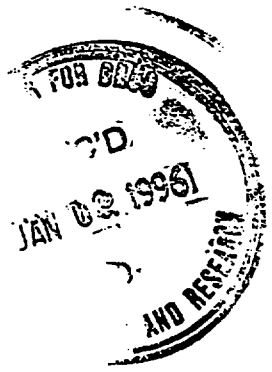
1-0001

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

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
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 20-404 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

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

PENEDERM

March 9, 1995

FAXED 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 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 withdraw 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 withdraw from the Acticin gel and cream NDAs.

Sincerely,

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