CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020475

TRADE NAME: Retin-A Micro Microsphere 0.1%

GENERIC NAME: Tretinoin gel

SPONSOR: Advanced Polymer Systems

APPROVAL DATE: 02/07/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-475

Advanced Polymer Systems
Attention: Subhash Saxena, Ph.D.
3696 Haven Avenue
Redwood City, California 94063

FEB 7 1997

Dear Dr. Saxena:

Please refer to your February 6, 1995, new drug application (NDA) and to your resubmission dated August 7, 1996, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Retin-A Micro (tretinoin gel) Microsphere, 0.1%, originally submitted as Nuretin (tretinoin microsponge gel) Gel, 0.1%.

Reference is also made to our not approvable letter dated May 6, 1996.

We acknowledge the receipt of your correspondence and amendments dated May 8, 13 and 21, June 28, August 7, October 24, November 18 and 19, and December 6, 18 and 19 (two), 1996, and January 13, 1997.

This new drug application provides for treatment of acne vulgaris.

We have completed the review of this application, as amended, including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling dated February 5, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-475. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We acknowledge your Phase 4 commitments specified in your submissions dated August 7, 1996, and January 13, 1997. These commitments are described below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitment."

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

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

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

Please submit one market package of the drug when its available.

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

If you have any questions, please contact:

Olga Cintron, R.Ph.
Consumer Safety Officer
(301) 827-2020

Sincerely yours,

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

Enclosure

Kozma Tornan

MAY 6 1996

NDA 20-475

Advanced Polymer Systems, Inc.
Attention: Sergio Nacht, Ph.D.
3696 Haven Avenue
Redwood City, California 94063

Dear Dr. Nacht:

Please refer to your February 6, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nuretin (tretinoin microsponge gel) Gel, 0.1%.

We acknowledge receipt of your additional correspondence dated March 8 and 30, April 7, 13, and 28, May 11 and 24, June 8, 15, 21, 22, 23, and 29, July 17, August 28, September 6, October 17 and December 15, 1995; January 2 and 3, and February 20, 1996.

We have completed our review of this application, as amended, and find that the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and the sections of the Code of Federal Regulations (CFR) as follows:

1. Under 21 CFR 314.125(b)(1), the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailabililty. The failed assay results for the bulk tretinoin raise questions about the clinical trials.

2. Under 21 CFR 314.125(b)(13), the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211.

Also, please provide the following information in the Environmental Assessment Section to complete the Environmental Assessment Evaluation:

1. The exact location of the drug product manufacturing facilities.

2. A brief, general description of the methods of disposal to include:

   a. Method of destruction,
   b. Identification of current facility used plus:

      i. license or permit number,
      ii. license or permit issuing agent,
      iii. license or permit expiration dates.

3. Complete information for the bulk drug production sites.

4. A Material Data Safety Sheet (MSDS)) for all-trans retinoic acid.

5. A citation of and statement of compliance with applicable emission requirements for domestic manufacturing facilities.

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

1. Please clearly identify the specific formulation used in each of the preclinical studies. Provide the composition of each specific formulation and characterize the vehicle against which it was tested.

2. Please provide a commitment to conduct as a Phase 4 study, an expanded battery of mutagenicity tests on the contaminant . If the product gives positive results, a dermal carcinogenicity bioassay may be required.

3. Please perform chemical assays for preservatives at each time station. However, please note that Preservative Effectiveness

Testing (PET) need not be completed at each time station, but PET testing should be carried out initially and at expiry.

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

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

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

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

If you have any questions, please contact:

Mary Jean Kozma-Fornaro, RN, MSA
Project Manager
(301) 827-2020

Sincerely yours,

5/16/96

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

cc:

Original NDA 20-475
HFD-540/Div. File
NOL-DO
SF-DO
SJ-DO
HFA-100
HFD-2/Lumpkin
HFD-105/Weintraub
HFD-105/Walling
HFD-613
HFD-80
HFD-830/Sheinin/5/6/96
HFD-40
HFD-170/CHEM/Maturu
HFD-540/PHARM/Alam/5/1/96
HFD-540/MO/Huene
HFD-160/MICRO/Stinavage/5/1/96
HFD-880/BIOPHARM/Ajayi/5/1/96
HFD-725/BIOSTAT/Thomson/5/1/96
HFD-540/DIV DIR/Wilkin5/6/96
HFD-540/DEP DIR/Katz
HFD-324/Lynch
HFD-324/Hartman
HFD-540/PM/Fornaro

Concurrence:

HFD-540/CHEM TL/DeCamp/5/3/96
HFD-540/PHARM TL/Jacobs/5/1/96
HFD-880/BIOPHRAM TL/Pelsor/5/2/96
HFD-725/BIOSTAT TL/Srinivasan/5/1/96
HFD-160/MICRO TL/ Cooney/5/1/96
HFD-540/SPM/Cook/5/1/96/5/6/96

NOT APPROVABLE (NA)

DEC - 6 1995

MEDICAL OFFICER'S REVIEW OF LABELING
NDA 20-475

November 13, 1995

SPONSOR: Advanced Polymer Systems, Inc.
Redwood City, CA

DRUG: Nuretin gel 0.1%

CLINICAL INDICATION: Acne

The following is the package insert for Nuretin gel, with the recommended revisions of the clinical portion made by this reviewer. Those words crossed out are to be deleted, and those words shaded are to be added.

Other portions of the labeling are to be reviewed by the chemist, ~~pharmacologist~~, and the Division of Biopharmaceutics.

done done

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Jacobs
HFD-540/DeCamp
HFD-540/Kozma-Fornaro

WHC 11/27/95

PAH 12/6/95

12 Pages
Deleted
Revised Labeling

DEC - 6 1999

INDEX
MEDICAL OFFICER'S REVIEW OF NDA 20-475

MEDICAL OFFICER'S REVIEW OF NDA 20-475 DEC - 6 1995
ORIGINAL SUBMISSION

May 1, 1995

SPONSOR: Advanced Polymer Systems, Inc.
Redwood City, CA

DRUG: Nuretin Gel 0.1% (Tretinoin Microsponge gel)

CLINICAL INDICATION: Acne

FORMULATION:

1% tretinoin in Acrylates Copolymer*	%
Glycerin	%
Carbomer 934P	%
Propylene glycol	%
PPG-20 methyl glucose ether distearate	%
Cyclomethicone and dimethicone copolyol	%
Benzyl alcohol	%
Trolamine	%
Sorbic acid	%
Edetate disodium	%
Butylated hydroxytoluene	%
Purified water	%

* The quantitative formula for tretinoin in Acrylates Copolymer is as follows:

Tretinoin	%
	%
Butylated hydroxytoluene	%
Acrylates copolymer (Microsponge)	%

PROPOSED DOSAGE AND ADMINISTRATION: Applications once daily for at least four weeks.

DATE OF SUBMISSION: February 6, 1995

RELATED SUBMISSIONS: IND

PHARMACOLOGY AND CONTROLS REVIEWS: These are not as yet available.

Rationale for use

Topical tretinoin in various vehicles at concentrations of 0.01% to 0.1% have been marketed in the U.S. for the treatment of acne under the brand name Retin-A (R.W. Johnson Pharmaceuticals) for the past

25 years. The tretinoin Microsponge gel formulation has been developed with the goal of minimizing the cutaneous irritation associated with topical tretinoin products. The sponsor states that this novel formulation uses patented acrylates copolymer porous microspheres (the Microsponge system) to enable inclusion of tretinoin in an aqueous gel without the use of oils or organic solvents like ethanol or acetone which themselves can contribute to irritation. They further describe each Microsponge particle as consisting of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. Tretinoin is entrapped on the surface of and within the Microsponge polymer.

Formulations used in clinical studies

In certain of the clinical studies, one or more of several different formulations of tretinoin Microsponge gel were studied; these were designated as TMG IA 0.1%, TMG IB 0.1%, and TMG IC 0.1%. The formulation which is the subject of this NDA is the same as TMG IC 0.1%. The composition of the other formulations differed in the nature of the stabilizers and preservatives.

The composition of the three formulations was as follows.

Formulations of Tretinoin Microsponge gel 0.1%			
	TMG IA 0.1%	TMG IB 0.1%	TMG IC 0.1%
1% tretinoin in Acrylates Copolymer			
Water			
Carbomer 934P			
Glycerin			
Propylene glycol			
PPG-20 methyl glucose ether distearate			
Cyclomethicone and dimethicone copolyol			
Trolamine			
--			
Butylated hydroxytoluene			
Disodium edetate			
Benzyl alcohol			
Sorbic acid			

Percutaneous absorption studies

Study BO281S was performed by James Kisicki, M.D., Harris Laboratories, Lincoln, Nebraska. The objective of the study was to determine the absorption of ^{3}H-tretinoin from tretinoin Microsponge gel 0.1% and Retin-A cream 0.1% following single and multiple applications to normal facial skin. The TMG formulation used was TMG IB 0.1%.

A total of 44 subjects were randomized to one of four treatment groups, to receive either single or multiple applications of the test formulations. The subjects in the single application groups received a single 500 mg application of the assigned formulation containing ^{3}H-tretinoin. Subjects in the multiple dose groups received applications of 500 mg of the assigned non-radioactive formulation once daily to the face for 28 days, followed by a single 500 mg application of the same formulation containing ^{3}H-tretinoin. Blood samples were obtained at baseline and for 72 hours, and urine and feces were collected for seven days, and analyzed for radioactivity.

The mean total percutaneous absorption was as follows.

Mean percutaneous absorption of ^{3}tretinoin	
TMG 0.1% Single dose	0.82%
TMG 0.1% Multiple dose	1.4%
Retin-A 0.1% Single dose	1.1%
Retin-A 0.1% Multiple dose	2.3%

Reviewer's note: This study is being further reviewed by Dr. Funmi Ajayi of the Division of Biopharmaceutics.

Phase I studies

1. Cumulative irritancy. The investigator for this study was Lynne Harrison, Ph.D., Harrison Research Laboratories, Maplewood, New Jersey. The objective of the study was to compare the irritancy potential of TMG IB 0.1% and TMG IC 0.1% and their respective vehicles, and Retin-A cream 0.1% (RA) and its vehicle.

Fifty Caucasian subjects, 18 males and 32 females, entered into and completed the study. Applications of each of the six test formulations were made under semi-occlusive patches to randomly designated sites on the back of each subject, five times weekly for three weeks. Each patch remained in place for 24 hours during the week, and for 72 hours over each weekend. At each patch removal the amount of irritation was graded on the following scale:

0 = no reaction
± = minimal erythema
1+ = erythema
2+ = erythema and induration
3+ = erythema, induration, and vesicles
4+ = erythema, induration, and bullae

A further notation was made if one or more of the following were present: edema, itching, peeling, slight glazing, or burning/stinging.

According to the protocol the evaluator of the skin reactions was to be blinded as to the identity of the test products applied. However, during the first two weeks of the study the person who applied the products also evaluated the reactions; this was rectified during the remainder of the study.

If a grade 2+ or greater reaction was observed at any site, no further applications were made to that site, and the maximum grade was assigned to that test formulation for the duration of the study.

For each test formulation, the 15 individual scores for a given subject were summed, with a grade of ± given a score of 0.5. A total cumulative irritation score for each test formulation was obtained by adding the aggregate scores for all subjects. For each formulation, the maximum aggregate score for each subject was 60, and the maximum total cumulative irritation score for the 50 subjects was 3000.

The total cumulative scores for the six test formulations were as follows.

Total cumulative irritation scores			
	7 day total	14 day total	21 day total
RA 0.1%	23	269	887
RA vehicle	2	4	7
TMG IB 0.1%	6	81	308
TMG IB vehicle	0	3	5
TMG IC 0.1%	7	77	332
TMG IC vehicle	0	1	2

Statistical analysis showed Retin-A cream 0.1% to be significantly more irritating at 14 and 21 days than TMG IC 0.1% ($p = 0.0001$).

The number of subjects by maximum grade recorded was as follows.

Number of subjects categorized by maximum grade recorded * (N=50)					
	0	0.5	1	2	4
RA 0.1%	0	3	11	0	36
RA vehicle	47	3	0	0	0
TMG IB 0.1%	13	9	17	0	11
TMG IB vehicle	46	3	1	0	0
TMG IC 0.1%	6	10	22	1	11
TMG IC vehicle	48	1	1	0	0
* no maximum 3 grades were recorded					

Twelve of the 50 subjects had a maximum grade of 2+ or greater at the TMG IC 0.1% sites, as compared to 36 of the 50 subjects who had a maximum grade of 2+ or greater at the 0.1% Retin-A cream site.

The most frequent noted sign or symptom at the two TMG sites and at the Retin-A site was peeling. Reports of edema, itching, and glazing were infrequent, and no burning or stinging occurred.

2. Cumulative irritancy patch test with challenge. This was performed by Leo Orris, M.D., Derma-Test Laboratories, Long Island City, NY. The objective of the study was to assess the irritancy and sensitization potential of various concentrations of tretinoin Microsponge gel (TMG) and Retin-A cream 0.1%.

Twenty-six subjects, 8 males and 18 females, completed the induction phase of the study. Twenty-five of these completed the challenge phase; the other subject discontinued due to an unrelated adverse event. The test formulations were TMG 0.025%, TMG 0.05%, TMG 0.1%, the TMG 0.05% vehicle, and Retin-A cream 0.1%. The TMG 0.1% formulation was TMG IA 0.1%. Applications of each of the five test formulations were made under semi-occlusive patches to randomly designated sites on the back of each subject, five times weekly for three weeks. Each patch remained in place for 24 hours during the week, and for 72 hours over each weekend. At each patch removal the amount of irritation was graded on the following scale:

0	=	no reaction
0.5	=	minimal erythema
1	=	definite erythema
2	=	erythema with edema
3	=	erythema with vesiculation and edema
4	=	intense erythema with bullae

If a subject had a severe reaction to a formulation, no further testing with that formulation was done, and this reaction score was carried forward for each remaining evaluation.

At 7 days after removal of the last induction patch the subjects were challenged at new skin sites with each of the test formulations. The challenge patches were left in place for 24 hours, and evaluations for skin reactions were made according to the same scale at 24, 48, 72, and 96 hours after application.

The Cumulative Response Index (CRI) was calculated for each test formulation as the sum of the daily mean scores during the induction phase of all subjects tested; the highest possible CRI for the induction phase was 60. The CRIs were as follows.

Relative Irritancy Potential	
	Cumulative Response Index
TMG 0.05% vehicle	0.14
TMG 0.025%	1.58
TMG 0.05%	1.91
TMG 0.1%	2.43
Retin-A 0.1% cream	3.53

The distribution of subjects according to the reaction scores at day 21 of the induction phase with 0.1% TMG and with Retin-A cream 0.1% were as follows.

Irritation scores at day 21 # subjects		
	TMG 0.1%	Retin-A
0	21	19
0.5	1	0
1	2	5
2	1	1
3	1	1
4	0	0

The conclusions of the sponsor in regard to irritancy potential were that with the exception of the TMG vehicle, all the test formulations showed weak irritancy patterns, and are considered to have a weak to mild potential for irritancy during normal intended use. All of the TMG formulations had a distinctly lower potential for irritancy than Retin-A cream 0.1%.

The reactions to the challenge patch with 0.1% TMG were as follows.

Reactions to challenge - TMG 0.1% # subjects				
Score	24 hrs	48 hrs	72 hrs	96 hrs
0	25	24	24	24
0.5	0	0	0	0
1	0	1	0	1
2	0	0	1	0
3	0	0	0	0
4	0	0	0	0

The sponsor states that materials with a distinct potential for sensitization would develop an upward trend in the response index by the 96 hour reading, and no such trend was observed for any of the test materials.

Reviewer's note: The irritation potential of 0.1% TMG appears in this study to be somewhat lower than for 0.1% Retin-A, in that 5/19 of the Retin-A subjects developed a definite erythema, as compared to 2/21 of the 0.1% TMG subjects; the reactions were otherwise almost identical with the two products. The differences between the two may not be significant, and do not appear to lead to the conclusion that the 0.1% TMG has a distinctly lower potential for irritancy. The reaction in one 0.1% TMG subject of erythema with edema and vesiculation during the induction phase might seem to be sensitization; however, it is felt by this reviewer that the results of the challenge patch do not show sensitization. The only reactions at challenge were transient erythema which had disappeared 24 hours later.

3. Half face comparative safety study. The investigators for this study were James Leyden, M.D. and Gary Grove, Ph.D., Skin Study Center, Broomall, PA. The objective of the study was to compare the tolerance and irritation of tretinoin Microsponge gel 0.1% and Retin-A cream 0.1%, when used on sensitive facial skin in a double blind, randomized, half face study. The TMG formulation used in this study was TMG IA 0.1%.

The study population was composed of 25 Caucasian female subjects, age 18 to 45 years, who had a history of sensitive skin. The selection process put emphasis on the enrollment of lightly complexioned blondes and redheads. The subjects were 'pre-conditioned' with use of Ivory soap and absence of moisturizer use for one week prior to the study. During the study the subjects used only Ivory soap and were admonished to not apply any other products to the face.

One test product was randomly assigned to one half of the face, with the other product assigned to the contralateral side. Applications of 0.1 gm of the respective products were made to the cheek areas once daily in the afternoon and remained until the following morning; this was continued for up to 14 days as tolerance permitted. Each subject was queried daily as to which side of the face had less burning and stinging, and if there was a difference between sides, was asked to assess whether the difference was slightly, moderately, much, or dramatically less. For purposes of analysis the non-favored side was given a score of 0 and the favored side was given a score of 1, 2, 3, or 4, coresponding to assessments of slightly, moderately, much, and dramatically less, respectively.

The two sides were also graded daily for dryness and erythema on the following scales:

Dryness

0 = none
1 = slight flaking
2 = moderate flaking/scaling
3 = marked scaling, slight fissuring
4 = severe scaling, fissuring

Erythema

0 = none
1 = mild erythema
2 = moderate confluent erythema
3 = marked erythema
4 = deep erythema

Once a subject reached a score of 3 or more for either erythema or dryness on either or both sides of the face, treatment with that test product(s) was terminated, and a series of instrumental readings were taken. These were measurements of a) skin erythema using a b) evaporative water loss using a and c) the hydration state of the skin using an The Grade 3 scores were carried forward to the conclusion of the study.

None of the 25 subjects enrolled in the study discontinued from the study, although only two subjects were able to complete the entire treatment period with both study drugs without reaching a Grade 3 in dryness or erythema on either side of the face. An additional four subjects completed the entire treatment period on the TMG 0.1% side of the face. In all cases except one, it was severe erythema and not dryness that prompted termination. Irritation with TMG 0.1% was solely responsible for the termination of 2 subjects, whereas irritation with 0.1% Retin-A caused termination in 18 subjects. Three other subjects reached Grade 3 scores simultaneously with both products.

The mean erythema and dryness scores on day 14, the mean number of days taken to reach a score of 3, and the mean patient assessment scores at final followup were as follows.

Mean irritation scores on day 14 or final followup			
	TMG 0.1%	Retin-A 0.1%	p value
Dryness	1.5	1.9	0.0004
Erythema	2.0	2.8	0.0004
Days to reach Grade 3 dryness or erythema*	8.4	6.1	0.0016
Patient assessment of burning/stinging	1.88	0.10	0.0002
* 2 cases failed to reach Grade 3 on either side, and 4 additional cases did not reach Grade 3 on the TMG side.			

The conclusions were that the rating of erythema and the assessment of erythema with the Chromameter indicated that the side of the face treated with Retin-A cream 0.1% was significantly more irritated than the side treated with TMG 0.1%. Water loss rates measured with the Evapometer showed that the barrier function of the stratum corneum was disrupted to a significantly greater extent with Retin-A cream 0.1% than with TMG 0.1%. The rating of skin surface dryness showed that TMG 0.1% was significantly less drying than Retin-A cream 0.1%, and the conductivity measurements with the Conductance Meter showed a trend in the same direction. From day 2 on, the subjects perceived TMG 0.1% as less likely to cause burning and stinging than Retin-A cream 0.1%.

4. Contact sensitization. This study compared the sensitization potential of TMG IC 0.1% with the TMG IC vehicle, and was performed by Lynne Harrison, Ph.D., Harrison Research Laboratories, Maplewood, New Jersey. The study population enrolled was 220 subjects, 77 males and 143 females, of which 190 subjects completed the challenge phase; the other 30 subjects discontinued for personal reasons unrelated to the study.

In the induction phase, applications of the test products were made under semi-occlusive patches to randomly designated sites on the back of each subject, three times weekly for three weeks. After a rest period of two weeks, challenge applications of the test products were made to previously untreated sites.

The test sites were evaluated for reactions by a blinded observer at 24 hours after patch removal in the induction phase, and at 24, 48, and 96 hours after the challenge patch application. Reactions were graded on the following scale:

0 = no reaction
± = faint, minimal erythema
1+ = erythema
2+ = erythema and induration
3+ = erythema, induration, and vesicles
4+ = erythema, induration, vesicles and pustules

A further notation was made if one or more of the following were present: edema, itching, peeling, slight glazing, or burning/stinging.

If a subject developed a reaction of 2+ or greater during the induction phase, the patch site was changed to a previously untreated site. If a 2+ or greater reaction was observed at the new site, the subject was not to be repatched with that test product for the remainder of the induction phase, but was to be challenged as scheduled.

Of 192 subjects who completed the induction phase, 97 (51%) exhibited erythema of grades ±, 1+, and/or 2+ during the induction phase at the TMG 0.1% site, and 5 subjects (3%) showed erythema at the TMG vehicle site. In 10 subjects the site of the TMG 0.1% patch was changed after a 2+ score at the first site; no subject developed a 2+ score at a changed site. One subject had the vehicle patch site changed after a 2+ reaction at the first site. Another 3 subjects had the TMG 0.1% patch sites changed because of dryness, edema, or peeling.

The number of subjects by maximum grade recorded during the induction phase was as follows.

Number of subjects by maximum grade recorded (N=192)		
Grade	TMG 0.1%	TMG vehicle
0	95 (50%)	187 (97%)
±	40 (21%)	3 (2%)
1	46 (24%)	1 (0.5%)
2	11 (6%)	1 (0.5%)
3	0	0
4	0	0

After the challenge patch, no reactions were seen with either of the test products in any of the subjects at any of the evaluation times.

5. Phototoxicity. Two studies were performed by Kays Kaidbey, M.D., Ivy Laboratories, Philadelphia, PA. The first was done on TMG 0.1% and its vehicle, and the second study was done on TMG 0.025%, TMG 0.1%, the TMG vehicle, and Retin-A cream.

a) In this study the TMG formulation was TMG IC 0.1%, and the study population was 10 male Caucasian subjects.

Occlusive applications of TMG 0.1% and the TMG vehicle were each made to two randomly designated sites on the back. Six hours later the patches were removed from all sites, and one of the TMG sites, one of the vehicle sites, and an untreated control site were irradiated with 20 joules/cm^2 of UVA. The sites were evaluated for responses at 0.5, 24, and 48 hours after irradiation by a blinded observer. Results were that there were no reactions at any of the skin sites at any of the evaluation times.

b) This study compared TMG 0.025%, TMG 0.1%, the TMG 0.1% vehicle, and Retin-A cream in 5 male and 5 female Caucasian subjects. The formulation of TMG 0.1% was TMG IA 0.1%. Each of the test products was applied under occlusive patches to duplicate sites on the back of each subject. Six hours later the patches were removed and the sites were exposed to 20 joules/cm^2 of UVA. The sites were evaluated immediately and at 24 and 48 hours after irradiation by a blinded observer. Results were that there were no reactions at any of the skin sites at any of the evaluation times.

6. Photosensitization. This study was performed by Kays Kaidbey, M.D., Ivy Laboratories, Philadelphia, PA., using the TMG IC 0.1% formulation and its vehicle. The study population enrolled was 14 male and 11 female Caucasian subjects. Of these, two subjects were lost to followup and one subject discontinued for unrelated reasons.

Duplicate semi-occlusive patches of the test materials were applied to the back of each subject twice weekly for three weeks during the induction phase. At 24 hours after each application the sites were irradiated with 2 MEDs from a xenon arc solar simulator. After a rest period of 14 days challenge applications were made to new duplicate sites. At 24 hours later one set of sites was irradiated with 4 joules/cm^2 UVA, while the other set served as unirradiated controls. Skin responses were evaluated by a blinded observer twice weekly during the induction phase, and at 48 and 72 hours after the elicitation phase photoexposure.

Results were that all of the 22 subjects who completed the induction phase had mild reactions in response to the ultraviolet exposure during the induction phase, seen at both the TMG and the vehicle sites. During the elicitation phase, no reactions were seen at the TMG 0.1% sites or at the vehicle sites.

Clinical effectiveness studies

I. Study BO222E.

The formulation used in this study is designated TMG IB 0.1%; this differs slightly from the formulation proposed for marketing, as described previously (page 2). The vehicle contained in acrylates copolymer in place of the tretinoin in acrylates copolymer.

The investigators for the study were:

Leonard Swinyer, M.D.
Salt Lake City, Utah

Jonathan Weiss, M.D.
Snellville, GA

Jon Hanifin, M.D.
Portland, Oregon

The conduct of the study was as follows.

1) Study objective: This was to evaluate the safety and effectiveness of Tretinoin Microsponge gel (TMG) 0.1% compared with its vehicle in the treatment of acne.

2) Study design: This was a double blind, multicenter, randomized, parallel group comparison of TMG 0.1% with its vehicle in patients with acne.

3) Patient selection: Those selected were males and females, 11 to 40 years old, with acne which met the following criteria:

- a Cunliffe Visual Acne Score of at least 1 on a scale of from 0 to 8, with 8 being the most severe.
- 20-250 total facial acne lesions, of which 10 to 200 were comedones, and 10 to 50 were inflammatory lesions (papules, pustules, and cysts), with no more than two cysts.

4) Patient exclusions: Patients with the following conditions were excluded from the study.

a. An initial generalized erythema, peeling, burning/stinging, or itching score of moderate or greater on the rating scale described under 'Safety evaluation'.

b. History of skin reactions to topical medications, cosmetics, or soaps, particularly products containing tretinoin or other retinoids, or any of the other ingredients in Tretinoin Microsponge gel 0.1%.

c. Treatment with systemic retinoids within six months of study entry, or with systemic antibiotics, antihistamines, or steroids within 30 days of study entry.

d. Treatment with topical retinoids within three months of study entry, or with topical steroids, keratolytics, antimicrobials, or other acne products within two weeks of study entry.

e. Concurrent therapy, such as acne surgery, intralesional or topical steroids, etc., or disease that might influence therapeutic response or evaluation of safety.

f. Pregnancy or lactation.

5) Treatment regimen: Applications were made once daily for 12 weeks. The patients were instructed to avoid or minimize excessive exposure to the sun or sunlamps during the study, and to apply a sunscreen of SPF 15 or higher to the face before extended sun exposure.

6) Effectiveness parameters: These were as follows.

a. Lesion counts for inflammatory and noninflammatory lesions, done at baseline and at weeks 2, 4, 7, 10, and 12.

b. An investigator's global evaluation of treatment response at week 12 or endpoint as excellent, good, fair, no change, or poor.

7) Safety evaluation: At baseline and at each return visit the severity of erythema, peeling, burning/stinging, and itching was graded as 0 - none, 1 - mild, 2 - moderate, or 3 - severe. These symptoms were not recorded as adverse reactions unless they were severe enough to cause suspension or discontinuation of treatment.

Results of the study were as follows.

1) Patient enrollment and demographic characteristics: 178 patients were enrolled in the study, of which 158 were evaluable for effectiveness. The demographic and baseline disease characteristics of all patients enrolled were as follows.

Demographic and disease characteristics		
	TMG 0.1% (n=88)	Vehicle (n=90)
Age		
Mean	19	19
Range	[redacted]	[redacted]
Sex		
Male	46 (52%)	44 (49%)
Female	42 (48%)	46 (51%)
Race		
Caucasian	84 (95%)	88 (98%)
Black	0	1 (1%)
Hispanic	1 (1%)	0
Other	3 (3%)	1 (1%)
Visual Acne Score*		
1	48 (55%)	57 (63%)
1.25	7 (8%)	7 (8%)
1.5	17 (19%)	18 (20%)
1.75	8 (9%)	4 (4%)
2	8 (9%)	4 (4%)
* At baseline the highest Cunliffe visual scores were 2		

2) Patient discontinuations and protocol violations: The reasons for patient discontinuations were as follows.

Patient discontinuations		
	TMG 0.1% (n=88)	Vehicle (n=90)
Adverse event	6	0
Treatment failure	0	5
Protocol violation	1	1
Personal reasons	0	1
Lost to followup	1	3
Total # pts	11	9

A patient was considered to be not evaluable for effectiveness if the patient had violated any of the inclusion or exclusion criteria, or had not completed at least 7 weeks of treatment, or if more than 50% of the medication had not been used. Under these criteria 11 patients in the TMG 0.1% group and 9 patients in the vehicle group were not considered evaluable for effectiveness. In addition, 5 patients in the TMG 0.1% group and 7 patients in the vehicle group used concomitant medication during the treatment period which might have had an effect on the course of the acne; for these patients the visit at which concomitant medication was used and all subsequent visits were excluded from the efficacy analyses.

The number of patients with valid data for the efficacy analysis at each return visit was as follows.

# of patients with valid efficacy data		
	TMG 0.1%	Vehicle
Baseline	77	81
Week 2	77	80
Week 4	77	78
Week 7	75	77
Week 10	74	74
Week 12	72	72

3) Effectiveness parameters: The results of the lesion counts and the investigator's Global Evaluation were as follows.

a. Lesion counts.

The mean total lesion counts and the mean percent reduction in total lesion counts at each return visit were as follows.

Mean total lesion counts		
	TMG 0.1%	Vehicle
Baseline	66.3	66.5
Week 2	52.2	61.9
Week 4	50.4	57.9
Week 7	39.5	55.3
Week 10	34.9	53.5
Week 12	36.0	52.5

Mean percent reduction in total lesion counts			
	TMG 0.1%	Vehicle	p values
Week 2	18.3%	6.3%	0.006
Week 4	22.3%	14.4%	0.127
Week 7	38.9%	18.2%	0.004
Week 10	45.6%	19.6%	0.001
Week 12	44.5%	22.8%	0.001

The mean non-inflammatory lesion counts (comedones), the mean reduction from baseline and the mean percent reduction from baseline in non-inflammatory lesion counts at each return visit were as follows.

Mean non-inflammatory lesion counts

	TMG 0.1%		Vehicle	
	# pts	Mean	# pts	Mean
Baseline	77	44.1	81	45.5
Week 2	77	32.2	80	41.4
Week 4	77	31.9	78	40.2
Week 7	75	24.2	77	37.2
Week 10	74	21.6	74	36.1
Week 12	72	22.2	72	35.1

Mean reduction
Non-inflammatory lesion counts

	TMG 0.1%		Vehicle	
	# pts	Mean	# pts	Mean
Week 2	77	11.8	80	3.4
Week 4	77	12.2	78	4.7
Week 7	75	20.1	77	7.1
Week 10	74	22.5	74	9.0
Week 12	72	21.4	72	9.8

Mean percent reduction
Non-inflammatory lesion counts

	TMG 0.1%		Vehicle		
	# pts	Mean	# pts	Mean	p values
Week 2	77	20.6%	80	2.1%	0.002
Week 4	77	22.5%	78	10.6%	0.067
Week 7	75	42.3%	77	18.5%	<0.001
Week 10	74	48.6%	74	17.1%	<0.001
Week 12	72	48.5%	72	21.6%	<0.001

The mean inflammatory lesion counts, and the mean reduction from baseline and the mean percent reduction from baseline in inflammatory lesion counts at each return visit were as follows.

Mean inflammatory lesion counts				
	TMG 0.1%		Vehicle	
	# pts	Vehicle	# pts	Vehicle
Baseline	77	22.2	81	21.0
Week 2	77	19.9	80	20.5
Week 4	77	18.5	78	17.8
Week 7	75	15.3	77	18.1
Week 10	74	13.3	74	17.4
Week 12	72	13.8	72	17.4

Mean reduction Inflammatory lesion counts				
	TMG 0.1%		Vehicle	
	# pts	Mean	# pts	Mean
Week 2	77	2.3	80	0.5
Week 4	77	3.7	78	3.2
Week 7	75	7.0	77	3.0
Week 10	74	9.1	74	3.9
Week 12	72	8.4	72	4.0

Mean percent reduction Inflammatory lesion counts					
	TMG 0.1%		Vehicle		
	# pts	Mean	# pts	Mean	p values
Week 2	77	11.7%	80	3.1%	0.240
Week 4	77	19.8%	78	17.3%	0.668
Week 7	75	30.8%	77	13.7%	0.096
Week 10	74	40.9%	74	16.3%	0.004
Week 12	72	36.7%	72	18.3%	0.028

b. Global Evaluation.

The investigator's Global Evaluation of the clinical response at week 12 or at endpoint was as follows.

Global evaluation		
	TMG 0.1%	Vehicle
Excellent	25 (35%)	8 (11%)
Good	22 (31%)	17 (23%)
Fair	9 (13%)	16 (22%)
No change	9 (13%)	22 (30%)
Poor	7 (10%)	10 (14%)
Total # pts	72	73

TMG 0.1% was significantly superior to the vehicle in the Global Evaluation ($p < 0.001$).

4) Safety parameters.

a. Symptomatology.

All of the 178 patients enrolled were included in the safety analysis. The incidence and severity, and the mean scores, for erythema, peeling, and burning/stinging at each return visit were as follows.

Incidence and severity of erythema					
	Severity scores *				
Visit	1	2	3	4	Total # pts
Baseline					
TMG	75 (85%)	13 (15%)	0	0	88
Vehicle	78 (87%)	12 (13%)	0	0	90
Week 2					
TMG	43 (51%)	33 (39%)	8 (9%)	1 (1%)	85
Vehicle	81 (92%)	7 (8%)	0	0	88
Week 4					
TMG	48 (59%)	31 (38%)	2 (2%)	0	81
Vehicle	81 (93%)	6 (7%)	0	0	87
Week 7					
TMG	52 (65%)	28 (35%)	0	0	80
Vehicle	78 (91%)	8 (9%)	0	0	86
Week 10					
TMG	55 (69%)	24 (30%)	1 (1%)	0	80
Vehicle	74 (90%)	8 (10%)	0	0	82
Week 12					
TMG	57 (71%)	22 (28%)	1 (1%)	0	80
Vehicle	74 (93%)	6 (8%)	0	0	80
* 1 = none; 2 = mild; 3 = moderate, 4 = severe					

Mean severity scores - erythema		
	TMG 0.1%	Vehicle
Baseline	1.1	1.1
Week 2	1.6	1.1
Week 4	1.4	1.1
Week 7	1.4	1.1
Week 10	1.3	1.1
Week 12	1.3	1.1

Incidence and severity of peeling					
	Severity scores *				
Visit	1	2	3	4	Total # pts
Baseline					
TMG	85 (97%)	3 (3%)	0	0	88
Vehicle	85 (94%)	5 (6%)	0	0	90
Week 2					
TMG	35 (41%)	36 (42%)	13 (15%)	1 (1%)	85
Vehicle	84 (95%)	4 (5%)	0	0	88
Week 4					
TMG	47 (58%)	29 (36%)	5 (6%)	0	81
Vehicle	81 (93%)	6 (7%)	0	0	87
Week 7					
TMG	42 (53%)	30 (38%)	8 (10%)	0	80
Vehicle	81 (94%)	5 (6%)	0	0	86
Week 10					
TMG	56 (70%)	23 (29%)	1 (1%)	0	80
Vehicle	73 (89%)	9 (11%)	0	0	82
Week 12					
TMG	58 (73%)	22 (28%)	0	0	80
Vehicle	78 (98%)	2 (3%)	0	0	80
* 1 = none; 2 = mild; 3 = moderate, 4 = severe					

Mean severity scores - peeling		
	TMG 0.1%	Vehicle
Baseline	1.0	1.1
Week 2	1.8	1.0
Week 4	1.5	1.1
Week 7	1.6	1.1
Week 10	1.3	1.1
Week 12	1.3	1.0

Incidence and severity of burning/stinging					
Visit	Severity scores *				Total # pts
	1	2	3	4	
Baseline TMG Vehicle	86 (98%) 90 (100%)	2 (2%) 0	0 0	0 0	88 90
Week 2 TMG Vehicle	47 (55%) 85 (97%)	24 (28%) 3 (3%)	9 (11%) 0	5 (6%) 0	85 88
Week 4 TMG Vehicle	61 (75%) 86 (99%)	18 (22%) 1 (1%)	2 (2%) 0	0 0	81 87
Week 7 TMG Vehicle	67 (84%) 82 (95%)	9 (11%) 3 (3%)	4 (5%) 0	0 1 (1%)	80 86
Week 10 TMG Vehicle	65 (81%) 81 (99%)	15 (19%) 1 (1%)	0 0	0 0	80 82
Week 12 TMG Vehicle	71 (89%) 78 (98%)	7 (9%) 2 (3%)	1 (1%) 0	1 (1%) 0	80 80
* 1 = none; 2 = mild; 3 = moderate, 4 = severe					

Mean severity scores - burning/stinging		
	TMG 0.1%	Vehicle
Baseline	1.0	1.0
Week 2	1.7	1.0
Week 4	1.3	1.0
Week 7	1.2	1.1
Week 10	1.2	1.0
Week 12	1.1	1.0

b. Adverse events.

The incidence and severity of adverse events at the treatment site which were considered to be possibly, probably, or definitely related to treatment were as follows.

Adverse events - treatment site						
	TMG 0.1%			Vehicle		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Acne	1	0	0	0	0	0
Bullous eruption	0	1	0	0	0	0
Bacterial infection	1	0	0	0	0	0
Paresthesia	1	0	0	0	0	0
Facial irritation	6	18	1	2	1	1
Dry skin	1	1	0	0	0	0

The case of bacterial infection was impetigo on the chin.

A moderate rash occurred on the neck of one patient who reportedly spilled the medication on her neck.

Six patients in the TMG group discontinued treatment because of facial irritation. Of these, one also had blisters, one also had acne, and one also had dry skin. These are described further as follows.

Patient - moderate facial erythema after 4 days of treatment.

Patient - severe burning and itching, with peeling, erythema and facial blistering on the fourth day of treatment.

Patient - severe erythema and burning after 3 days of treatment.

Patient - discontinued after one month of treatment with continued dryness and burning since the third day of treatment, and painful, enlarged acne lesions.

Patient moderate facial irritation, including erythema, peeling, burning/stinging, and itching after one week of treatment.

Patient - facial irritation and dryness after two days of treatment.

There were additionally 19 patients in the TMG group and 3 subjects in the vehicle group in whom treatment was temporarily interrupted because of skin irritation.

Reviewer's note: In summary, the results of this study show a significant superiority of 0.1% TMG over the vehicle in the reduction of non-inflammatory lesion counts at weeks 2, 7, 10, and 12, in the reduction of inflammatory lesion counts at weeks 10 and 12, and in the investigator's global evaluation. Mild irritation was found in about one-third of the patients throughout the study, with moderate irritation in 9% and severe irritation in one patient during the second week of the study, and moderate irritation in 1-2% thereafter.

II. Study BO223E.

This study utilized the same protocol as the preceding study, # BO222E. The TMG formulation used was TMG IB 0.1%.

The investigators for the study were:

Anne Lucky, M.D.
Dermatology Research Associates
Cincinnati, Ohio

Guy Webster, M.D.
Department of Dermatology
Jefferson Medical College
Philadelphia, PA.

James Leyden, M.D.
Ivy Laboratories
Philadelphia, PA

Results were as follows.

1) Patient enrollment and demographic characteristics: 169 patients were enrolled in the study, of which 152 were evaluable for effectiveness. The demographic and baseline disease characteristics of all patients enrolled were as follows.

Demographic and disease characteristics		
	TMG 0.1% (n=84)	Vehicle (n=85)
Age		
Mean	18	18
Range	[redacted]	[redacted]
Sex		
Male	48 (57%)	51 (60%)
Female	36 (43%)	34 (40%)
Race		
Caucasian	76 (90%)	77 (91%)
Black	8 (10%)	8 (9%)
Visual Acne Score*		
1	46 (55%)	47 (55%)
1.5	22 (26%)	22 (26%)
1.75	8 (10%)	7 (8%)
2	5 (6%)	5 (6%)
2.5	3 (4%)	2 (2%)
2.75	0	1 (1%)
3.5	0	1 (1%)
* At baseline the highest Cunliffe visual scores were 3.5		

2) Patient discontinuations and protocol violations: The reasons for patient discontinuations were as follows.

Patient discontinuations		
	TMG 0.1% (n=84)	Vehicle (n=85)
Adverse event	5	3
Protocol violation	0	2
Personal reasons	0	1
Lost to followup	5	6
Other	0	1
Total # pts	10	13

A patient was considered to be not evaluable for effectiveness if the patient had violated any of the inclusion or exclusion

criteria, or had not completed at least 7 weeks of treatment, or if more than 50% of the medication had not been used. Under these criteria 10 patients in the TMG 0.1% group and 7 patients in the vehicle group were not considered evaluable for effectiveness. In addition, 2 patients in the TMG 0.1% group and 7 patients in the vehicle group had visits which were not evaluable for efficacy due to use of concomitant medication during the treatment period which might have had an effect on the course of the acne; for these patients the visit at which concomitant medication was used and all subsequent visits were excluded from the efficacy analyses. Five patients who were otherwise evaluable discontinued prior to completing 12 weeks of treatment. Thus, 138 patients completed the study and had week 12 data which were evaluable for efficacy.

The number of patients with valid data for the efficacy analysis at each return visit was as follows.

# of patients with valid efficacy data		
	TMG 0.1%	Vehicle
Baseline	74	78
Week 2	74	77
Week 4	74	77
Week 7	72	73
Week 10	71	69
Week 12	71	67

3) Effectiveness parameters: The results of the lesion counts and the investigator's Global Evaluation were as follows.

a. Lesion counts.

The mean total lesion counts and the mean percent reduction in total lesion counts at each return visit were as follows.

Mean total lesion counts		
	TMG 0.1%	Vehicle
Baseline	59.7	56.5
Week 2	50.8	52.6
Week 4	51.4	53.6
Week 7	46.9	50.4
Week 10	39.4	47.0
Week 12	37.9	46.5

Mean percent reduction in total lesion counts			
	TMG 0.1%	Vehicle	p values
Week 2	5.6%	2.9%	0.205
Week 4	9.2%	2.7%	0.026
Week 7	16.1%	4.9%	0.016
Week 10	31.0%	9.7%	<0.001
Week 12	32.3%	16.2%	0.002

The mean non-inflammatory lesion counts (comedones), and the mean reduction from baseline and the mean percent reduction from baseline in non-inflammatory lesion counts at each return visit were as follows.

Mean non-inflammatory lesion counts				
	TMG 0.1%		Vehicle	
	# pts	Mean	# pts	Mean
Baseline	74	39.3	78	35.7
Week 2	71	30.8	75	34.5
Week 4	74	33.0	77	35.5
Week 7	70	30.2	71	33.5
Week 10	68	24.9	66	30.4
Week 12	71	24.3	67	30.6

Mean reduction Non-inflammatory lesion counts				
	TMG 0.1%		Vehicle	
	# pts	Mean	# pts	Mean
Week 2	71	8.4	75	0.2
Week 4	74	6.3	77	0.1
Week 7	70	9.7	71	-0.9
Week 10	68	14.9	66	-0.1
Week 12	71	15.2	67	3.4

Mean percent reduction Non-inflammatory lesion counts					
	TMG 0.1%		Vehicle		
	# pts	Mean	# pts	Mean	p values
Week 2	71	10.9%	75	-4.3%	<0.001
Week 4	74	7.2%	77	-9.2%	0.005
Week 7	70	15.5%	71	-11.1%	<0.001
Week 10	68	31.4%	66	-1.4%	<0.001
Week 12	71	32.4%	67	2.6%	<0.001

The mean inflammatory lesion counts, and the mean reduction from baseline and the mean percent reduction from baseline in inflammatory lesion counts at each return visit were as follows.

Mean inflammatory lesion counts				
	TMG 0.1%		Vehicle	
	# pts	Mean	# pts	Mean
Baseline	74	20.4	78	20.9
Week 2	71	20.0	75	18.2
Week 4	74	18.4	77	18.1
Week 7	70	16.7	71	16.9
Week 10	68	14.5	66	16.7
Week 12	71	13.7	67	15.9

Mean reduction Inflammatory lesion counts				
	TMG 0.1%		Vehicle	
	# pts	Mean	# pts	Mean
Week 2	71	-0.3	75	2.7
Week 4	74	2.0	77	2.9
Week 7	70	3.3	71	3.7
Week 10	68	5.9	66	3.5
Week 12	71	6.7	67	4.4

Mean percent reduction Inflammatory lesion counts					
	TMG 0.1%		Vehicle		
	# pts	Mean	# pts	Mean	p values
Week 2	71	-5.4%	75	10.1%	0.003
Week 4	74	7.4%	77	9.9%	0.508
Week 7	70	12.6%	71	18.6%	0.160
Week 10	68	28.7%	66	19.0%	0.802
Week 12	71	28.5%	67	23.5%	0.630

b. Global Evaluation.

The investigator's Global Evaluation of the clinical response at week 12 or at endpoint was as follows.

Global evaluation		
	TMG 0.1%	Vehicle
Excellent	20 (28%)	6 (9%)
Good	21 (30%)	17 (25%)
Fair	17 (24%)	20 (29%)
No change	9 (13%)	17 (25%)
Poor	4 (6%)	9 (13%)
Total # pts	71	69

TMG 0.1% was significantly superior to the vehicle in the Global Evaluation ($p < 0.001$).

4) Safety parameters.

a. Symptomatology.

All of the 169 patients enrolled were included in the safety analysis. The incidence and severity, and the mean scores, for erythema, peeling, and burning/stinging at each return visit were as follows.

Incidence and severity of erythema					
	Severity scores *				
Visit	1	2	3	4	Total # pts
Baseline					
TMG	75 (89%)	9 (11%)	0	0	84
Vehicle	73 (86%)	12 (14%)	0	0	85
Week 2					
TMG	42 (55%)	29 (38%)	6 (8%)	0	77
Vehicle	70 (86%)	11 (14%)	0	0	81
Week 4					
TMG	55 (72%)	19 (25%)	2 (3%)	0	76
Vehicle	68 (82%)	15 (18%)	0	0	83
Week 7					
TMG	56 (77%)	16 (22%)	1 (1%)	0	73
Vehicle	71 (93%)	5 (7%)	0	0	76
Week 10					
TMG	57 (80%)	14 (20%)	0	0	71
Vehicle	68 (94%)	4 (6%)	0	0	72
Week 12					
TMG	65 (88%)	9 (12%)	0	0	74
Vehicle	67 (93%)	5 (7%)	0	0	72
* 1 = none; 2 = mild; 3 = moderate, 4 = severe					

Mean severity scores - erythema		
	TMG 0.1%	Vehicle
Baseline	1.1	1.1
Week 2	1.5	1.1
Week 4	1.3	1.2
Week 7	1.2	1.1
Week 10	1.2	1.1
Week 12	1.1	1.1

Incidence and severity of peeling					
	Severity scores *				
Visit	1	2	3	4	Total # pts
Baseline					
TMG	83 (99%)	1 (1%)	0	0	84
Vehicle	84 (99%)	1 (1%)	0	0	85
Week 2					
TMG	35 (45%)	31 (40%)	11 (14%)	0	77
Vehicle	77 (95%)	4 (5%)	0	0	81
Week 4					
TMG	52 (68%)	22 (29%)	2 (3%)	0	76
Vehicle	80 (96%)	3 (4%)	0	0	83
Week 7					
TMG	55 (75%)	18 (25%)	0	0	73
Vehicle	75 (99%)	1 (1%)	0	0	76
Week 10					
TMG	55 (77%)	15 (21%)	1 (1%)	0	71
Vehicle	71 (99%)	1 (1%)	0	0	72
Week 12					
TMG	70 (95%)	4 (5%)	0	0	74
Vehicle	70 (97%)	2 (3%)	0	0	72
* 1 = none; 2 = mild; 3 = moderate, 4 = severe					

Mean severity scores - peeling		
	TMG 0.1%	Vehicle
Baseline	1.0	1.0
Week 2	1.7	1.0
Week 4	1.3	1.0
Week 7	1.2	1.0
Week 10	1.2	1.0
Week 12	1.1	1.0

Incidence and severity of burning/stinging					
	Severity scores *				
Visit	1	2	3	4	Total # pts
Baseline					
TMG	82 (98%)	2 (2%)	0	0	84
Vehicle	83 (98%)	2 (2%)	0	0	85
Week 2					
TMG	44 (57%)	28 (36%)	5 (6%)	0	77
Vehicle	77 (95%)	4 (5%)	0	0	81
Week 4					
TMG	66 (87%)	7 (9%)	3 (4%)	0	76
Vehicle	82 (99%)	1 (1%)	0	0	83
Week 7					
TMG	71 (97%)	1 (1%)	1 (1%)	0	73
Vehicle	76 (100%)	0	0	0	76
Week 10					
TMG	71 (100%)	0	0	0	71
Vehicle	71 (99%)	1 (1%)	0	0	72
Week 12					
TMG	72 (97%)	2 (3%)	0	0	74
Vehicle	72 (100%)	0	0	0	72
* 1 = none; 2 = mild; 3 = moderate, 4 = severe					

Mean severity scores - burning/stinging		
	TMG 0.1%	Vehicle
Baseline	1.0	1.0
Week 2	1.5	1.0
Week 4	1.2	1.0
Week 7	1.0	1.0
Week 10	1.0	1.0
Week 12	1.0	1.0

b. Adverse events.

The incidence and severity of adverse events at the treatment site which were considered to be possibly, probably, or definitely related to treatment were as follows.

Adverse events - treatment site						
	TMG 0.1%			Vehicle		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Acne	0	0	0	0	1	1
Nevus	0	1	0	1	0	0
Rash	0	1	0	0	0	0
Seborrhea	0	1	0	0	0	0
Facial irritation	3	15	4	0	0	0
Dry skin	1	0	0	0	0	0

In addition, one patient had a severe conjunctivitis.

Five patients in the TMG group and 3 patients in the vehicle group discontinued treatment because of adverse events. These are described further as follows.

Patient TMG group: moderate skin irritation characterized by erythema, tightness, peeling, and burning/stinging after five days of treatment.

Patient TMG group: moderate oiliness and erythema after four days of treatment.

Patient TMG group: severe irritation, with erythema, itching, scaling, and burning/stinging after five days of treatment.

Patient TMG group: severe irritation (not further described) after three days of treatment.

Patient severe irritation, with erythema, peeling, itching, burning and stinging after four days of treatment.

Patient vehicle group: acne flare after seven weeks of treatment.

Patient vehicle group: acne flare after one month of treatment.

Patient vehicle group: conjunctivitis on the first day of treatment, which became severe during the one month of treatment, and was still continuing when the patient was last seen at two months after study discontinuation. The investigator felt that this was probably related to treatment.

There were additionally 18 patients in the TMG group in whom treatment was temporarily interrupted because of skin irritation.

Reviewer's note: In summary, 0.1% TMG was significantly superior to the vehicle in the reduction of non-inflammatory lesions at weeks 2, 4, 7, 10 and 12, and in the investigator's global evaluation. 0.1% TMG was superior to the vehicle in the reduction of inflammatory lesions only at week 2. About one-third of patients had mild irritation at week 2, which tapered to 12% with mild irritation at week 12. Eight percent of patients had moderate irritation at week 2, which tapered to none with moderate irritation at weeks 10 and 12. No patients had severe irritation.

III. Study CP1

The formulations used in this study were TMG IB 0.1% and TMG IB 0.025%; these differed slightly from those in the formulation proposed for marketing, as previously described.

The investigators for this study were:

James Leyden, M.D.
Philadelphia, PA

Alan Shalita, M.D.
Long Island City, NY

Donald Lookingbill, M.D.
Hershey, PA

The conduct of the study was as follows.

1) Study objective: This was to evaluate the safety and effectiveness of two concentrations of Tretinoin Microsponge gel (TMG) compared with the vehicle formulation in the treatment of acne.

2) Study design: This was a double blind, multicenter, randomized comparison of TMG 0.1%, TMG 0.025%, and the vehicle in patients with acne.

3) Patient selection: Those selected were males and females, 13 to 35 years old, with acne that met the following criteria:

- between 10 and 100 comedones (open and closed).
- between 5 and 50 inflammatory lesions (papules and pustules).
- a score of at least 0.5 on a global assessment scale of 0 to 8.0.

In addition, the patients were to have moderately to extremely oily skin.

4) Patient exclusions: Patients with the following conditions were excluded from the study.

a. History of skin reactions to topical medication, particularly to trans-retinoic acid, or to cosmetics or soaps.

b. Treatment within the previous month with systemic or topical medication which may be considered to affect or produce skin reactions, such as antibiotics, antihistamines, and steroids.

c. Treatment with any topical facial acne medication during the two weeks prior to study entry.

d. Pregnancy and lactation.

e. An inflammation score of 3 or greater or a peeling score of 2 or greater on the scale described under 'Safety evaluations'.

5) Treatment regimen: Applications were made once daily for 12 weeks.

6) Effectiveness parameters: The following were done at baseline and at weeks 2, 4, 7, 10, and 12.

a. Lesion counts for inflammatory and noninflammatory lesions.

b. Global assessment of the acne based on the Cunliffe visual acne scale of from 0 to 8.0, with 8.0 being the most severe. The investigator assigned a score to each patient based on a comparison with sixteen control photographs depicting facial acne of varying severity. Thus, a reduction from the baseline score represented a decrease in acne severity.

7) Safety evaluation: The patients were assessed at each return visit for inflammation, peeling, and degree of oiliness/dryness, using the following scales.

Inflammation

0 = no erythema
0.5 = doubtful erythema
1 = mild erythema
2 = moderate erythema
3 = marked erythema
4 = erythema and edema
5 = vesiculation
6 = bullae, hemorrhage, or ulceration

Peeling

0 = none
0.5 = doubtful
1 = slight
2 = moderate
3 = marked
4 = severe

Dryness/oiliness was graded on a scale of from + 4 to - 4.

Results of the study were as follows.

1) Patient enrollment and demographic characteristics: 165 patients were enrolled into the study, of which 158 patients were evaluable for efficacy; this included 52 in the 0.1% TMG group, 52 in the 0.025% TMG group, and 54 in the vehicle group. The demographic characteristics of all patients enrolled were as follows.

Demographic and baseline disease characteristics			
	TMG 0.025%	TMG 0.1%	Vehicle
Age Mean Range	19	18	18
Sex Male Female	34 (65%) 18 (35%)	33 (63%) 19 (37%)	34 (63%) 20 (37%)
Mean Cunliffe acne score *	0.9	0.9	1.0
* Based on a scale of from 0 (no acne) to 8.0 (severe acne)			

2) Patient discontinuations and protocol violations: The reasons for patient discontinuations were as follows.

Patient discontinuations			
	TMG 0.025%	TMG 0.1%	Vehicle
Adverse event	1	3	0
Protocol violation	1	0	0
Personal reasons	2	3	1
Lost to followup	2	4	0
Total # pts	6	10	1

The number of patients with valid data for the efficacy analysis at each return visit was as follows.

# of patients with valid efficacy data			
	TMG 0.025%	TMG 0.1%	Vehicle
Baseline	52	52	54
Week 2	51	51	54
Week 4	51	48	54
Week 7	51	46	54
Week 10	50	45	54
Week 12	48	45	54

It appeared that most patients complied with the treatment regime; however, compliance in this regard was not formally monitored. The use of concomitant medications that might have affected treatment were to have been recorded by the investigator as comments on the case report form; other than this, no systematic attempts were made to elicit information on concomitant therapy. There were no significant concomitant medications recorded for the 0.1% TMG group.

3) Effectiveness parameters: The results of the lesion counts and the global evaluation were as follows.

a. Lesion counts.

The mean total lesion counts and the mean percent reduction in total lesion counts at each return visit were as follows.

Mean total lesion counts			
	TMG 0.025%	TMG 0.1%	Vehicle
Baseline	52.7	58.4	63.3
Week 2	52.5	56.8	58.3
Week 4	49.0	51.6	58.8
Week 7	49.1	46.6	54.5
Week 10	45.1	41.5	55.0
Week 12	41.9	37.6	52.5

Mean percent reduction in total lesion counts			
	TMG 0.025%	TMG 0.1%	Vehicle
Week 2	0.5%	- 2.0%	2.0%
Week 4	5.0%	6.4%	2.9%
Week 7	6.6%	15.5%	4.5%
Week 10	12.5%	22.1%	7.9%
Week 12	20.9%	30.2%	12.2%

In the mean percent reduction in total lesion counts at week 12, TMG 0.1% was significantly superior to the vehicle ($p = 0.001$); there was no significant difference between 0.1% and 0.025% TMG ($p = 0.09$).

The mean non-inflammatory lesion counts (comedones) and the mean percent reduction in non-inflammatory lesion counts at each return visit were as follows.

Mean non-inflammatory lesion counts			
	TMG 0.025%	TMG 0.1%	Vehicle
Baseline	41.0	46.7	49.1
Week 2	41.1	44.9	45.6
Week 4	38.5	41.4	45.6
Week 7	38.7	37.0	42.2
Week 10	35.6	33.6	44.0
Week 12	33.2	30.9	42.6

Mean percent reduction Non-inflammatory lesion counts			
	TMG 0.025%	TMG 0.1%	Vehicle
Week 2	- 0.1%	- 3.7%	0.2%
Week 4	4.3%	6.0%	2.4%
Week 7	5.7%	14.9%	8.4%
Week 10	11.6%	18.8%	5.3%
Week 12	19.8%	27.3%	8.7%

In the mean percent reduction in non-inflammatory lesion counts at week 12, TMG 0.1% was significantly superior to the vehicle ($p = 0.001$); there was no significant difference between 0.1% and 0.025% TMG ($p = 0.19$).

The mean inflammatory lesion counts (papules and pustules) and the mean percent reduction in inflammatory lesion counts at each return visit were as follows.

Mean inflammatory lesion counts			
	TMG 0.025%	TMG 0.1%	Vehicle
Baseline	11.7	11.7	14.2
Week 2	11.4	11.9	12.7
Week 4	10.4	10.2	13.2
Week 7	10.4	9.6	12.3
Week 10	9.5	7.8	11.0
Week 12	8.5	6.7	9.9

Mean percent reduction Inflammatory lesion counts			
	TMG 0.025%	TMG 0.1%	Vehicle
Week 2	- 8.4%	- 0.6%	- 0.7%
Week 4	- 0.6%	- 0.2%	- 2.8%
Week 7	2.5%	4.2%	- 11.6%
Week 10	3.9%	24.4%	6.1%
Week 12	17.7%	36.1%	14.9%

The sponsor states that there were no significant differences among treatment groups in the mean percent reduction in inflammatory lesion counts at week 12; however, the p value for the comparison between 0.1% TMG and the vehicle was 0.038.

b. Global assessment.

The mean acne scores and the mean percent reduction in acne scores at each return visit were as follows.

Global assessment Mean acne scores			
	TMG 0.025%	TMG 0.1%	Vehicle
Baseline	0.9	0.9	1.0
Week 2	0.9	0.9	1.0
Week 4	0.8	0.9	0.9
Week 7	0.8	0.9	0.9
Week 10	0.7	0.8	0.9
Week 12	0.7	0.7	0.8

Global assessment Mean percent reduction in acne scores			
	TMG 0.025%	TMG 0.1%	Vehicle
Week 2	0.0%	0.0%	0.0%
Week 4	- 0.1%	0.0%	0.0%
Week 7	0.1%	0.1%	0.1%
Week 10	0.2%	0.1%	0.1%
Week 12	0.2%	0.2%	0.1%

As shown, the changes in acne scores were minor in all groups; there were no significant differences among any of the treatment groups.

4) Safety parameters.

a. Symptomatology.

All of the 158 patients enrolled were included in the safety analysis; this comprised 52 patients in the 0.025% TMG group, 52 in the 0.1% TMG group, and 54 in the vehicle group.

The incidence and severity, and the mean scores, for inflammation and peeling at each return visit were as follows.

Incidence and severity of inflammation

Visit	Severity scores *			
	0	0.5	1.0	2.0
Baseline				
TMG 0.025%	32 (62%)	12 (23%)	5 (10%)	3 (6%)
TMG 0.01%	36 (69%)	10 (19%)	4 (8%)	2 (4%)
Vehicle	38 (70%)	9 (17%)	5 (9%)	2 (4%)
Week 2				
TMG 0.025%	34 (67%)	6 (12%)	8 (16%)	3 (6%)
TMG 0.01%	34 (67%)	9 (18%)	3 (6%)	5 (10%)
Vehicle	40 (74%)	8 (15%)	4 (7%)	2 (4%)
Week 4				
TMG 0.025%	37 (73%)	8 (16%)	5 (10%)	1 (2%)
TMG 0.01%	36 (75%)	7 (15%)	2 (4%)	3 (6%)
Vehicle	44 (81%)	6 (11%)	4 (7%)	0
Week 7				
TMG 0.025%	38 (75%)	8 (16%)	3 (6%)	2 (4%)
TMG 0.01%	33 (72%)	8 (17%)	4 (9%)	1 (2%)
Vehicle	43 (80%)	6 (11%)	4 (7%)	1 (2%)
Week 10				
TMG 0.025%	41 (82%)	3 (6%)	4 (8%)	2 (4%)
TMG 0.01%	35 (78%)	6 (13%)	2 (4%)	2 (4%)
Vehicle	47 (87%)	6 (11%)	1 (2%)	0
Week 12				
TMG 0.025%	39 (80%)	5 (10%)	4 (8%)	1 (2%)
TMG 0.01%	41 (91%)	2 (4%)	2 (4%)	0
Vehicle	48 (89%)	5 (9%)	1 (2%)	0

* on a scale of from 0 to 6; no patients had a score higher than 2.0.
0 = no erythema; 0.5 = doubtful erythema;
1 = mild erythema, 2 = moderate erythema

Mean severity scores - inflammation			
	TMG 0.025%	TMG 0.1%	Vehicle
Baseline	0.3	0.2	0.2
Week 2	0.3	0.3	0.2
Week 4	0.2	0.2	0.1
Week 7	0.2	0.2	0.2
Week 10	0.2	0.2	0.1
Week 12	0.2	0.1	0.1

Incidence and severity of peeling				
	Severity scores *			
Visit	0	0.5	1.0	2.0
Baseline				
TMG 0.025%	49 (94%)	3 (6%)	0	0
TMG 0.01%	44 (85%)	6 (12%)	2 (4%)	0
Vehicle	51 (94%)	3 (6%)	0	0
Week 2				
TMG 0.025%	37 (73%)	3 (6%)	10 (20%)	1 (2%)
TMG 0.01%	32 (63%)	6 (12%)	7 (14%)	6 (12%)
Vehicle	46 (85%)	7 (13%)	1 (2%)	0
Week 4				
TMG 0.025%	37 (73%)	10 (20%)	3 (6%)	1 (2%)
TMG 0.01%	35 (73%)	7 (15%)	3 (6%)	3 (6%)
Vehicle	49 (91%)	2 (4%)	3 (6%)	0
Week 7				
TMG 0.025%	40 (78%)	6 (12%)	5 (10%)	0
TMG 0.01%	35 (76%)	4 (9%)	6 (13%)	1 (2%)
Vehicle	49 (91%)	4 (7%)	1 (2%)	0
Week 10				
TMG 0.025%	41 (82%)	6 (12%)	1 (2%)	2 (4%)
TMG 0.01%	35 (78%)	3 (7%)	5 (11%)	2 (4%)
Vehicle	49 (91%)	3 (6%)	2 (4%)	0
Week 12				
TMG 0.025%	42 (86%)	4 (8%)	1 (2%)	2 (4%)
TMG 0.01%	36 (80%)	3 (7%)	5 (11%)	1 (2%)
Vehicle	50 (93%)	3 (6%)	1 (2%)	0

* on a scale of from 0 to 4; no patients had a score higher than 2.0.
0 = none; 0.5 = doubtful; 1 = slight,
2 = moderate; 3 = marked, 4 = severe

Mean severity scores - peeling			
	TMG 0.025%	TMG 0.1%	Vehicle
Baseline	0	0.1	0
Week 2	0.3	0.4	0.1
Week 4	0.2	0.3	0.1
Week 7	0.2	0.2	0.1
Week 10	0.2	0.2	0.1
Week 12	0.1	0.2	0

In the assessment of oiliness/dryness, the mean scores decreased from a baseline of moderately oily to slightly oily at week 2, and remained in this range for the remainder of the treatment period. There were no scores of +3 or +4 (severe dryness) in any patient.

b. Adverse events.

The adverse events related to the skin that apparently were considered to be possibly related to treatment were as follows.

Adverse events - skin			
	TMG 0.025%	TMG 0.1%	Vehicle
Dermatitis	0	1	0
Pruritus	1	0	0
Erythematous rash *	0	1	0
Facial irritation	1	2	0
Dry skin	4	2	1
Skin ulceration **	1	0	0
*Patient #124, described below ** Patient #154, described below			

Three patients in the 0.1% TMG group and one subject in the 0.025% TMG group discontinued treatment because of adverse events. These are described further as follows.

Patient 0.1% TMG group: moderate skin irritation with erythema and burning at the two week return visit.

Patient 0.1% TMG group: facial edema reported by the patient after 10 days of treatment. Patient did not return.

Patient 0.1% TMG group: facial erythema associated with sun exposure.

Patient 0.025% TMG group: skin ulceration on the nose after 10 weeks of treatment, which was considered by the investigator to have no relationship to treatment.

In addition, 9 patients in the 0.1% TMG group, 5 in the 0.025% TMG group, and 2 vehicle patients temporarily suspended treatment due to adverse events.

Reviewer's note: It is felt that this study is inadequate for a determination of effectiveness because the patients had minimal acne at baseline, and compliance with the protocol was not formally monitored.

Labeling review

The indication for Nuretin gel is for topical application in the treatment of acne vulgaris.

It is felt that the labeling should describe more precisely the adverse events that occurred in clinical trials. The labeling should also be revised to be in accordance with the labeling for the Retin-A products.

Summary and evaluation

Nuretin gel 0.1% is felt to be safe and effective for the topical treatment of acne vulgaris, with certain labeling revisions, as described above.

It is noted that much of the clinical safety studies, and both of the pivotal clinical effectiveness studies were performed with formulations that differed from the formulation proposed for marketing in the nature of the stabilizers and preservatives. It is felt by this reviewer that these differences are minor, and would not have affected the outcome of these studies.

Clinical safety: The clinical safety studies performed were cumulative irritancy, half face comparative irritation, contact sensitization, phototoxicity, and photosensitization.

In the first cumulative irritancy study the tretinoin microsponge gel 0.1% (TMG) was compared with 0.1% Retin-A cream, and it was found that Retin-A cream was significantly more irritating under these conditions of exaggerated exposure, in which repeated applications were made under semi-occlusive patches. However, 11 of the 50 subjects treated with 0.1% TMG had a maximum recorded grade of 4+, which was the highest grade in the scale, given to a reaction described as erythema, induration, and bullae. (With Retin-A, 36 of 50 subjects had a maximum grade of 4+). A second cumulative irritancy test performed by a separate investigator showed little difference between 0.1% TMG and Retin-A cream 0.1% in the distribution of reaction scores at day 21. Of the 26 subjects tested, there was one 2+ reaction to each test product, which represented erythema with edema, and one 3+ reaction to each test product, which represented erythema with vesiculation and edema.

The half face comparative study was a comparison of 0.1% TMG and 0.1% Retin-A cream performed on the normal facial skin of fair-skinned subjects with a history of sensitive skin. Once daily applications were to be made for 14 days, with scoring of the amount of dryness and erythema. The subjects were discontinued from treatment if marked erythema or marked flaking occurred. There were a significantly higher number of terminations due to irritation with Retin-A cream, and significantly higher mean irritation scores with Retin-A. However, only six of the 25 subjects were able to complete the 14 day treatment period with 0.1% TMG. Thus, it is felt that although 0.1% TMG gel has been demonstrated to be less irritating than 0.1% Retin-A cream in this study and in one of the cumulative irritancy studies, it is not a 'low irritancy formulation' and does not have 'minimal irritancy' as stated in the proposed labeling. This is also apparent in the adverse effects which were found in the clinical effectiveness studies.

No reactions indicative of contact sensitization, phototoxicity, or photosensitization were elicited in these studies, which were adequately performed.

Clinical effectiveness studies: Three double blind, multicenter studies were performed which compared 0.1% TMG with its vehicle in patients with acne. The first two studies, which used the same protocol, were considered by this reviewer to be the primary studies. In these the effectiveness parameters were lesion counts and an investigator's global evaluation of the treatment response.

In the first study, 144 evaluable patients completed the 12 week treatment period. TMG 0.1% was significantly superior to the vehicle in the mean percent reduction in total lesion counts, non-inflammatory lesion counts, and inflammatory lesion counts. TMG 0.1% was also superior to the vehicle in the physician's global evaluation, with 66% of the patients reported to have a good to excellent clinical response.

In the second study, 138 evaluable patients completed the 12 week treatment period. TMG 0.1% was significantly superior to the vehicle in the mean percent reduction in total lesion counts and in non-inflammatory lesion counts; it was not superior to the vehicle in the mean percent reduction in inflammatory lesion counts. TMG 0.1% was significantly superior to the vehicle in the physician's global evaluation, with 58% of patients reported to have a good or excellent clinical response.

In the third study two concentrations of TMG were studied. The effectiveness parameters were lesion counts and an investigator's global evaluation based on the Cunliffe visual acne scale. A total of 99 evaluable patients in the 0.1% TMG and vehicle groups completed the 12 week treatment period. TMG 0.1% was significantly superior to the vehicle in the mean percent reduction in total lesion counts and non-inflammatory lesion counts. In the global assessment, the changes in acne scores were minor, and there was no difference between the two groups. It is felt by this reviewer that the conduct of this study was such that it was inadequate for a determination of effectiveness. The primary reason for this assessment is that the patients had such minimal acne at baseline; on a scale of severity of from 0 to 8.0, the mean score at baseline in the 0.1% TMG group was 0.9, and in the vehicle group was 1.0. Also, compliance with the treatment regime was not formally monitored, and no systematic attempts were made to elicit information on concomitant therapy.

Recommendations: It is recommended that Nuretin gel be approved for the treatment of acne, with certain revisions in the labeling.

The proposed labeling has been submitted in electronic form by the sponsor. This has been revised by this reviewer to reflect the specific labeling recommendations, and is presented in an addendum to this review.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/MO/PHuene
HFD-540/Pharm/Jacobs
HFD-540/Chem/DeCamp
HFD-540/CSO/Holmes
MAC 11/21/95
9 2) 12/6/95

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 20-475

December 2, 1996

SPONSOR: Advanced Polymer Systems, Inc
Redwood City, CA

DEC 4 1996

DRUG: Nuretin Gel 0.1% (Tretinoin Microsponge gel)

NEW TRADE NAME: RETIN-A MICRO (tretinoin microsphere gel) 0.1%

INDICATION: Acne

DATE OF AMENDMENT: November 18, 1996

This submission is in response to the comments made by this reviewer on the Nuretin labeling, specifically the request to revise the "Irritation Potential" subsection of the CLINICAL PHARMACOLOGY section. In addition, the sponsor requests two other labeling changes.

CLINICAL PHARMACOLOGY SECTION

The sponsor proposes the following "Irritation Potential" section:

Reviewer's evaluation: It is recommended that the following additional revisions be made to the proposed "Irritation Potential" section.

Other labeling revisions

The sponsor has made the following additional revisions.

Reviewer's evaluation: There is no objection to these two additional revisions.

Conclusions and Recommendations: Additional revisions should be made in the "Irritation Potential" section of the labeling. Two revisions made by the sponsor in other portions of the labeling are satisfactory.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Cintron
HFD-540/DeCamp
HFD-540/Jacobs

September 23, 1996

MEDICAL OFFICER'S REVIEW OF LABELING
NDA 20-475

SPONSOR: Advanced Ploymer Systems, Inc.
Redwood City, CA

DEC 6 1996

DRUG: Nuretin gel 0.1%

CLINICAL INDICATION: Acne

MATERIAL REVIEWED: Patient instruction leaflet

The following is a review of the the leaflet for Nuretin which is entitled "Patient Instructions for Treatment of Acne". It is felt that certain revisions should be made in this leaflet, as follows.

1. Under fourth line, the word should be inserted after so that the last portion of this sentence reads

Without

this word inserted the next sentence would be difficult for the consumer to understand.

2. The following sentence should be added at the end of the section on as part of the same paragraph:

3. Under the word should be inserted before to read

4. Under the word should be added to the first sentence to read

5. The following paragraph should be added under

6. The paragraph title reading should be chamged to

Phyllis A. Huene, M.D.

Phyllis A. Huene,. M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Cintron
HFD-540/Jacobs
HFD-540/DeCamp

MEDICAL OFFICER'S AMENDMENT TO REVIEW OF LABELING
NDA 20-475

December 12, 1996

SPONSOR: Advanced Polymer Systems, Inc.
Redwood City, CA

DEC 31 1996

DRUG: Nuretin gel 0.1%

NEW NAME: Retin-A Micro (tretinoin gel) Microsphere 0.1%

CLINICAL INDICATION: Acne

FIRST REVIEW OF LABELING: Review of patient instruction leaflet, dated 9/23/96.

This amendment is in response to Dr. Wilkin's note of 12/6/96, attached to my review of 9/23/96. Dr. Wilkin's note is as follows.

1. All references to the drug product should give the complete trade name: Retin-A Micro (tretinoin gel) Microsphere 0.1%.

1. Dr. Wilkin states that the sentence

can be used only if supported by data that show tretinoin-induced pigmentary changes disappearing on tretinoin therapy and tretinoin-induced pigmentary changes not increasing while on tretinoin therapy. Otherwise, patients are encouraged to continue tretinoin therapy after the onset of tretinoin-induced pigmentary changes.

<u>Reviewer's note:</u> This statement has been permitted in the labeling of the Retin-A products. As I remember, there are some data showing that tretinoin-induced pigmentary changes regress on continued therapy or after discontinuation of treatment in those patients that have been sufficiently followed. However, it is doubtful that all such patients, or that even most such patients, have been sufficiently followed. Therefore, this statement should be deleted; however, it should also be deleted from the labeling of the Retin-A products.

3. The first sentence under should be deleted.
This sentence reads:

Reviewer's note: This statement has also been permitted in the labeling of the Retin-A products. I agree that it is essentially meaningless, except for advising the patient that results will not be immediate. If deleted it should also be deleted from the labeling of the Retin-A products.

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Cintron
HFD-540/Jacobs
HFD-540/DeCamp

12/31/96

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF LABELING
NDA 20-475

January 23, 1997

SPONSOR: Advanced Polymer Systems, Inc.
Redwood City, CA

JAN 29 1997

DRUG: RETIN-A MICRO GEL 0.1%
(Old name: Nuretin gel 0.1%)

CLINICAL INDICATION: Acne

The following section should be added to the package insert.

CLINICAL STUDIES

In two vehicle-controlled clinical studies, Retin-A Micro gel 0.1% applied once daily was significantly more effective than vehicle in reducing the severity of acne lesion counts. The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in the following tables.

Mean reduction in lesion counts				
	Retin-A Micro Gel 0.1%		Vehicle gel	
	Study # 1 72 pts	Study # 2 71 pts	Study # 1 72 pts	Study # 2 67 pts
Non-inflammatory lesion counts	- 21.4	- 15.2	- 9.8	- 3.4
Inflammatory lesion counts	- 8.4	- 6.7	- 4.0	- 4.4

Mean percent reduction in lesion counts				
	Retin-A Micro Gel 0.1%		Vehicle gel	
	Study # 1 72 pts	Study # 2 71 pts	Study # 1 72 pts	Study # 2 67 pts
Non-inflammatory lesion counts	- 48.5%	- 32.4%	- 21.6%	- 2.6%
Inflammatory lesion counts	- 36.7%	- 28.5%	- 18.3%	- 23.5%
Total lesion counts	- 44.5%	- 32.3%	- 22.8%	- 16.2%

Retin-A Micro Gel 0.1% was significantly superior to the vehicle in the investigator's global evaluation of the clinical response at endpoint in these two studies, as shown in the following table.

Global evaluation of clinical response				
	Retin-A Micro Gel 0.1%		Vehicle gel	
	Study # 1 72 pts	Study # 2 71 pts	Study # 1 73 pts	Study # 2 67 pts
Excellent	25 (35%)	20 (28%)	8 (11%)	6 (9%)
Good	22 (31%)	21 (30%)	17 (23%)	17 (25%)
Fair	9 (13%)	17 (24%)	16 (22%)	20 (29%)
No change	9 (13%)	9 (13%)	22 (30%)	17 (25%)
Poor	7 (10%)	4 (6%)	10 (14%)	9 (13%)

Phyllis A. Huene, M.D.

Phyllis A. Huene, M.D.

cc: NDA 20-475
HFD-540
HFD-540/Huene
HFD-540/Walker
HFD-540/Cintron
HFD-540/DeCamp
HFD-540/Jacobs

SW 1/27/97
See attached MOTL addendum.

As above per MOTL addendum of 1/29/97

1/29/97

Team Leader Addendum to Medical Officer's Review of Labeling
NDA 20-475

CLINICAL STUDIES

JAN 29 1997

In two vehicle-controlled clinical studies, Retin-A Micro gel 0.1% applied once daily was significantly more effective than vehicle in reducing the severity of acne lesion counts. The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in the following table.

Mean percent reduction in lesion counts				
	Retin-A Micro Gel 0.1%		Vehicle gel	
	Study # 1 72 pts	Study # 2 71 pts	Study # 1 72 pts	Study # 2 67 pts
Non-inflammatory lesion counts	49%	32%	22%	3%
Inflammatory lesion counts	37%	29%	18%	24%
Total lesion counts	45%	32%	23%	16%

Retin-A Micro Gel 0.1% was also significantly superior to the vehicle in the investigator's global evaluation of the clinical response. In study #1, thirty five percent (35%) of patients using Retin-A Micro Gel 0.1% achieved an excellent result compared to eleven percent (11%) of patients on vehicle control. In study #2, twenty eight percent (28%) of patients using Retin-A Micro Gel 0.1% achieved an excellent result compared to nine percent (9%) of patients on vehicle control.

1/29/97

Susan Walker, M.D.

1/29/97

cc: NDA 20-475
HFD-540
HFD-540/Cintron
HFD-540/Huene
HFD-540/Walker
HFD-540/Wilkin

MEMO

Date: 30 Jan 97

JAN 3 0 1997

The Team Leader addendum to Medical Officer's Review of Labeling for NDA 20-475 has been reviewed by biostatistics. This clinical studies section of the labeling is in concurrence with the results of the statistical review.

Susan Walker, M.D.
Acting Team Leader, Dermatology

R. Srinivasan, Ph.D.
Team Leader, Biostatistics

cc: NDA 20-475
HFD-540
HFD-540/Wilkin
HFD-540/Walker
HFD-725/Srinivasan

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

PATENT CERTIFICATION

In accordance with the Federal Food, Drug and Cosmetic Act, as amended September 24, 1984, Patent Certification is hereby provided for Tretinoin MICROSPONGE® Gel 0.1%. The undersigned certifies that the drug and the formulation or composition of Tretinoin MICROSPONGE® Gel 0.1% is covered by U.S. Patents No. 4,690,825 and 5,145,675. This product is the subject of this application for which approval is being sought. We certify that, to the best of our knowledge, these are valid patents that cover the use of the new drug product for the following indication or other conditions of use included in this application:

Topical treatment of acne vulgaris.

To the best of our knowledge, this patent information has not been previously submitted to the FDA. This certification is made in accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

NDA 20-475
NURETIN™ 0.1% Gel
PATENT INFORMATION
ITEM 13

NURETIN™ 0.1% Gel, the drug product subject of this application, is covered by two U.S. patents:

1. U.S. Patent No. 4,690,825 issued on September 1, 1987, and
2. U.S. Patent No. 5,145,675 issued on September 8, 1992

Copies of these two patents are attached.

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

2.11 Certification of Non-Debarment

This is to certify that to the best of my knowledge, neither Advanced Polymer Systems, Inc. (hereinafter referred to as "Company") nor any person employed thereby has been debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetic Act and no debarred person will in the future be employed by the "Company" in connection with any work to be performed for, or on behalf of Advanced Polymer Systems, which may later become part of any application for approval of a drug or biologic by the Food and Drug Administration. The "Company" is also not aware of any outside contract laboratory, consultant or contract research organization or employees thereof engaged by the "Company" being debarred. If at any time after execution of this certification, the "Company" becomes aware that the "Company" or any person employed by the "Company" is in the process of being debarred, the "Company" hereby certifies that the "Company" will so notify the Food & Drug Administration.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-475 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Retin-A Micro (tretinoin gel) Microsphere Action: AP AE NA

Applicant Advanced Polymer Systems Therapeutic Class retinoid

Indication(s) previously approved 2#

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

Indication in this application acne vulgaris

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

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

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

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

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

_✓_ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

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

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

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

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

Olga Tsintsun 11/27/96

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

cc: Orig NDA/PLA # 20-475
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

P. Huene 12/2/96 JW 4/2/97

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

5/95

1/19/96 The sponsor has some data on product use with 13 years old. FDA defines "pediatric age group" as birth to 16 years old. Sponsor defines product use as potential with "puberty".

Sponsor is willing to conduct further studies in the pediatric age group to satisfy FDA requirements if product is used in under or at 16 years of age group. Obiston fm. S. Kozma-Fornaro

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20475 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade (generic) name/dosage form: Renova (Tretinoin microsponge) gel) Gel, 0.1% Action: AP AE (NA)

Applicant Advanced Polymer Systems Therapeutic Class Retinoid

Indication(s) previously approved NA

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

Indication in this application acne vulgaris

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

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

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

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

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

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

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

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

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

Mary Jean Tenaro 11/19/96 11/19/96

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

cc: Orig NDA/PLA # 20475
HFD 540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

P. Hurne 12/2/96

JW 5/5/96

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

5/95

DEC 5 1995

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20,475 **Submission Date:** February 6, 1995

Tretinoin microsphere Gel, 0.1% (Nuretin).

Advanced Polymer Systems, Inc. **Reviewer:** Funmilayo O. Ajayi, Ph.D
3696 Haven Avenue
Redwood City, CA 94063 **Type of submission:** Original NDA **Code:** 3 S

Synopsis: This NDA was submitted for a 0.1% gel formulation of tretinoin in a polymeric carrier (MICROSPONGE^R System) which consists of acrylates copolymer porous microspheres. The MICROSPONGE^R System made it possible to have tretinoin in an aqueous gel without the use of organic solvents such as ethanol or acetone which can contribute to irritation. At present, the gel formulation, the subject of this application, is not marketed anywhere in the world.

The product is intended for topical application as required. In support of the application, the sponsor submitted the report of an *in-vivo* percutaneous penetration study in healthy subjects following both single and multiple topical application of the product for a period of 28 days; and a report of an *in-vitro* release study where gel from 3 batches were compared.

Study B0281S, the pivotal biopharmaceutics study in this application, demonstrated that the systemic absorption of ^{3}H-tretinoin related radioactivity following topical administration of ^{3}H-tretinoin in TMG 0.1% and RETIN-A Cream 0.1% to normal male and female subjects was minimal after single and multiple applications. In general, no differences were found between endogenous tretinoin and metabolite concentrations and concentrations found after multiple daily applications of TMG 0.1% or RETIN-A Cream 0.1%. The results are consistent with those previously observed with various 0.05% tretinoin cream formulations.

The *in vitro* release rates of formulations containing ^{3}H-tretinoin produced on a small laboratory scale were observed to be comparable to the corresponding nonradiolabeled formulations produced at full scale. Also, TMG IA 0.1%, TMG IB 0.1%, and TMG IC 0.1% (the proposed market formula) have similar *in vitro* release rate characteristics for tretinoin.

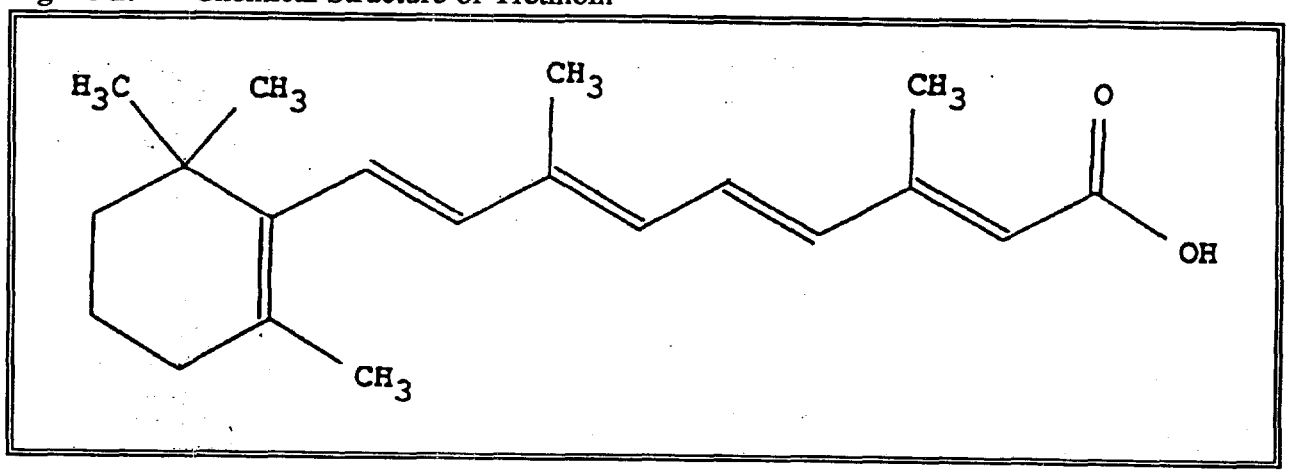
Recommendation: The Biopharmaceutics and Pharmacokinetics section of NDA 20,475 is acceptable because it meets the requirements of 21 CFR 320.

Table of contents

Organization of review: Following the background is a description of the drug formulation. Thereafter, is a summary of the studies followed by the general comments and comments to the Firm.

Background: The active ingredient in this product is tretinoin. It is the prototype member of the retinoid family of compounds and an endogenous metabolite of naturally occuring vitamin A. The product is intended for the treatment of acne vulgaris, a dermatologic disease. Topical tretinoin products (0.01 to 0.1%) in different vehicles have been marketed in the US for the treatment of acne vulgaris since 1971 under the brand name RETIN-A^{R}. Varying degree of skin irritation have been observed with topical tretinoin products. The sponsor claims that the tretinoin microsponge gel is developed with the aim of minimizing the cutaneous irritation. The formulation uses patented acrylates copolymer porous microspheres (MICROSPONGE). Tretinoin is entrapped on the surface of and within the MICROSPONGE polymer.

Figure 1: Chemical Structure of Tretinoin



Drug Formulation:

QUANTITATIVE COMPOSITION OF VARIOUS INVESTIGATIONAL FORMULATIONS OF TRETINOIN MICROSPONGE® GEL, 0.1%			
Ingredients	**TMG IA 0.1% %w/w**	**TMG IB[1] 0.1% %w/w**	**TMG IC 0.1% (%w/w) (Market Formula)**
1% Tretinoin in Acrylates Copolymer (Entrapment)[2]			
Vehicle			
Water			
Carbomer 934P, NF			
Glycerin USP			
Propylene Glycol USP			
PPG-20 Methyl Glucose Ether Distearate			
Cyclomethicone and Dimethicone Copolyol			
Trolamine NF			
Propylene Glycol,			
Butylated Hydroxytoluene (BHT) NF			
Disodium Edetate (EDTA)			
Benzyl Alcohol NF			
Sorbic Acid, NF			
TOTAL			

[1] TMG IB was initially formulated with a 12% overage of tretinoin entrapment (Master Formula No. P006D-43). Lot numbers 20107, 20303, 21006 and 21007 used this formulation. Later formulations of TMG IB were made with a 10% overage of tretinoin entrapment (Master formula P006D-48). Lot numbers 21201 and 30901 used this formulation. (Lot numbers 20303 and 21006 were not tested in the nonclinical program).

[2] Theoretical composition of Tretinoin in Acrylates Copolymer:

Ingredient	%w/w
Tretinoin, USP	
Butylated Hydroxytoluene (BHT), NF	
Acrylates Copolymer	
Total	

[3] 12% overage formula.
[4] 10% overage formula.
[5] Purified Water USP was used.
[6] 4.8% overage.
[7] Tretinoin in Acrylates Copolymer (Entrapment) contains BHT as shown in footnote 2 above. Total BHT concentration in TMG IC is 0.02%.

Summary of studies: Study B0281S is the pivotal biopharmaceutics study. Study B0225S was aborted due to an analytical error and inadvertent loss of test specimens, and had to be repeated as Study B0281S. Preliminary analytical data from the first study (B0225S) showed extremely low amounts of radioactivity in the plasma, and in most cases these values were below the detection limit. Therefore, in the second study (B0281S), the amount of radioactivity was increased from the μCi tritium used in the first study to μCi tritium in mg of formulation. Study B0281S, a parallel study design, was conducted in 44 healthy male and female subjects who received single or repeated daily topical applications of TMG 0.1% or RETIN-A Cream 0.1%. Percutaneous absorption was determined by cumulative excretion of radioactivity into the urine and feces. Mean (SD) total absorption was 0.82 (0.11)% and 1.41 (0.54)% of the dose, respectively, for subjects administered single or multiple dose(s) of TMG 0.1%. Mean (SD) total absorption with RETIN-A Cream 0.1% was 1.13 (0.31)% and 2.26 (0.55)% of the dose, respectively, for subjects who received single or multiple dose(s). Mean (SD) peak total plasma radioactivity concentrations were 0.062 (0.03) and 0.163 (0.078) ng.equivalents/mL after a single dose and after multiple doses of TMG 0.1%, respectively. Mean (SD) peak total plasma radioactivity concentrations with RETIN-A Cream 0.1% were 0.105 (0.046) and 0.242 (0.096) ng·equivalents/mL after a single dose and after multiple doses, respectively. Although absorption in all treatment groups was minimal, there was a statistically significant difference in overall absorption between subjects administered multiple doses of TMG 0.1% and subjects administered multiple doses of RETIN-A Cream 0.1% ($p=0.0001$). Endogenous concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid (*CIS*-RA), all-*trans*-4-oxo-retinoic acid (OXO-RA), and 13-*cis*-4-oxo-retinoic acid (*CIS*-OXO), generally ranged from ng/mL and were essentially unaltered after either single or multiple applications of either TMG 0.1% or RETIN-A Cream 0.1%.

In vitro release tests were performed using the Franz Diffusion Cell apparatus by measuring the release of tretinoin through an artificial membrane into receptor that contained 50% isopropyl alcohol + 0.1% butylated hydroxytoluene (BHT) at 34^{0}C. Tretinoin content was assayed by HPLC method. This was to demonstrate that the formulations containing ^{3}H-tretinoin and used in percutaneous absorption studies B0281S and B0225S have similar release rate characteristics as the corresponding nonradiolabeled formulations. The same *in vitro* test method was used to evaluate the differences in the release rates among TMG IA 0.1%, TMG IB 0.1%, and TMG IC 0.1% (the proposed market formula) and form a part of the TMG IC 0.1% stability program.
The data demonstrated that the *in vitro* release rates of formulations containing ^{3}H-tretinoin produced on a small laboratory scale and used in Studies B0281S and B0225S are comparable to the corresponding nonradiolabeled formulations produced at full scale; and that TMG IA 0.1%, TMG IB 0.1%, and TMG IC 0.1% (the proposed market formula) have similar *in vitro* release rate characteristics for tretinoin.

General Comment (need not be sent to the sponsor):

It would have been more informative if the *in-vivo* percutaneous penetration was evaluated in patients with acne vulgaris.

Comment to the Firm: The sponsor is encouraged to adopt the *in-vitro* release rate method described in this application as part of the batch-to-batch quality control test. As a result, it will be necessary to set the release rate specification using data so far obtained from the stability testing.

gajayi 12/5/95

Funmilayo O. Ajayi, Ph.D
Div. of Pharmaceutical Evaluation III.

Biopharm Day (Nov. 30, 1995): Fleischer, Hunt, Baweja, Ajayi.

FT initialed by Frank Pelsor, Pharm.D.....F. L. Pelsor.....

cc: NDA 20,475, HFD-540 (Clinical Division), HFD-880 (Fleischer, Pelsor, Ajayi), Drug, Reviewer.

DIO. FILE
HFD 540 - HUNT
HFD-540 - ALAM
HFD-540 - DECOMP
HFD-160 SHELDON
HFD-540 FOLLMER

Appendix I

(Summary of Studies)

Title of the Study: An Open-Label Study to Determine the Percutaneous Absorption of ^{3}H-Tretinoin from APS Tretinoin MICROSPONGE® Gel 0.1% and RETIN-A® 0.1% Cream in Normal Male and Female Volunteers.

Study: B0281S Volume: 1.32

Investigator:

Objectives: The objective of this study was to determine the percutaneous absorption of ^{3}H-tretinoin from each of two 0.1% formulations (APS Tretinoin MICROSPONGE Gel 0.1% and RETIN-A 0.1% Cream) following single and multiple applications.

Methodology: This single-center, Phase I, open-label, parallel group study using 44 healthy volunteers evaluated the percutaneous absorption of ^{3}H-tretinoin from APS Tretinoin MICROSPONGE Gel (TMG) 0.1% and RETIN-A 0.1% Cream following single and multiple administration to normal facial skin. There were 22 male subjects and 22 female subjects; they ranged in age from 19 to 58 years and all were Caucasian. The subjects were randomized to one of four treatment groups to receive either single or multiple applications of either TMG 0.1% or RETIN-A 0.1% Cream. Subjects in the single application groups received a single 500 mg topical application of the assigned formulation containing μCi tritium in the form of ^{3}H-tretinoin. The remaining subjects (that is, multiple dose groups) received 500 mg of the assigned formulation (non-radioactive) once daily to the face for 28 days, followed by a single 500 mg application of the same formulation containing μCi tritium in the form of ^{3}H-tretinoin. Prestudy venous samples were obtained in all treatment groups prior to the first dose of tretinoin. Following the application of ^{3}H-tretinoin, urine and feces were collected for seven days. Venous blood samples were obtained during the first 72-hour period.

Number of Subjects: Forty-four subjects were enrolled, 12 in each of the multiple applications groups and 10 in each of the single application groups. There were three dropouts, one in the RETIN-A 0.1% multiple applications group, one in the TMG 0.1% single application group, and one in the RETIN-A 0.1% single application group. One of the dropouts was discontinued because of noncompliance (i.e., urine drug screen was positive for cannabinoids), one discontinued for personal reasons, and one discontinued because of severe urinary tract infection. The subject who dropped out of the TMG 0.1% single application group discontinued before receiving study drug and, therefore, was not valid for safety; none of the three dropouts were included in the analyses of percutaneous absorption and pharmacokinetic data.

Test Product: (1) TMG 0.1%, Formula No. P006D-48, Lot No. 30901. The TMG 0.1% formulation used in this study is designated as TMG IB 0.1%. (2) ^{3}H-TMG 0.1%, Formula No. P006D-56, Lot No. 30803.
Reference Therapy: (1) RETIN-A Cream 0.1%, Formula No. FD 8203-B-63, Lot No. R5585. (2) ^{3}H-RETIN-A Cream 0.1%, Formula No. FD 8203-000-FDZ-63, Lot No. R5662.

SAMPLE COLLECTION

Blood (10 mL) was collected from all subjects prior to the study for baseline values at 0, 1, 2, 4, 6, 8, 10, 12, and 24 hours. Blood (15 mL) was collected from the single dose application group at 0 (predose) and 1, 2, 4, 6, 8, 10, 12, 24, 48, and 72 hours postdose. Blood (10 mL) was collected from the repeated dose application group 24 hours after the last nonradiolabeled dose and 15 mL each collected at 0, 1, 2, 4, 6, 8, 10, 12, 24, 48, and 72 hours postdose. All blood collection and handling was carried out under subdued or yellow lighting. The blood was transferred to heparinized venoject tubes, the plasma fraction separated, and immediately frozen to less

Urine samples were collected and pooled over the following intervals after radioactive dosing: 0-4, 4-8, 8-12, and 12-24 hours. For Days 1-7 postdose, pooled 24 hour urine collections were made. Urine samples were labeled and stored refrigerated until the end of the collection period. At that time, total volume recorded and a 1 mL aliquot was withdrawn for immediate analysis. An additional 50 mL aliquot was transferred to a container, labeled (as above), and stored at -20 °C.

Fecal samples were pooled and collected on a 24 hour basis for 7 days postdose. Samples were labeled and stored at -20 °C until analysis.

All materials used in the dosing procedure (i.e., weight paper, gloves, spatulas) were collected for analysis of radioactivity to determine the exact amount of drug applied. Materials used in the washing procedure (i.e., rinse water, gauze pads, gloves) were collected for analysis to determine recovery.

DRUG SUPPLIES

1. Drug Substance

^{3}H-Tretinoin [11-^{3}H-all-*trans*-retinoic acid) was supplied by Specific activity was mCi/mg.

2. Drug Products

APS Tretinoin MICROSPONGE® Gel 0.1% (TMG 0.1%), Lot No. 30901, was supplied by Advanced Polymer Systems, Inc. (APS) Redwood City, CA, in 20 gram tubes for the 28 day pretreatment period. This formulation is also designated as TMG IB 0.1%.

RETIN-A® Cream 0.1%, Lot No. R5585, was supplied by in 20 gram tubes for the 28 day pretreatment period.

^{3}H-APS Tretinoin MICROSPONGE® Gel 0.1% (TMG 0.1%) (0.4 mCi ^{3}H-tretinoin/g), Lot No. 30803, was supplied by APS in 20 gram tubes for the single dose application.

^{3}H-RETIN-A® Cream 0.1% (0.4 mCi ^{3}H-tretinoin/g), Lot No. R5662, was supplied by in 20 gram tubes for the single dose application.

3 Pages (9-11)
Deleted

TABLE 1: MEAN PERCUTANEOUS ABSORPTION OF ^{3}H-TRETINOIN FOLLOWING TOPICAL ADMINISTRATION[a]

Drug	Treatment	N	Urine (% of Dose)[b,c]	Fecal (% of Dose)[b,c]	Total Percutaneous Absorption (% of Dose)[b,c]
TMG 0.1%	Single	9	0.62 (0.08)	0.20 (0.07)	0.82 (0.11)
TMG 0.1%	Multiple	12	1.05 (0.42)[d,e]	0.36 (0.18)[d,e]	1.41 (0.54)[d,e]
RETIN-A Cream 0.1%	Single	9	0.89 (0.26)	0.24 (0.08)	1.13 (0.31)
RETIN-A Cream 0.1%	Multiple	11	1.71 (0.43)[d,e]	0.55 (0.16)[d,e]	2.26 (0.55)[d,e]

[a] As determined by total cumulative excretion into urine and feces.
[b] Percent of administered dose.
[c] Mean (±SD)
[d] Statistically significant difference between single and multiple dose ($p \leq 0.05$).
[e] Statistically significant difference between TMG 0.1% and RETIN-A Cream 0.1% ($p < 0.05$).

TABLE 2: PHARMACOKINETIC ANALYSIS OF TOTAL PLASMA RADIOACTIVITY CONCENTRATIONS IN INDIVIDUAL SUBJECTS AFTER SINGLE AND MULTIPLE TOPICAL APPLICATION(S) OF 500 MG OF TMG 0.1% AND RETIN-A CREAM 0.1%[a]

Drug	Treatment	N	C_{max} (ng·equiv/mL)	T_{max} (h)	AUC (ng·equiv/mL·h)
TMG 0.1%	Single	9	0.062 (0.03)	16.00 (6.0)	2.40 (1.14)
TMG 0.1%	Multiple	12	0.163 (0.078)[b,c]	12.20 (3.9)	5.11 (2.82)[b,c]
RETIN-A Cream 0.1%	Single	9	0.105 (0.046)	17.33 (6.32)	3.93 (1.37)
RETIN-A Cream 0.1%	Multiple	11	0.242 (0.096)[b,c]	10.91 (1.64)	7.77 (2.58)[b,c]

[a] Mean (SD)
[b] Statistically significant difference between TMG 0.1% and RETIN-A Cream 0.1% ($p < 0.05$).
[c] Statistically significant difference between single and multiple doses ($p < 0.05$).

TABLE 3: Mean Peak Plasma Concentrations of Tretinoin and its Metabolites After Single and Multiple Applications of Either TMG 0.1% or RETIN-A Cream 0.1%[a]

			C_{max} (ng/mL)			
Drug	Treatment		RA	*CIS*-RA	OXO-RA	*CIS*-OXO
TMG 0.1%	Predose	Single	1.60 (0.37)	1.12 (0.68)	0.14 (0.41)	2.05 (1.04)
	Postdose	Single	2.30 (0.34)	1.56 (0.39)	0.72 (0.69)	2.40 (0.65)
RETIN-A Cream 0.1%	Predose	Single	1.66 (0.33)	1.02 (0.82)	0.00 (0.00)	2.01 (1.08)
	Postdose	Single	2.96 (0.59)	1.85 (0.92)	0.44 (0.68)	2.45 (0.79)
TMG 0.1%	Predose	Multiple	2.26 (0.75)	1.54 (0.67)	0.54 (0.82)	2.98 (1.10)
	Postdose	Multiple	2.06 (0.53)	1.49 (0.62)	1.28 (0.54)[b]	3.09 (1.61)
RETIN-A Cream 0.1%	Predose	Multiple	2.02 (0.62)	2.45 (4.27)	0.55 (1.04)	2.22 (0.63)
	Postdose	Multiple	1.73 (0.61)	1.25 (0.67)	1.67 (0.55)[b]	2.53 (0.83)

[a] Mean (SD)
[b] Statistically significant difference between predose and postdose values ($p \leq 0.05$)

Table 4. Percutaneous Absorption of ^{3}H-Tretinoin in Individual Subjects Following Single and Multiple Topical Application(s) of 500 mg of TMG 0.1%[a]

Treatment	Subject	Sex	Urine (% of Dose)[b]	Feces (% of Dose)[b]	Total Percutaneous Absorption (% of Dose)[b]
Single		M			
		M			
		M			
		M			
	Mean (SD)		0.57 (0.02)	0.21 (0.04)	0.78 (0.03)
		F			
		F			
		F			
		F			
		F			
	Mean (SD)		0.66 (0.09)	0.19 (0.10)	0.85 (0.15)
Multiple		M			
		M			
		M			
		M			
		M			
		M			
	Mean (SD)		1.34 (0.41)	0.40 (0.25)	1.74 (0.58)
		F			
		F			
		F			
		F			
		F			
		F			
	Mean (SD)		0.76 (0.18)	0.32 (0.09)	1.08 (0.20)

[a] As determined by total cumulative excretion into urine and feces.
[b] Percent of administered dose.

Table 5 : Percutaneous Absorption of ^{3}H-Tretinoin in Individual Subjects Following Single and Multiple Topical Application(s) of 500 mg of RETIN-A® Cream 0.1%[a]

Treatment	Subject[b]	Sex	Urine (% of Dose)[c]	Feces (% of Dose)[c]	Total Percutaneous Absorption (% of Dose)[c]
Single		M			
		M			
		M			
		M			
	--	M			
	Mean (SD)		1.00 (0.26)	0.28 (0.06)	1.28 (0.30)
		F			
		F			
		F			
		F			
	Mean (SD)		0.75 (0.22)	0.19 (0.08)	0.94 (0.22)
Multiple		M			
		M			
		M			
		M			
		M			
		M			
	Mean (SD)		1.99 (0.33)	0.66 (0.07)	2.64 (0.38)
		F			
		F			
		F			
		F			
		F			
	Mean (SD)		1.37 (0.28)	0.42 (0.13)	1.79 (0.39)

[a] As determined by total cumulative excretion into urine and feces.
[b] Day 2 urines for subjects 33 and 35 were inadvertently combined and subsequently discarded.
[c] Percent of administered dose.

Table 6 : Total ^{3}H-Tretinoin Recovered After Administration of ^{3}H-TMG 0.1%

Treatment	Subject	Sex	Non-Biologicals[a,b]	Feces % Dose[b]	Urine % Dose[b]	Total % Dose[b]
Single		M				
		M				
		M				
		M				
		F				
		F				
		F				
		F				
		F				
	Mean (SD)		74.52 (2.49)	0.20 (0.07)	0.62 (0.08)	75.33 (2.56)
Multiple		M				
		M				
		M				
		M				
		M				
		M				
		F				
		F				
		F				
		F				
		F				
		F				
	Mean (SD)		72.91 (5.04)	0.36 (0.18)	1.05 (0.42)	74.29 (4.84)

[a] Nonbiologicals = Sum of subject bag, scrub bag and rinse water.
[b] % of administered dose.

Table 7 . Total ^{3}H-Tretinoin Recovered After Administration of ^{3}H-RETIN-A® Cream 0.1%

Treatment	Subject	Sex	Non-Biologicals[a,b]	Feces % Dose[b]	Urine % Dose[b]	Total % Dose[b]
Single		M				
		M				
		M				
		M				
		M				
		F				
		F				
		F				
		F				
	Mean (SD)		81.40 (3.90)	0.24 (0.08)	0.88 (0.26)	82.57 (3.75)
Multiple		M				
		M				
		M				
		M				
		M				
		M				
		F				
		F				
		F				
		F				
		F				
	Mean (SD)		82.19 (4.69)	0.55 (0.16)	1.71 (0.43)	84.45 (4.28)

[a] Nonbiologicals = Sum of subject bag, scrub and rinse water.
[b] % of administered dose.

Table 8 : Peak Total Plasma Radioactivity Concentrations in Individual Subjects After Single and Multiple Topical Application(s) of 500 mg of TMG 0.1%

Treatment	Subject	Sex	C_{max} (ng·equiv/mL)	T_{max} (h)	$AUC_{(0-72)}$ (ng·equiv/mL·h)	$t_{1/2}$
Single		M				
		M				
		M				
		M				
		Mean (SD)	0.044 (0.02)	15.0 (6.0)	1.723 (0.49)	24.2 (11.8)
		F				
		F				
		F				
		F				
		F				
		Mean (SD)	0.077 (0.03)	16.8 (6.57)	2.939 (1.26)	37.2 (1.55)
Multiple		M				
		M				
		M				
		M				
		M				
		M				
		Mean (SD)	0.170 (0.08)	11.0 (1.10)	5.381 (3.49)	46.4 (8.51)
		F				
		F				
		F				
		F				
		F				
		F				
		Mean (SD)	0.157 (0.08)	13.3 (5.32)	4.845 (2.27)	38.1 (4.05)

nc = not calculated

Table 9 .: Peak Total Plasma Radioactivity Concentrations in Individual Subjects After Single and Multiple Topical Application(s) of 500 mg of RETIN-A® Cream 0.1%

Treatment	Subject	Sex	C_{max} (ng-equiv/mL)	T_{max} (h)	AUC (ng-equiv/mL)	$t_{1/2}$
Single		M				
		M				
		M				
		M				
		M				
		Mean (SD)	0.099 (0.03)	21.6 (5.37)	4.113 (1.55)	36.4 (14.25)
		F				
		F				
		F				
		F				
		Mean (SD)	0.112 (0.06)	12.0 (0.0)	3.710 (1.28)	47.7 (17.96)
Multiple		M				
		M				
		M				
		M				
		M				
		M				
		Mean (SD)	0.288 (0.09)	10.3 (1.97)	8.675 (2.22)	63.0 (15.00)
		F				
		F				
		F				
		F				
		F				
		Mean (SD)	0.187 (0.07)	11.6 (0.89)	6.676 (2.78)	70.7 (11.05)

nc = not calculated

Table 10. Peak Tretinoin and Metabolite Concentrations in Individual Subjects After Single and Multiple Topical Application(s) of TMG 0.1%

			C_{max} (ng/mL)			
Treatment	Subject	Sex	RA	*CIS*-RA	OXO-RA	*CIS*-OXO
Single		M				
		M				
		M				
		M				
		Mean (SD)	2.33 (0.43)	1.50 (0.19)	0.27 (0.54)	2.56 (0.37)
		F				
		F				
		F				
		F				
		F				
		Mean (SD)	2.27 (0.29)	1.60 (0.52)	1.08 (0.61)	2.27 (0.84)
Multiple		M				
		M				
		M				
		M				
		M				
		M				
		Mean (SD)	2.02 (0.64)	1.50 (0.30)	1.33 (0.22)	2.67 (0.66)
		F				
		F				
		F				
		F				
		F				
		F				
		Mean (SD)	2.10 (0.46)	1.49 (0.87)	1.24 (0.77)	3.52 (2.20)

Table 11 : Peak Tretinoin and Metabolite Concentrations in Individual Subjects After Single and Multiple Topical Application(s) of RETIN-A® Cream 0.1%

			C_{max} (ng/mL)			
Treatment	Subject	Sex	RA	*CIS*-RA	OXO-RA	*CIS*-OXO
Single		M				
		M				
		M				
		M				
		M				
		Mean (SD)	3.12 (0.57)	2.12 (0.74)	0.58 (0.81)	2.91 (0.72)
		F				
		F				
		F				
		F				
		Mean (SD)	2.76 (0.62)	1.50 (1.10)	0.27 (0.54)	1.88 (0.45)
Multiple		M				
		M				
		M				
		M				
		M				
		M				
		Mean (SD)	1.46 (0.24)	1.30 (0.68)	1.84 (0.69)	2.85 (0.75)
		F				
		F				
		F				
		F				
		F				
		Mean (SD)	2.06 (0.77)	1.19 (0.73)	1.47 (0.27)	2.15 (0.82)

Attachments

IN VITRO RELEASE STUDIES ON TRETINOIN MICROSPONGE® GELS USING THE APPARATUS

INTRODUCTION

In vitro experiments using the Apparatus provide a valid way of comparing topical formulations, such as creams and gels by measuring the release of the drug through an artificial membrane, as recommended by Skelly et al[1] and Shah et al[2]. Comparisons can be made between various formulations and/or various lots and batch sizes of the same formulation using experimental conditions under which neither the artificial membrane nor the solubility of the active in the receptor fluid become rate-limiting.

OBJECTIVES

Using the above criteria, a procedure has been set up to evaluate the Tretinoin Microsponge® Gel (TMG) formulations. This procedure has been used for the following purposes:

1. To demonstrate that the minor changes in formulation implemented in TMG IA 0.1%, TMG IB 0.1% and TMG IC 0.1% formulations had no effect on drug release. Table 1 shows the formulations and experiments conducted.

---

1. Skelly, J.P., Shah, V.P., Maibach, H.I., Guy, R.H., Wester, R.C., Flynn, G., and Yacobi A. "FDA and AAPS Report of the Workshop on Principles and Practices of In Vitro Percutaneous Penetration Studies: Relevance to Bioavailability and Bioequivalence". Pharmaceutical Research, 4(3), 265-267 (1987).
2. Shah, V.P., Bebl, C.R., Flynn, G.L., Higuchi, W.I., and Schaefer, H. "Principles and Criteria in the Development and Optimization of Topical Therapeutic Products". Pharmaceutical Research, 9(8), 1107-1111 (1992).

Table 1

Experiment	Formulation	APS Lot No.*	Batch Size	Manufacturing Site	Partial List of Nonclinical/Clinical Studies Lot Used for (APS Study No.)
a)	TMG IA. 0.1%	10203	10 Kg	APS. Redwood City	B0145S. B0178S
	TMG IB. 0.1%	21201	2200 Kg	PRI/Ortho-McNeil. Raritan	B0222E. B0223E. B0225S. B0232S. B0233S. B/235S. B0236S. B0251S. B0252S
	TMG IC. 0.1%	30601	10 Kg	APS. Redwood City	B0265S. B0266S. B0267S
b)	TMG IB. 0.1%	21201	2200 Kg	PRI/Ortho-McNeil. Raritan	B0222E. B0223E. B0225S. B0235S. B0236S. B0251S. B0252S
	TMG IC. 0.1%	30703	2200 Kg	PRI/Ortho-McNeil. Raritan	B0285S. B0286S. B0287S. B0288S

* See Appendix C for cross-reference of APS and PRI lot numbers

2. To demonstrate equivalency of TMG IB 0.1% lots and small radiolabeled batches of TMG IB 0.1% containing tritiated tretinoin entrapment. See Table 2 for details.

Table 2

Experiment	Formulation	APS Lot No.*	Batch Size	Manufacturing Site	Partial List of Nonclinical/Clinical Studies Lot Used for (APS Study No.)
a)	TMG IB. 0.1%	21201	2200 Kg	PRI/Ortho-McNeil. Raritan	B0222E. B0223E. B0225S. B0232S. B0233S. B0235S. B0236S. B0251S. B0252S
	TMG IB. 0.1% (³H] Tretinoin)	30203	200 g	APS. Redwood City	B0225S. B0245S. B0246S. B0247S. B0248S
b)	TMG IB. 0.1%	30901	2200 Kg	PRI/Ortho-McNeil. Raritan	B0281S. B0285S. B0289S
	TMG IB. 0.1% (³H] Tretinoin)	30803	50 g	APS. Redwood City	B0281S

* See Appendix C for cross-reference of APS and PRI lot numbers

3. To determine if there is any change in the release profile of tretinoin from TMG IC 0.1% formulations over time. This is part of an ongoing stability program at PRI/Ortho-McNeil. Table 3 gives the details on the four lots being tested.

Table 3

Experiment	Formulation	PRI Lot No.*	Batch Size	Manufacturing Site	Partial List of Nonclinical/Clinical Studies Lot Used for (APS Study No.)
a)	TMG IC. 0.1%	PE-850	2200 Kg	PRI/Ortho-McNeil, Raritan	Stability Studies
	TMG IC. 0.1%	PE-849	2200 Kg	PRI/Ortho-McNeil, Raritan	Stability Studies
b)	TMG IC. 0.1%	PE-844	2200 Kg	PRI/Ortho-McNeil, Manati	Stability Studies
	TMG IC. 0.1%	PE-845	2200 Kg	PRI/Ortho-McNeil, Manati	Stability Studies

* See Appendix C for cross-reference of APS and PRI lot numbers

In addition to these studies, studies were conducted on Retin-A® Cream 0.1% to demonstrate equivalency of full scale batches of Retin-A Cream 0.1% and smaller batches of Retin-A cream 0.1% containing tritiated tretinoin. Table 4 shows the details on these batches.

Table 4

Experiment	Formulation	PRI Lot No.*	Batch Size	Manufacturing Site	Partial List of Nonclinical/Clinical Studies Lot Used for (APS Study No.)
a)	Retin-A® Cream. 0.1%	R5168	2200 Kg	PRI/Ortho-McNeil, Raritan	B02235
	Retin-A® Cream. 0.1% (^{3}H] Tretinoin)	R5440	50 g	PRI/Ortho-McNeil, Raritan	B02235
b)	Retin-A® Cream. 0.1%	R5583	2200 Kg	PRI/Ortho-McNeil, Raritan	B02815
	Retin-A® Cream. 0.1% (^{3}H] Tretinoin)	R5662	50 g	PRI/Ortho-McNeil, Raritan	B02815

* See Appendix C for cross-reference of APS and PRI lot numbers

METHOD

Diffusion-Cell System:

A standard 6.8 ml Franz diffusion cell of glass static design with a 15-mm orifice was used. A nine-unit system was utilized.

Membrane System:

Supor-450 (Gelman), 0.45 μm pore size, 47 mm diameter.

Receptor Phase:

A /% isopropyl alcohol (IPA) solution with % BHT was used as the receptor phase. The medium was degassed by vacuum before using. Medium was made up fresh before each experiment.

Determination of tretinoin:

All samples were analyzed by HPLC {APS Method No. P-72 for TMG IA and IB and P-259 (which is the same as Method AD93012) for TMG IC} by the Analytical Services department at APS.

The standard method developed for measuring the release of tretinoin from APS gel is described in Appendix A. Briefly, the release of tretinoin from APS gel formulation is determined using the Franz diffusion cell appararus. The lower chamber is filled with receptor phase medium. An artificial membrane is mounted on the diffusion cells. The membrane has a known amount of formulation applied on its surface using a template to produce a layer of uniform thickness and diameter. A teflon O-ring is placed on top of the membrane around the formulation followed by the donor chamber. The diffusion cell temperature is maintained at 34°C by circulating water

through the jacketed portion of the diffusion cell via a temperature controlled circulator. At predetermined time intervals, the receptor fluid is removed and replaced with fresh solvent and analyzed for tretinoin content.

RESULTS AND DISCUSSION

Results for each of the above studies are attached. The release profiles of TMG IA 0.1%, TMG IB 0.1% and TMG IC 0.1% are shown in Figures 1 and 2. In Figure 1, the release profiles were determined for each formulation at the time of manufacture of the lots and the profiles have been "superimposed". On the other hand, Figure 2 shows the release profiles of the same three lots done in a single experiment. Data in Figure 2 represent the mean (± S.D.) of triplicate determinations for each formulation determined on the same day.

These curves demonstrate the equivalency of the three TMG formulations. The minor variations in their antioxidant and preservative systems, with the active and all other inactive vehicle components remaining the same, do not affect the release of tretinoin (See attached formulations of TMG IA 0.1%, TMG IB 0.1% and TMG IC 0.1%). TMG IA 0.1% and TMG IB 0.1% were the formulations used in the pilot and pivotal safety and efficacy studies. TMG IC 0.1% is the proposed final marketable formulation.

In the same manner, the data shown in Figure 3 demonstrate the equivalency of Formulations TMG IB 0.1% and TMG IC 0.1% both produced on a 2200 kg scale.

As is apparent from the data, the release profiles of radiolabeled batches of TMG IB 0.1% viz. Lot No. 30203 and Lot No. 30803, even though made on a small scale (50-200 g) in the laboratory, are superimposable on those from the full scale production batches (~2200 Kg), Lot No. 21201 and 30901, respectively. (Figures 4 and 5). Data on Retin-A® Cream 0.1% batches used in APS studies were generated at PRI and are attached as Appendix B.

In terms of stability, the studies are still ongoing. Up to the six month interval, no noticeable changes in the release profiles have been observed at any of the temperature of storage conditions tested. (Figures 6-10).

CONCLUSIONS

In summary, the data demonstrate:

1. the comparability of the three formulations, viz. TMG IA 0.1%, TMG IB 0.1% and TMG IC 0.1%
2. the comparability of radiolabeled batches produced on a small laboratory scale to full scale batches
3. the stability of TMG IC 0.1% formulation up to the six month interval.
4. that the release is quite consistent and does not change over time; thus, it should not be necessary to conduct in vitro release testing on a routine (QA) basis.

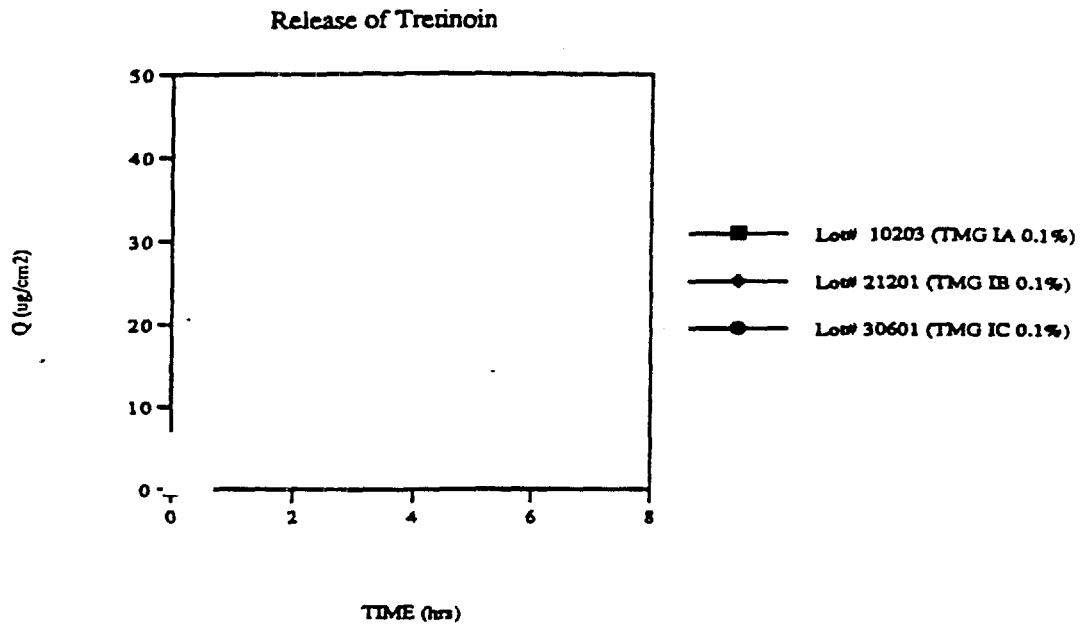


Figure 1: Evaluation of TMG 0.1% gel lots determined on different days. (ref. kl270-19 & el371-6)

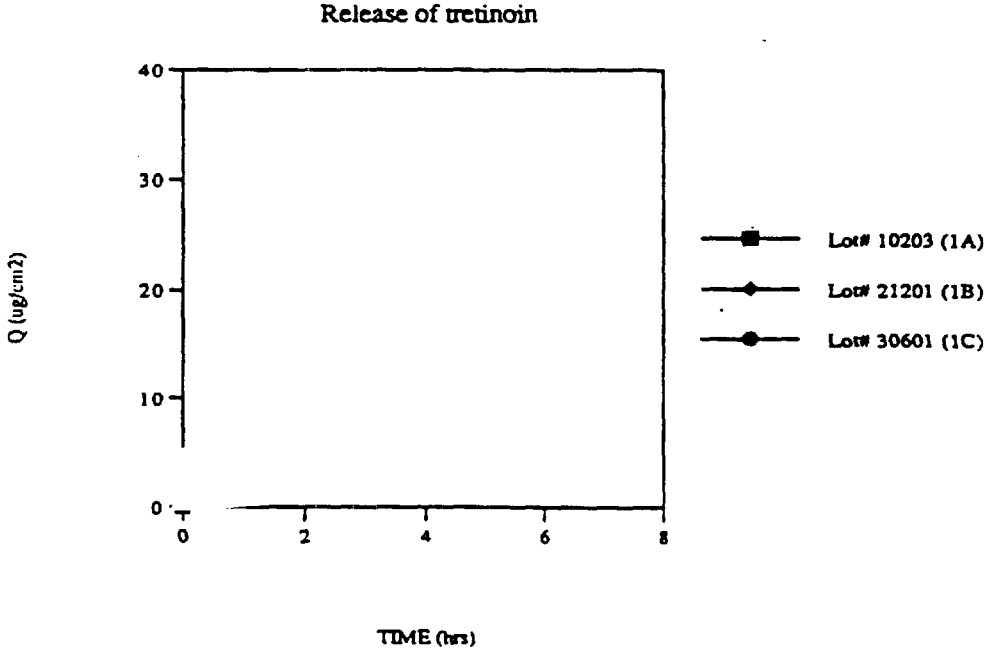


Figure 2: Evaluation of TMG 0.1% gel lots determine on the same day.

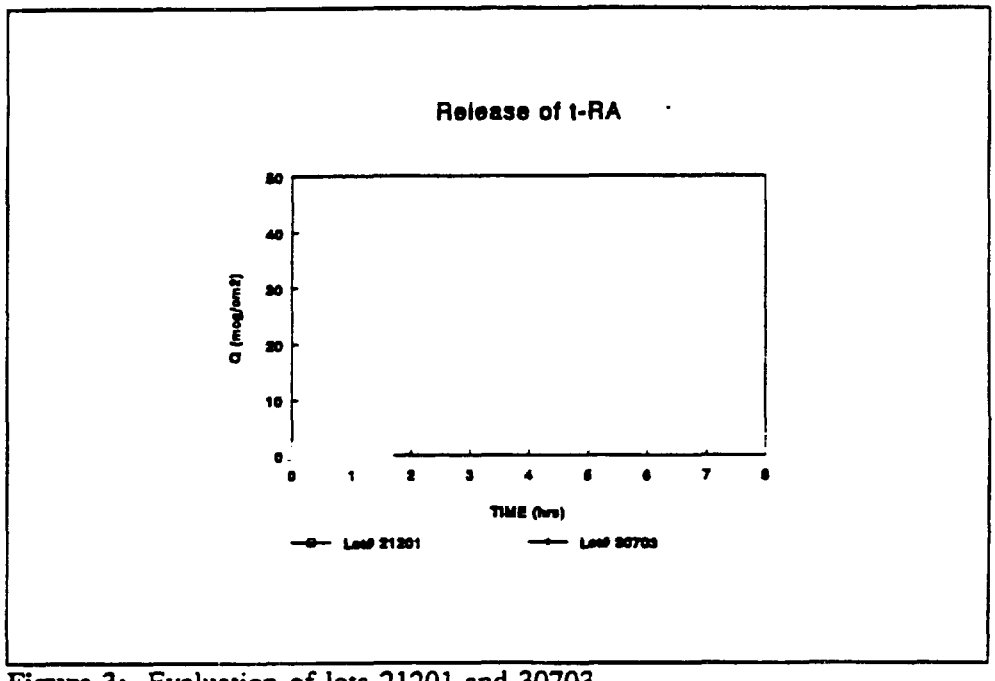


Figure 3: Evaluation of lots 21201 and 30703.
(ref. lk352-58 & sm374-80)

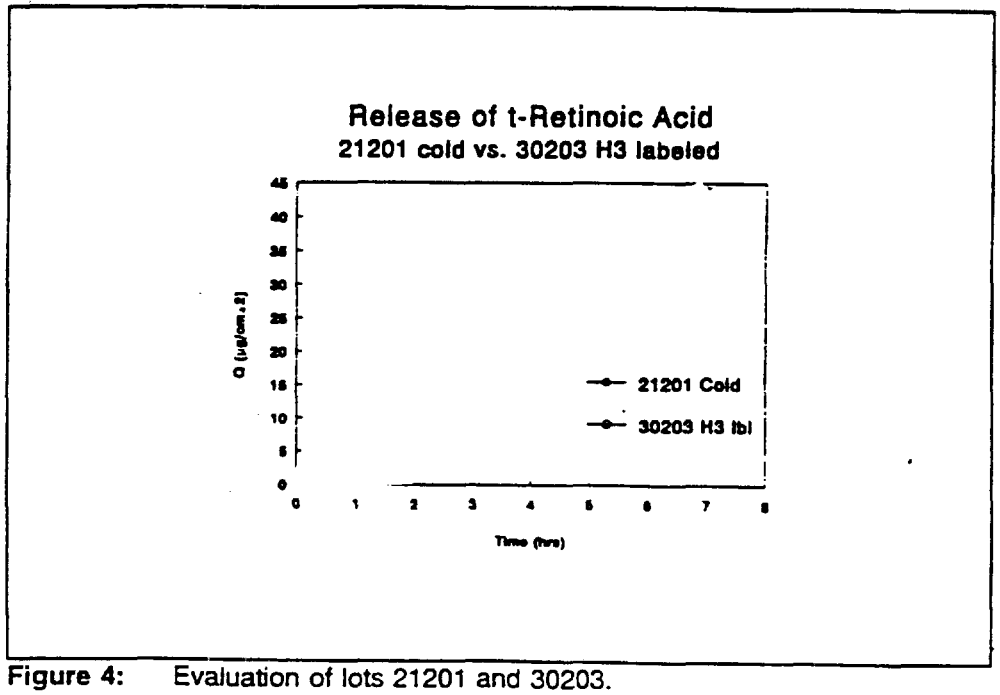


Figure 4: Evaluation of lots 21201 and 30203.
(ref. LK352-58)

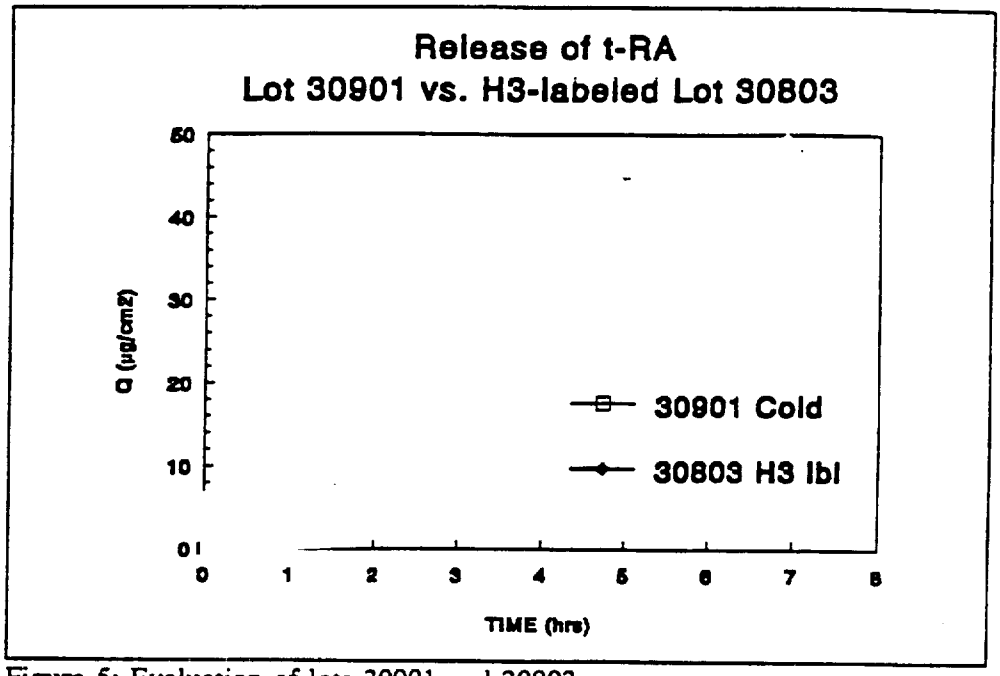


Figure 5: Evaluation of lots 30901 and 30803.
(ref. sm374-62)

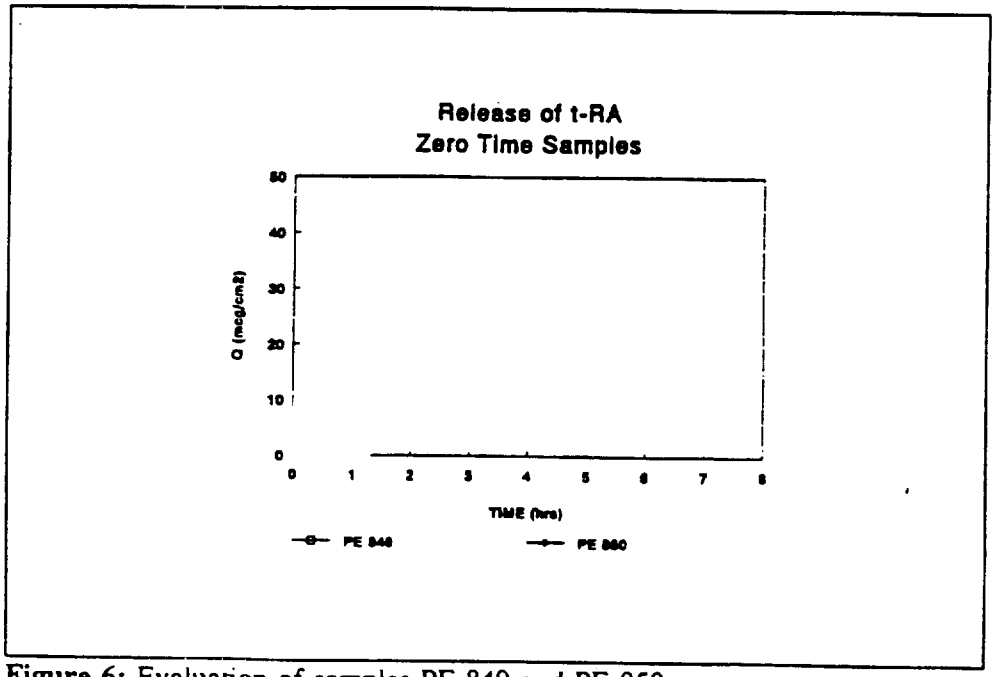


Figure 6: Evaluation of samples PE 849 and PE 850.
(ref. sm374-80)

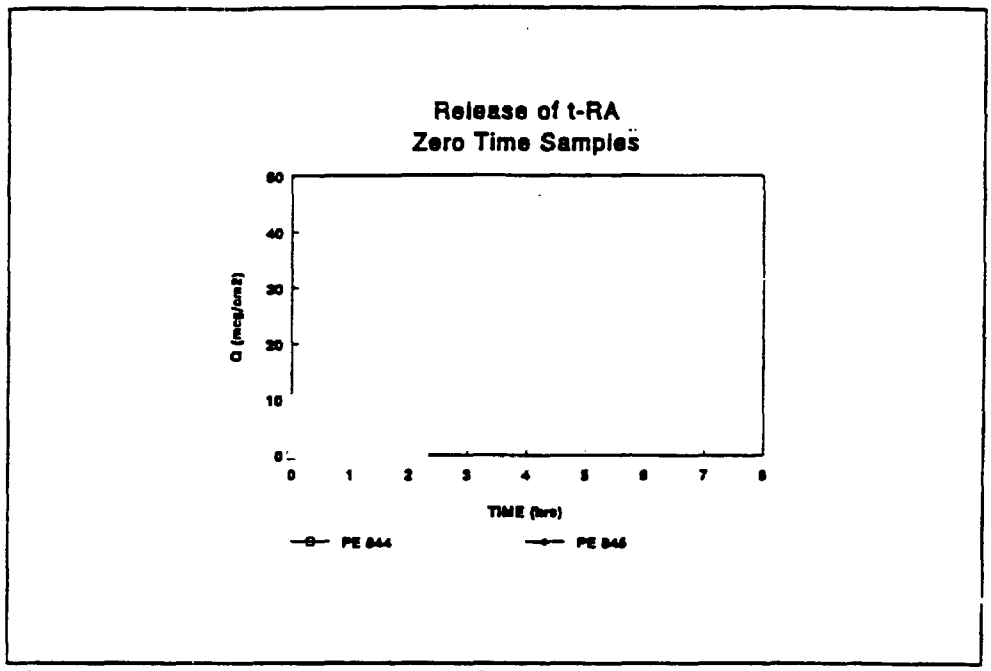


Figure 7: Evaluation of samples PE 844 and PE 845.
(ref. sm374-81)

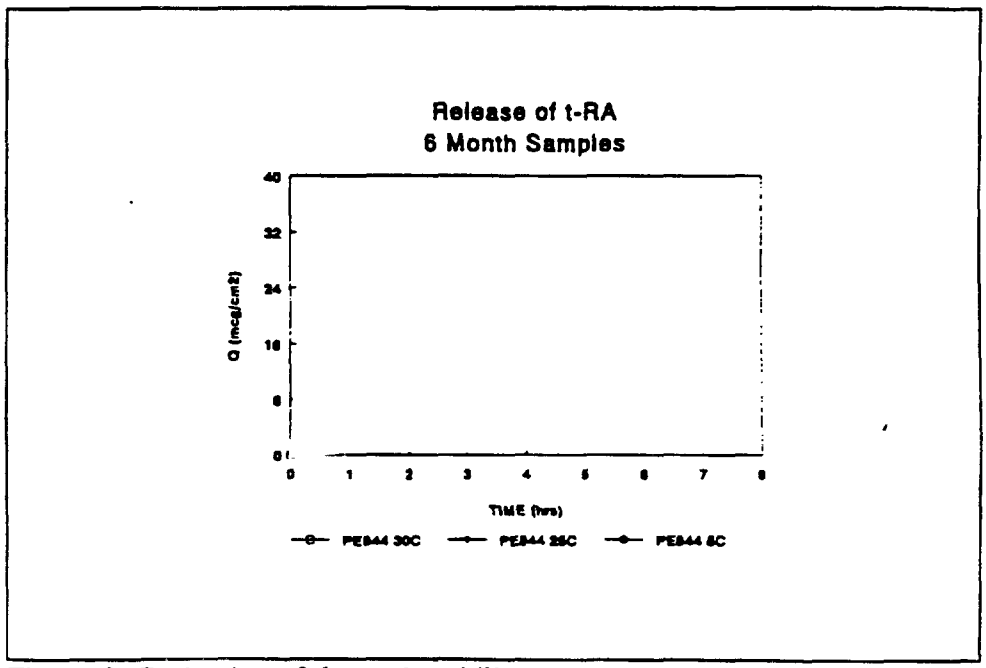


Figure 8: Evaluation of 6 month stability sample lot PE 844.
(ref. sm374-96)

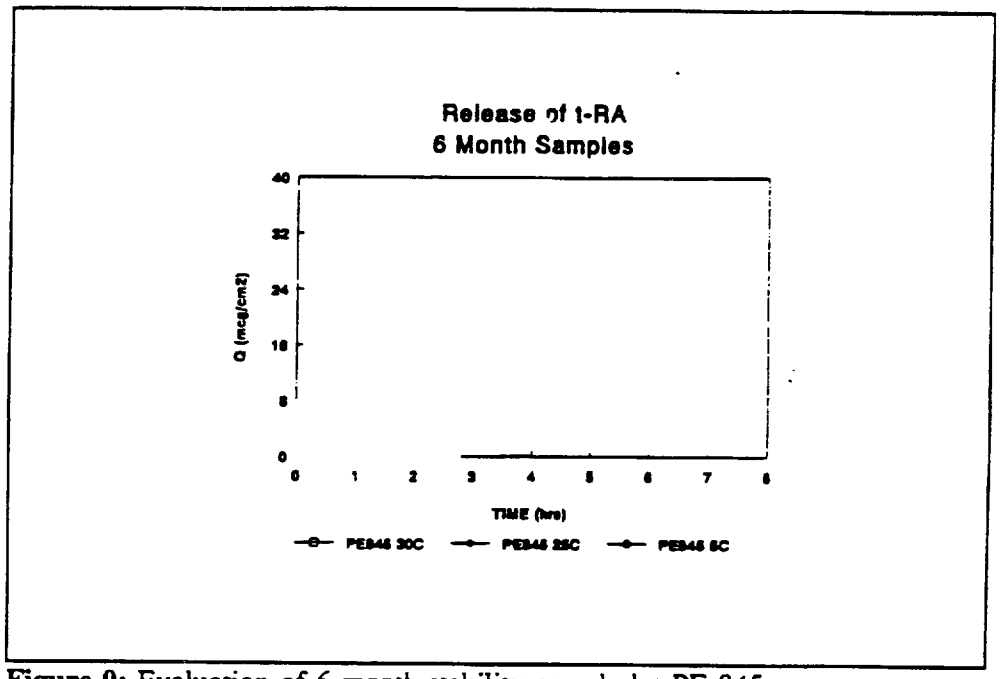


Figure 9: Evaluation of 6 month stability sample lot PE 845. (ref. sm374-97)

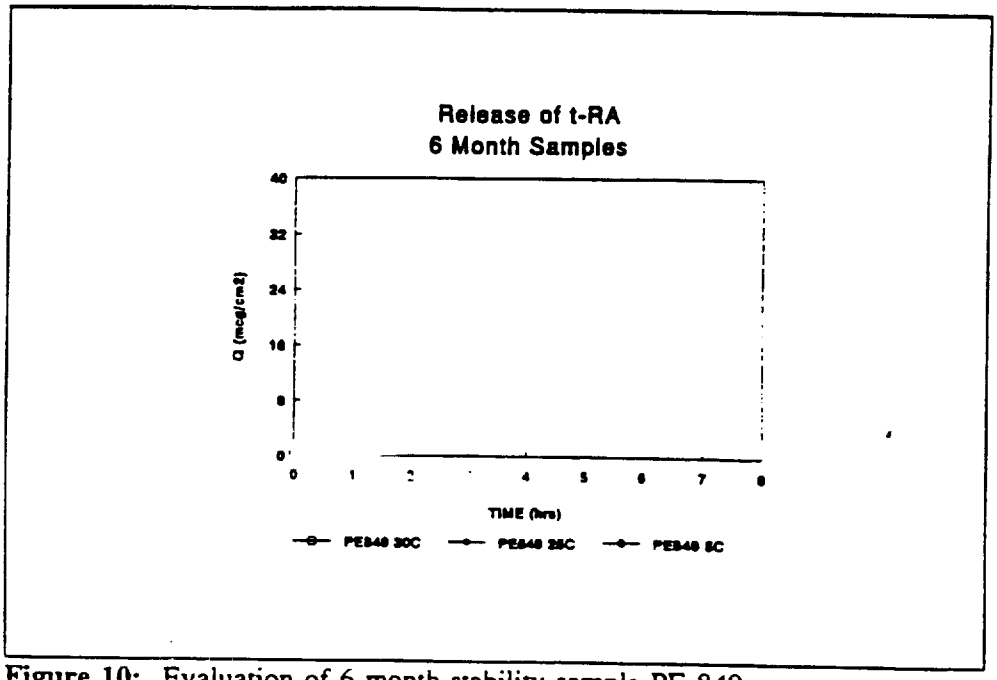


Figure 10: Evaluation of 6 month stability sample PE 849 (ref. sm374-98)

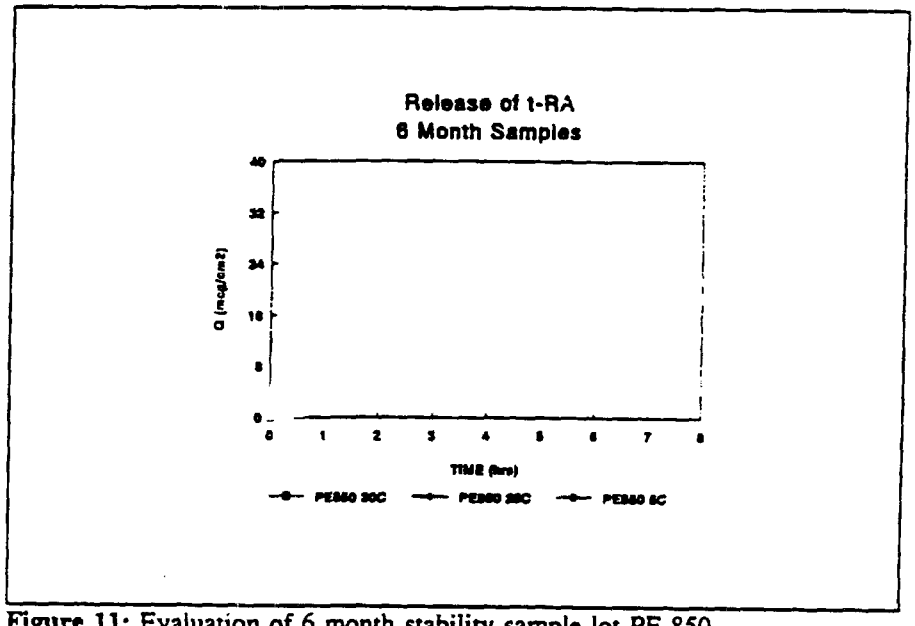
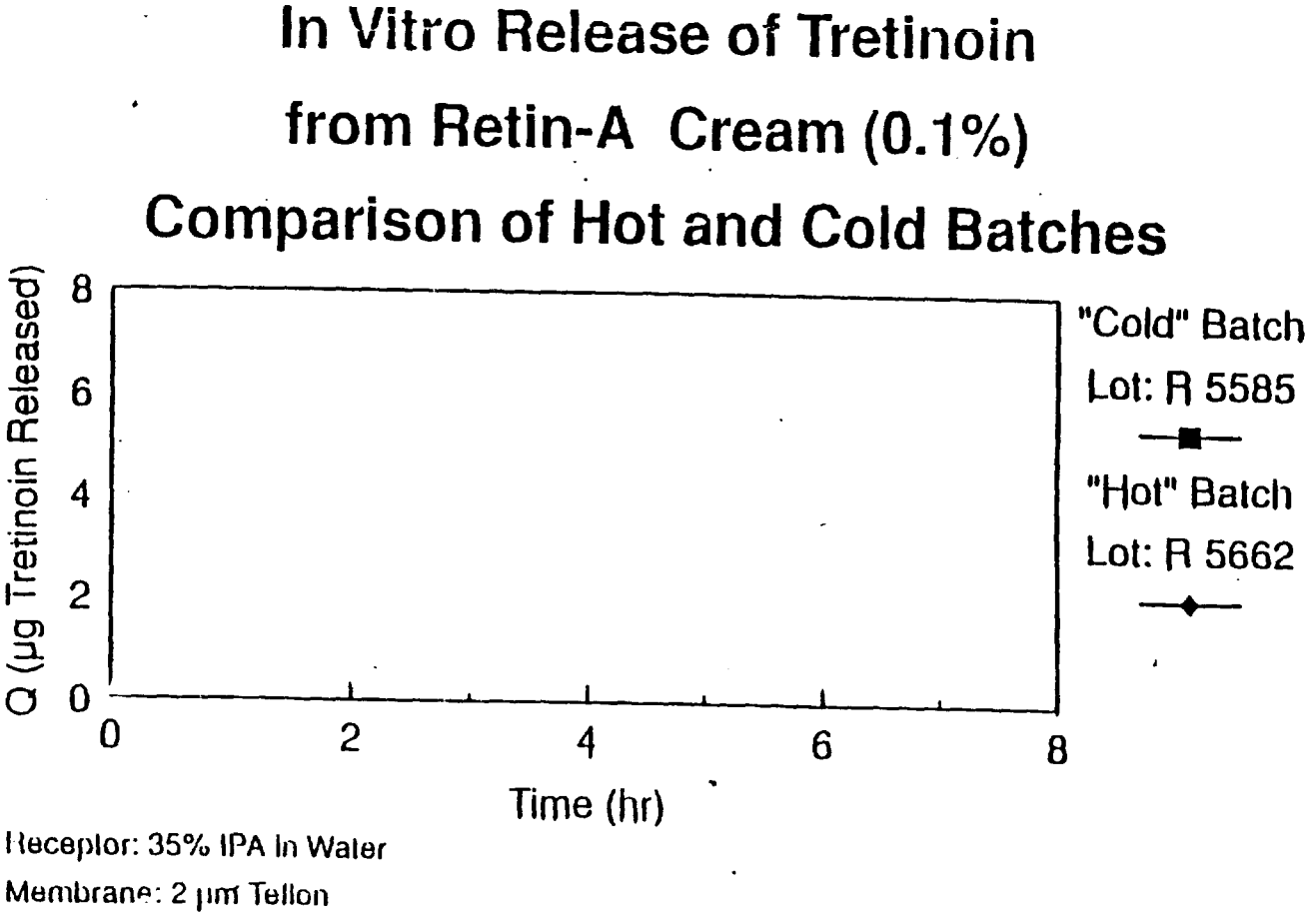


Figure 11: Evaluation of 6 month stability sample lot PE 850
(ref sm374-99)



APPENDIX A

Procedure for Determining the Release of t-retinoic acid (tretinoin) from APS Gel Formulations

1. Preparation of receptor medium (0.1% BHT in 50 % IPA):

   Weigh out 0.5 g of BHT into a 500 ml beaker. Add 250 ml of IPA to the BHT. Mix thoroughly until the BHT is completely dissolved. Next, add 250 ml of deionized water to the BHT solution. Degas the medium by filtering through a 0.45 µm filter using a vacuum. Maintain receptor medium at 34° C in water bath until needed.

2. Preparation of the diffusion cells:

   Install ' cells with 6.8 ml receptor chamber and 15 mm diameter opening in the diffusion apparatus drive unit. Attach jacketed portion of the cell to a circulating water bath maintained at 34°C. Place a small magnetic stir bar in receptor chamber. Apply adhesive (to the groove around the opening in the receptor chamber and press a membrane filter (Supor-450, Gelman; 0.45 um pore size, 47 mm diameter) firmly against the groove.

   Note: All the following procedures are to be carried out under yellow light.

3. Preparation of sample:

   Pre-weigh a separate sheet of membrane filter on glassine weighing paper. Place a template made from a sheet of Teflon, 0.7 mm thick with a circular hole 15 mm in diameter cut in the center, firmly on top of the membrane filter. Apply formulation to completely cover the hole. With another sheet of Teflon, this one having a straight edge, trowel the excess formulation away from the hole. This should produce a film of formulation conforming to the thickness and diameter of the template (0.7mm X 15mm). Then remove template and weigh formulation, membrane, and weighing paper assembly to determine the amount of formulation applied. Carefully place membrane filter with formulation, formulation side facing up, on top of the membrane filter glued to the receptor chamber. Place teflon O- ring on top of the membrane around the formulation followed by the donor chamber of the diffusion cell. Clamp receptor and donor cell chambers together with a Thomas C-clamp. Trim excess membrane around the rim of the two chambers with scissors. Cover opening of the donor chamber with Parafilm. Seal the junction between the two chambers by tightly wrapping Parafilm around it.

4. Fill receptor chamber with the preheated (34° receptor medium. Make sure there are no air bubbles in the receptor chamber after filling. Turn on the magnetic stirrer to mix the medium and insure homogeneity.

5. At 1, 2, 3, 5 and 7 hours into the experiment, remove the entire receptor medium with a syringe fitted with polyethylene tubing on its needle port. Transfer aliquot to a labeled amber tinted HPLC mini-vial. Place the remaining medium into amber tinted test tube fitted with a screw top cap. Refill receptor chamber with the preheated receptor medium. Make sure no air bubbles exist in the receptor chamber after refilling. At the end of the

experiment, store test tubes in refrigerator immediately.

6. Submit all samples collected to Analytical Services department for tretinoin content determination by HPLC.

7. Calculate the release profiles of tretinoin base on the results obtained from Analytical Services department.

8. After experiment has concluded, clean cells thoroughly. Unit should first be rinsed twice with isopropyl alcohol, followed by sonicate in soapy water for twenty minutes. Then rinsed 3 times with deionized water. Finally allow cell unit to air dry before next use.

RELEASE STUDIES

The standard method developed for measuring the release of tretinoin from APS gel is described in Appendix A. Briefly, the release of tretinoin from APS gel formulation is determined using the cell apparatus. The lower chamber is filled with receptor phase medium. An artificial membrane is mounted on the diffusion cells. The membrane has a known amount of formulation applied on its surface using a template to produce a layer of uniform thickness and diameter. A teflon O-ring is placed on top of the membrane around the formulation followed by the donor chamber. The diffusion cell temperature is maintained at 34°C by circulating water through the jacketed portion of the diffusion cell via a temperature controlled circulator. At predetermined time intervals, the receptor fluid is removed and replaced with fresh solvent and analyzed for tretinoin content.

RESULTS AND DISCUSSION

1. Reproducibility

The methodology developed for measuring *in vitro* release of tretinoin from APS gel formulation was studied to determine its variability. Figure 1 shows a typical release profile of tretinoin from APS gel formulation under our current method. Data points represent the mean (±SD) of four cells analyzed at each collection interval.

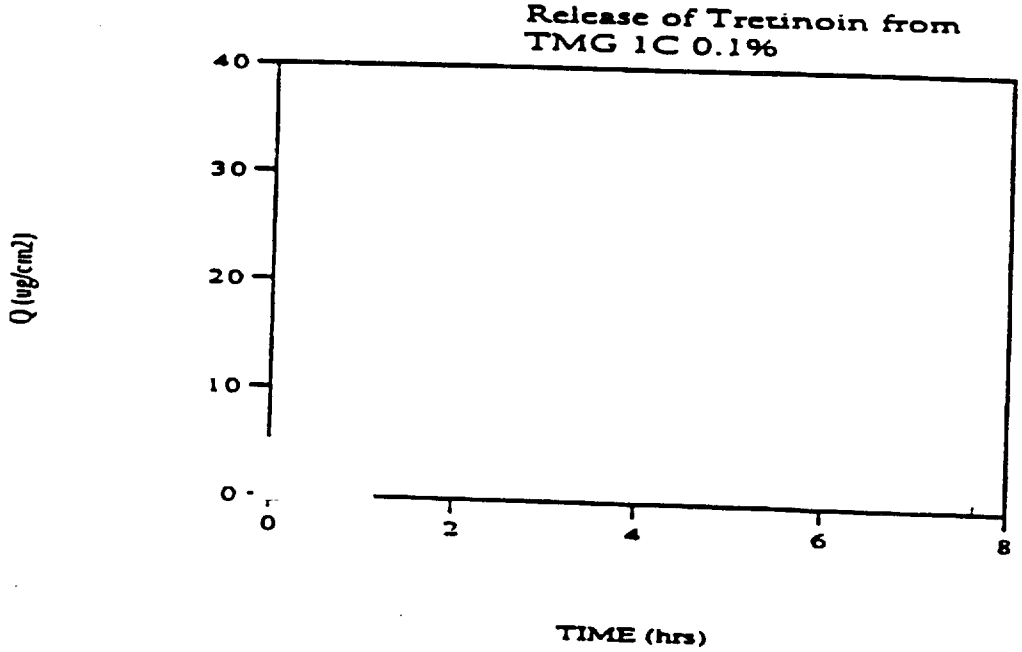


Figure 1 Typical Release Profile. (ref. SM413-12)

Using the standard method, the release of tretinoin APS gel formulation was studied on four different days. To assure maximum variability fresh receptor medium was made up immediately preceding each experiment. Figure 2 shows release profiles of tretinoin from APS gel formulation for experiments conducted on four different days. Data points represent the mean (±SD) of four cells analyzed at each collection interval.

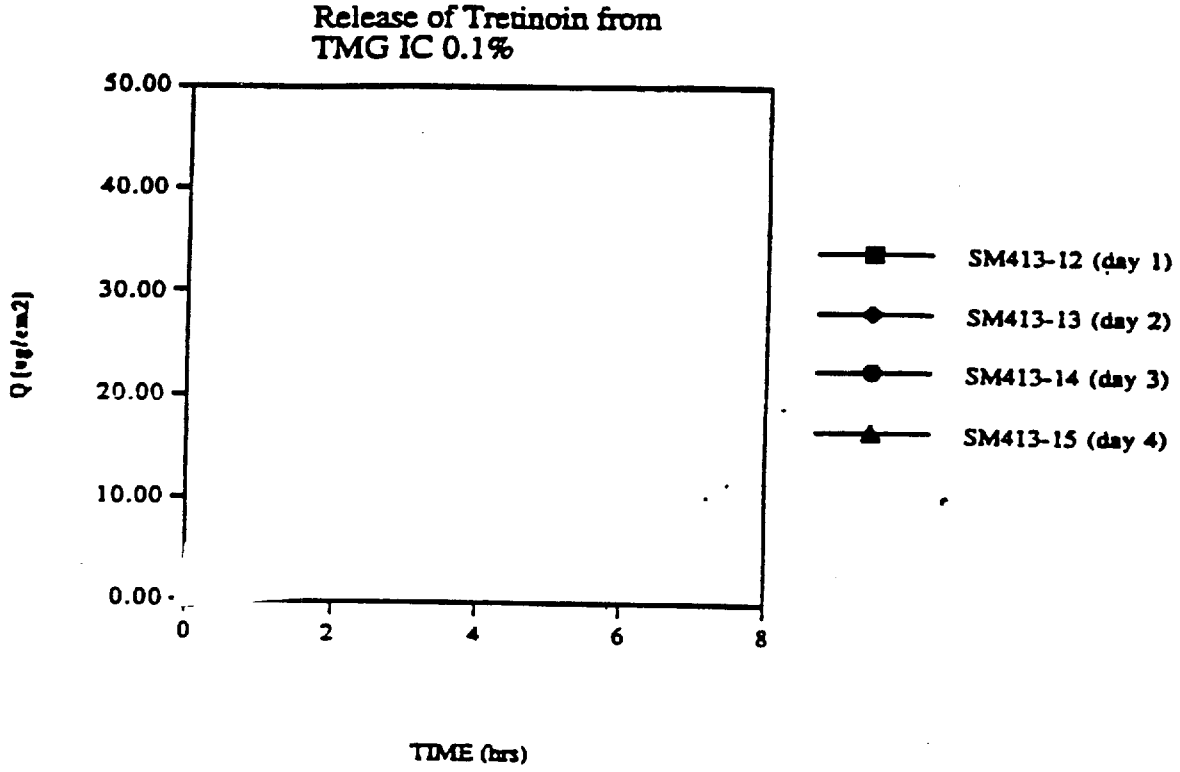


Figure 2 Release profiles of tretinoin from TMG IC studied on four different days. (ref. SM413-12,13,14,15)

Conclusion

As is apparent from figure 2, there is fairly good reproducibility from day to day in the release of tretinoin from Microsponge® gel over the seven hour period. However, there can be variations on different days and therefore it is recommended that positive controls be used when performing a release experiment.

2. Concentration Study:

In vitro release studies were performed on TMG IC gels containing 0.1%, 0.05%, and 0.025% tretinoin. Gels were evaluated in duplicate and simultaneously. Immediately following final collection interval samples were transferred to HPLC and analyzed for tretinoin content. Results are presented in figure 3. Each data point represents an average of duplicate determinations.

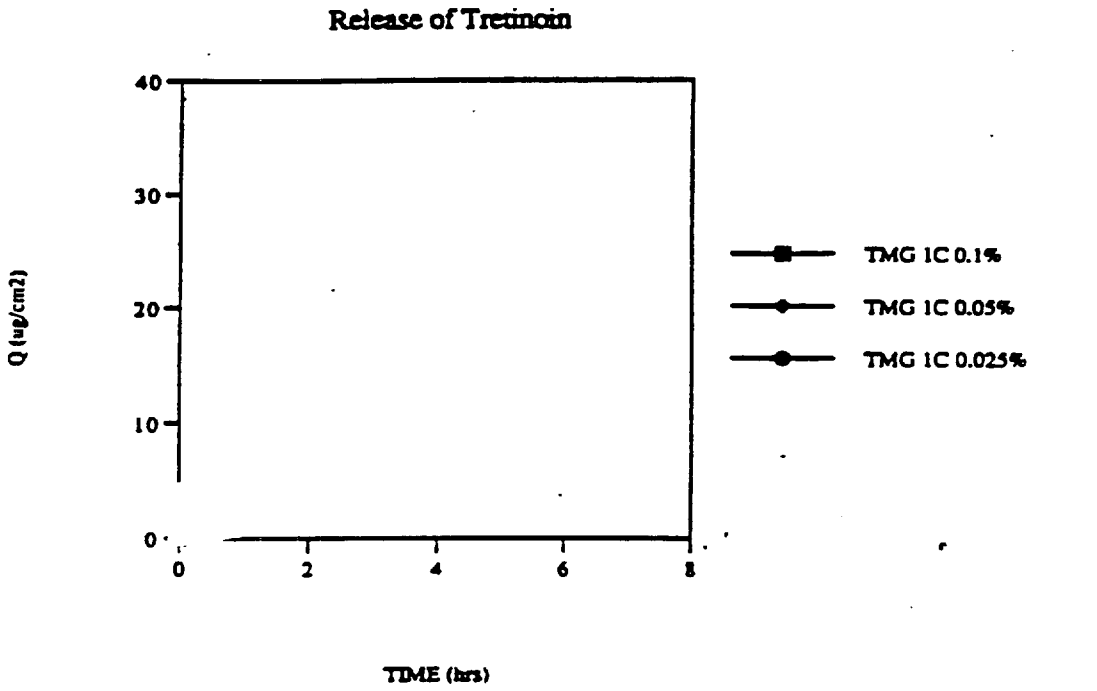


Figure 3 Concentration study. (ref. SM413-17)

Conclusion

Results indicate that the *in vitro* release method is capable of discerning differences in tretinoin concentration in TMG IC gels. This study also shows that under the conditions of these experiments, "sink conditions" are maintained in the receptor fluid and thus, drug solubility in the receptor side is not rate-limiting within the concentration range studied

3. Omission of Key Ingredients

A diffusion study was performed on four different TMG IC 0.1% gels. Three formulations with ingredients removed were tested against a control formulation,

lot# 30601. Data in figure 4 represents the mean result of duplicate determinations of each formulation.

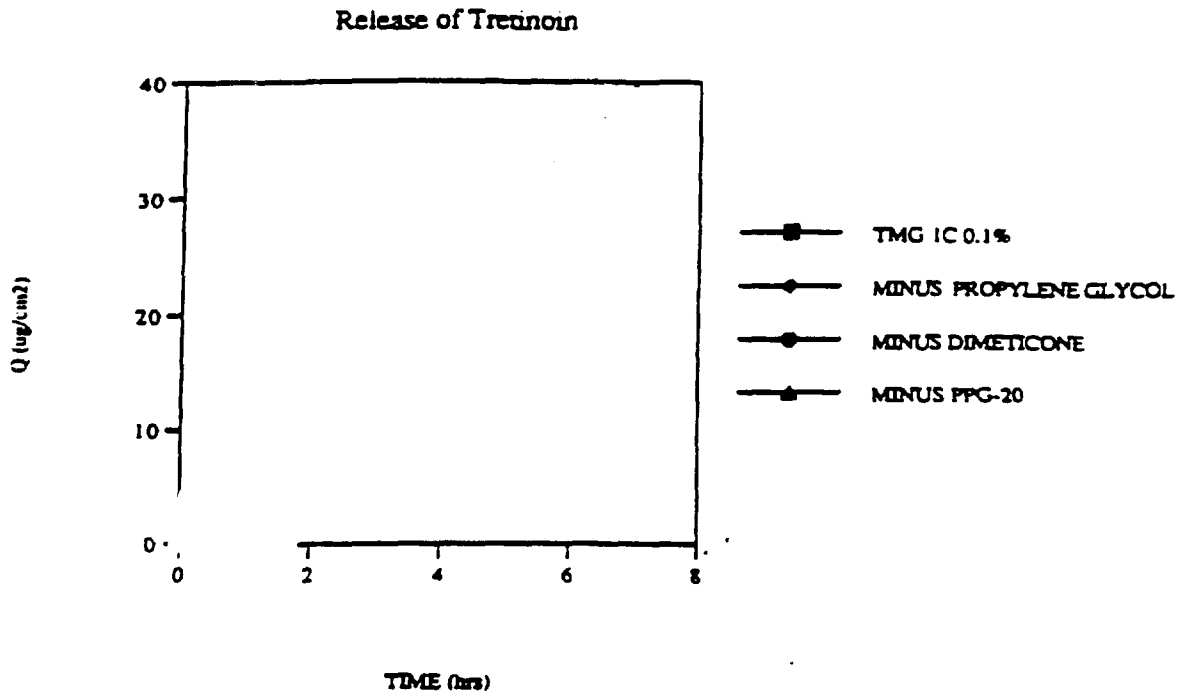


Figure 4 Omission of key ingredients. (ref. SM413-18)

Conclusion

Results indicate a small increase in rate of release of tretinoin for formulations without PPG-20 and propylene glycol, respectively. Little difference was seen in release profiles of control formulation and formulation minus dimethicone.

4. Micronized Tretinoin Study

A diffusion study was performed on a formulation containing placebo microsponges with micronized tretinoin (TMG IC lot# 389-29). APS formulation TMG IC lot #30601 was used as a control. Data in figure 5 represents the mean (±SD) of triplicate determinations for each formulation.

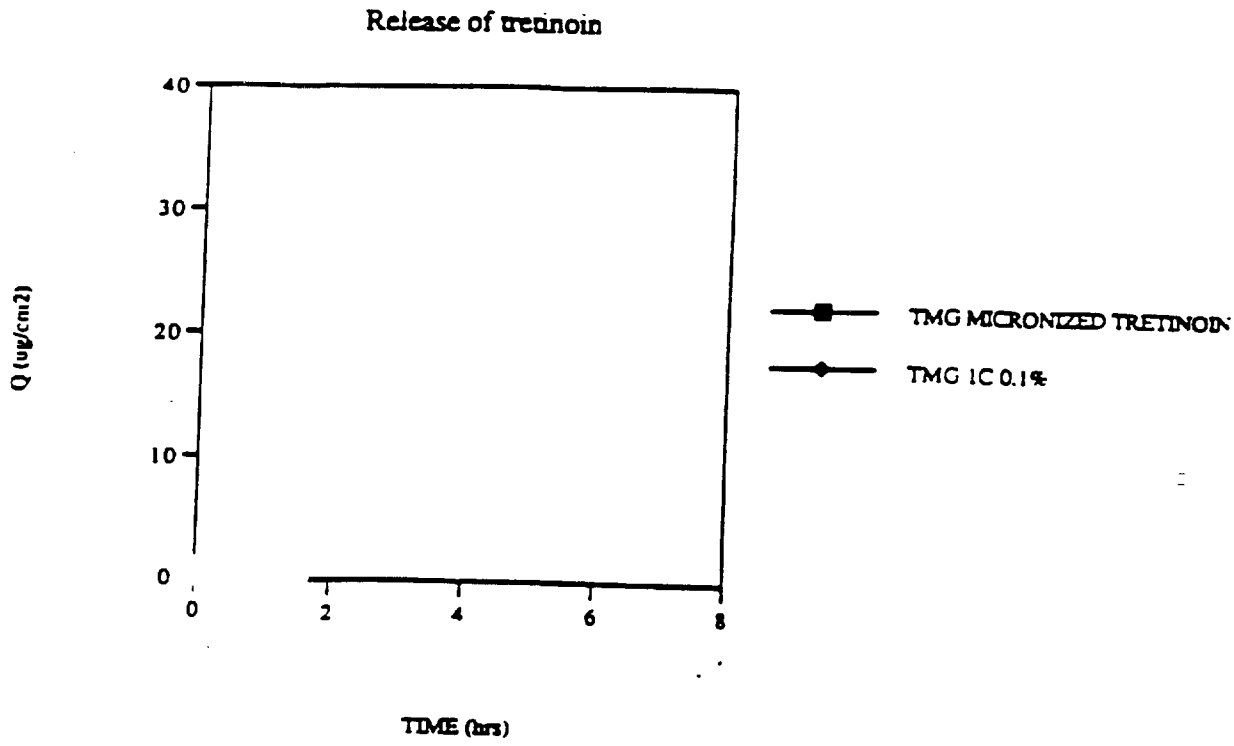


Figure 5 Micronized tretinoin study. (ref. SM413-20)

Conclusion

The results show no apparent difference in release profile from the 0.1% gel formulated with free micronized tretinoin and placebo Microsponge® particles compared with TMG IC 0.1% gel, suggesting that the method could not detect this formulation change.

Overall Conclusions

Overall, the results of the validation studies suggest that the *in vitro* release method shows fairly good reproducibility, however it is recommended to run a control sample during each study to ensure that each study is running correctly. The results from the validation formulations suggest that the method can discern differences in tretinoin concentration in TMG IC, and slight differences in release can be observed when minor formulation changes are made. The method did not discern between the TMG IC and the placebo Microsponge® with micronized tretinoin formulation.

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

NDA 20-475(N-000) (Original Submission, dated 2/6/95)

Drug Name: Nuretin^{R} Gel, 0.1%; Tretinoin Microsponge Gel (TMG), 0.1%

Route of Administration: Topical (dermal)

Category: Retinoid

Indication: Acne vulgaris

Sponsor: Advanced Polymer Systems, Redwood City, CA

Number of Vols.: 73

Date CDER Received: 2/8/95

Date Assigned: 2/13/95

Date Review Started: 6/6/95

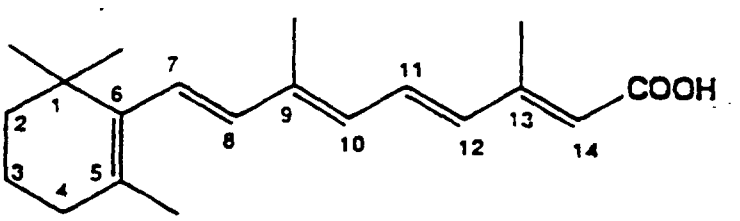
Date 1st Draft Completed: 10/31/95

Date Review Accepted by Supervisor:

Review Objectives: To review the submitted preclinical data to determine approvability of the application for commercial marketing.

Chemical Name: All-trans-retinoic acid (tRA)

Chemical Structure:



Related Submissions: INDs: NDAs:

16-921 Retin-A liquid), 17-340 (Retin-A Cream, 0.1%), 17-522 (Retin-A Cream, 0.05%), 17-579 (Retin-A Gel, 0.025%), 17-955 (Retin-A Gel, 0.01%), 19-049 (Retin-A Cream, 0.025%), 19-963 (Renova, 0.05%).

Composition (Present clinical formulation)[1]:

Ingredients	% w
1% Tretinoin in Acrylates Copolymer	
Glycerin USP	
Carbomer 934P NF	
Propylene Glycol USP	
PPG-20 Methyl Glucose Ethyl Distearate	
Cyclomethicone and Dimethicone Copolyol	
Benzyl Alcohol NF	
Trolamine NF	
Sorbic Acid NF	
Edetate Disodium USP	
Butylated Hydroxytoluene NF	
Purified Water: USP	

[1]APS Reference: Master Formula No.: P006D-53

[2]Includes 10% overage

Index of Preclinical Studies :

For formulations used in these studies see Appendix-1.

A. Pharmacology

i. TMG, 0.1% Gel: None have been performed

ii. Microsponge (Acrylate/EGDMA copolymer)

iii. Tretinoin (tRA): Summary with references have been provided.

B. Toxicology:

For all Advanced Polymer Systems (APS) studies:

Gel Vehicle = Vehicle without Microsponge (no tRA)

Vehicle = Gel vehicle with Microsponge (no tRA)

i. Studies Performed with **TMG 0.1% Gel** (APS studies):

1. Acute toxicity studies with TMG 0.1%
2. 4-Week dermal range-finding study in mice with TMG 0.1%
3. 3-Month dermal toxicity study of TMG 0.1% in mice
4. 4-Week dermal range-finding study of TMG 0.1% in dog
5. 3-Month dermal toxicity study of TMG 0.1% in dog
6. Primary irritation studies (dermal) in rabbits
7. Ocular irritation studies in rabbits
8. Dermal teratogenicity study of TMG 0.1% in pregnant rats
9. Dermal teratogenicity study of TMG 0.1% in pregnant rabbits

ii. Tretinoin toxicology: Summary has been provided in the following areas:

1. Acute toxicity studies with tretinoin
2. Multidose toxicity studies with tretinoin
3. Carcinogenicity study with tretinoin
4. Photocarcinogenicity study with tretinoin
5. Developmental toxicity study with tretinoin
6. Mutagenicity studies with tretinoin

iii. APS Microsponge Polymer Toxicology:

1. Acute oral toxicity study in rats
2. Rabbit eye irritation study
3. Rabbit dermal irritation study
4. Guinea pig delayed hypersensitization study
2. 4-Week dermal range-finding study in mice
3. 3-Month dermal toxicity study in mice
4. 4-Week dermal range-finding study in dogs
5. 13-Week dermal toxicity study in dogs
7. Rabbit primary eye irritation studies with vehicle
8. Ames mutagenicity assay

iv. Vehicle Toxicology:

1. Primary skin irritation studies in rabbits

2. Primary eye irritation studies in rabbits

C. ADME Studies

i. With TMG 0.1% gel

1. Plasma concentration of tretinoin following dermal application of ^{3}H-RWJ-8203 (tretinoin) 0.1% TMG gel to CD-1 mice

2. Determination of total plasma radioactivity in mice following repeated topical application of ^{3}H-tretinoin TMG gel 0.1%

3. Blood and plasma radioactivity concentrations in rats following dermal administration of a single dose of ^{3H}-TMG 0.1% gel

4. Blood and plasma radioactivity concentrations in rabbits following single dose dermal application of ^{3}H-tretinoin TMG gel 0.1%

5. Blood and plasma radioactivity concentrations in dogs following single dose dermal application of ^{3}H-tretinoin TMG 0.1% gel

ii. With tretinoin (performed by

1. Plasma radioactivity concentrations following dermal application of ^{3}H-RWJ-8203 (tretinoin) male CD-1 mice (NDA 19-963 Pharmacology Review).

2. 104-Week dermal carcinogenicity study of RWJ-8203 (tretinoin) in mice: plasma concentrations of tretinoin. (See Pharmacology Review of NDA 19-963).

Preclinical Studies

A. Review of pharmacology studies:

i. TMG 0.1% Gel: No pharmacology studies have been conducted with the TMG 0.1% Gel, the proposed clinical formulation.

ii. Microsponge: This is polymer made by copolymerization of methyl methacrylate (MMA) and ethylene glycol dimethacrylate (EGDMA). The Microsponge^{R} polymer is highly cross-linked with a mean particle diameter of 22μ. It does not penetrate the skin barrier and as such is considered a pharmacologically inactive material. *In vitro* skin penetration studies are reviewed elsewhere.

iii. Tretinoin (tRA):

The pharmacology of all-trans-retinoic acid (tRA) has been incorporated by reference to INDs and NDAs for Retin-A^{R} and Renova^{R} - drugs marketed by The RW Johnson Pharmaceutical Company. The Sponsor has included in the application authorization letters from RW Johnson to refer to these other submissions.

All applications for Retin-A had been approved many years ago. The application for Renova is pending approval subject to final labeling.

Significant numbers of reviews on the pharmacology and toxicology of tRA exists within the Division of Dermatologic and Ophthalmologic Drug Products. Also, the Sponsor has submitted many publications on these subjects. Results related to acne treatments reported are briefly presented here.

Decades of research has shown that retinoids have numerous sites and mechanisms of action. A representative sample of the pharmacologic properties of retinoids would be:

Inhibition of sebum production

Antikeratinization effects

Cellular differentiation

Anti-inflammatory effect

Immunomodulation

Suppression of ornithine decarboxylase

Morphogenic activity in developing fetus

Inhibition of tyrosinase activity in melanocytes

This is not a complete list.

Retinoids modulate cell growth, differentiation, and proliferation of skin cells such as keratinocytes, dermal fibroblasts, melanocytes, endothelial cells, sebocytes and Langerhans' cells. These effects are primarily due to changes in gene expression brought on through interaction of the ligand-bound retinoic acid nuclear receptors (RERs and RXRs) to the retinoid response element (RRE) of the genes. These receptors are homologs of thyroid and steroid receptors. Retinoids like the steroid and thyroid hormones, can act as transcription modulators to regulate the expression of target genes.

The effects of retinoid on abnormal keratinization have been studied in hairless rhino mice ($hr^{hr}hr^{hr}$ strain). These mice have numerous pilosebaceous skin structures known as "horn-filled utriculi" with excess amounts of keratin. In this animal model, retinoids have been shown to reverse the abnormal keratinizition by causing exfoliation of the keratinized material.

Another animal model used is the rabbit external ear canal where abnormal follicular keratinization

can be induced by applying for 2 weeks comedogenic substances such as coal tar and acetylated lanolin alcohol. A comedolytic effect is produced when tRA is applied after induction of comedones. A major factor in the therapeutic uses of tRA in the treatment of acne is the reversal of abnormal follicular keratinization by facilitating the extrusion of stratum corneum from poorly desquamating sebaceous follicles.

Another notable skin effect of retinoids is their ability to induce epidermal hyperplasia. This effect which appears to be due to keratinocyte proliferation, has been observed in normal and hairless mice, guinea pig and human skin.

Dermis appears to be an important site of action also for retinoid. In UVB-treated hairless mouse skin (photodamaged) tRA has been shown to induce synthesis of new collagen and elastin.

Local skin irritation commonly occurs with topical application of tretinoin (tRA) and other retinoids. This phenomenon appears to be different from primary skin irritation because it takes 4 or 5 consecutive treatments before developing. Recent studies indicate involvement of immune system in this reaction.

iii. Acrylate/EGDMA copolymer (Microsponge): No pharmacology studies have been done. The material presumably is an inactive polymer.

B. Review of toxicology studies

i. Trans-Retinoic Acid (tRA): Most recent review of these studies have been done in connection with NDA 19-963 (Renova). When applied dermally the most significant toxicity is irritation at the

application sites. Recently, equivocal results of teratogenic effects from dermal application have been reported in rabbits.

ii. Studies performed with APS formulations.

Acute Toxicities (Oral). Dose was 5 mg/kg. Sprague Dawley rats were used in all studies.

1. Acute oral toxicity testing of APS t-retinoic acid gel (lot # 10208). APS Study # B0 143S. (Ref. #T13), dated 3/26/91.

Lab Performing Study:

Material Tested: t-retinoic acid gel; lot #10208 identified in later submission as TMG lA vehicle

Species & Strain: "Sprague-Dawley derived" rats

No. of Animals/Group: 10 (5/sex)

Supplier: Zivic-Miller, Allison Park, PA

Weights at Initiation: 200 - 300 grams

Route of Administration: Oral by intubation

Dose Level: 5g/kg body weight once a day; single dose

Duration of Observations: 2 Weeks

Results: All animals appeared normal and survived the 14-day observation period. No gross observation in any animal was reported.

The test material was considered nontoxic.

2. Acute oral toxicity of APS t-retinoic acid gel vehicle (lot # 20108). APS Study # BO 184S, dated

12/7/1994. Ref. #T14.

Lab Performing Study:

The study was performed the same way as Toxicity Study #1, in all respects.

The material tested was TMG IA vehicle.

Results: All animals survived the 14-day observation period. Body weight gains were normal. No gross histopathology was reported. The test material was not considered toxic.

3. Acute oral toxicity testing of Retin-A Cream 0.1% (Lot #20K122A). APS Study #BO 143 S, dated 3/27/91. (Ref: #T15).

Lab Performing Study:

This study was done in the same way as the acute studies described previously.

Results:

There were no deaths. No signs of toxicity was reported. No gross lesions were observed. Body weight gains were noted in all animals.

The test material was considered nontoxic.

4. Acute oral toxicity study of t-retinoic acid gel (TMG lA, 0.1%) lot #10104. APS Study #BO 143S, Ref #T16.

Lab Performing Study:

Material Tested: Tretinoin Microsponge Gel, 0.1% formulation TMG lA

The same protocol used in the previously described acute studies was followed in this study also.

Results: All animals appeared normal and there was no mortality.

The material was considered nontoxic.

5. Acute toxicity study of t-retinoic acid gel, 0.025% (TMG lA, 0.025%). APS Study #BO 143S. Ref: #T17, lot #10102.

This is not the clinical formulation. It was done as a part of the previous acute studies.

No toxicity was reported.

6. Acute toxicity of t-retinoic acid gel, 0.05% (TMG lA, 0.05%). APS study #BO 143S; ref. # T18. Lot # 10103.

This study was also performed by as part of the acute studies reviewed above and identical methods were used.

At the end of the study, all animals appeared normal and there was no mortality during the 14-day observation period.

The test material was considered nontoxic.

7. Acute Toxicity of t-retinoic acid gel, 0.1% (TMG lB, 0.1%). APS Study # BO 184S. Ref. # T19,. lot # 20107.

Lab Performing Study:

Material Tested: t-Retinoic acid gel, 0.1%

Species: Sprague-Dawley derived rat

No. of Animals/Group: 10 (5/sex)

Methods: A single oral dose of 5 mg/kg was administered by gastric intubation, and were observed

Methods: A single oral dose of 5 mg/kg was administered by gastric intubation, and were observed for 14 days for signs of toxicity. At the end of the observation period, the animals were sacrificed for gross necropsy.

Results: There was no death and no significant toxicity was reported in any of the dose groups. Gross necropsy did not reveal any lesions.

The material was not considered toxic.

8. Acute Oral Toxicity Study with t-Retinoic Acid Gel, 0.05% (TMG lB, 0.05%); APS Study # BO 184S. Lot # 20106. Ref: #T20.

The methods used were the same as in #7 above.

Results: Again no toxicity or gross abnormalities were reported. No death occurred at any dose level.

The material was not considered to be toxic.

9. Acute Oral Toxicity Study with t-retinoic acid gel, 0.025% (TMG lB, 0.05%). lot # 20105. APS Study # BO 184S. Ref: #T 21.

Lab Performing Study:

Material tested: TMG lB

Methods: These were same as those used in #8 above.

Results: No death or loss of body weights or gross abnormalities were reported in any group.

The material was considered not toxic.

BO 267S. Ref: T22.

Lab Performing Study:

Material Tested: TMG IC, 0.1% (tretinoin microsponge gel, 0.1%)

Methods: Same as those used in other acute studies described before.

Results: No body weight loss or unusual signs of toxicity or deaths were reported in any of the groups.

The results indicated that the test material was not very toxic.

11. A 4-Week Dermal Range-Finding Study of RWJ-8203-000 (tretinoin) 0.1% Microsponge^{R} Gel in Mice.

This is a non-GLP study.

Lab Performing Study:

Material Tested: Tretinoin 0.1% microsponge gel (TMG lB, 0.1% Gel). Lot # 21201, and vehicle microsponge gel (TMG lB vehicle). Lot # 10341-1.

Objective: This was a range-finding study to determine the maximum tolerated dose for the drug formulation in CD-1 mice when administered topically for one month.

Methods: Groups (5/sex) of CD-1 mice (Charles River) were treated topically with the vehicle and 1.0, 2.0 or 5.0 mg/kg of the test article on the posterior dorsal skin sites (8 cm^2) once a day for 5 days/week for one month. The selected doses were 100, 200 and 500 times the proposed human dose (0.01 mg tretinoin/kg).

Parameters evaluated included daily mortality checks, weekly measurement of body weights, food consumption, weekly clinical and dermal observations, gross necropsy and histopathology of gross

lesions.

Results:

Mortality: None

Body Weights: No significant treatment-related effects were reported.

Food Consumption: Males were unaffected. Sporadic decreases in the treated females were reported on day 24.

Dermal Observations: Slight dermal dryness and erythema which became more apparent after 4 or 5 consecutive applications of the drug, were noted in the skin sites of all three treated groups. An increasing dose-response relationship was noted for dryness but not for erythema.

At day-28 observation point, dermal foci were noted on the treated skin of 7 males (2 low-dose, 3 mid-dose, 2 high-dose), and 1 mid-dose female.

Gross Pathology: The dermal observations were confirmed at necropsy. No other gross findings were reported.

Histopathology: Only grossly observed skin lesions in 8 animals reported above were examined. These lesions were confirmed to be microabscesses in the stratum corneum, epithelial hyperplasia and acanthosis.

12. Three-Month Dermal Toxicity Study of Tretinoin 0.1% Microsponge Gel in Mice. (GLP Study). APS Study # BO 235S. Ref: #T24.

Lab Performing Study:

Materials Tested: Vehicle gel without microsponge, lot # 30402; microsponge gel, lot #30307;

tretinoin 0.1% microsponge gel. lot # 21207.

Species and Strain: CD-1 mice (Charles River)

Age: 6-7 weeks

Dose Groups and No. of Animals/Group:

As shown in the following table.

Group No.	Treatment	Tretinoin Dose Level (mg/kg)	Dose Volume (mL/kg)*	Number of Animals		
				13 Week Toxicity	4 Week Recovery	Toxico-kinetics
1	Vehicle Gel	0	5.0	10M/10F	5M/5F	
2	Microsponge Gel	0	5.0	10M/10F	5M/5F	25M
3	Tretinoin Microsponge Gel	0.5	0.5	10M/10F		25M
4	Tretinoin Microsponge Gel	2.0	2.0	10M/10F		25M
5	Tretinoin Microsponge Gel	5.0	5.0	10M/10F	5M/5F	25M

* To the nearest 0.01 mL

Methods: The materials were administered topically to clipped posterior dorsal skin areas (10 cm^2) once daily, 5 days/week for 13 weeks. The sites were not washed before the next dose application. The dose volumes were insufficient to cover the entire shaved area in groups 2 (0.2 ml) and 3 (2.0 ml) animals. In other groups, the dose volume was 5.0 ml/site.

Results:

Mortality: One group 5 (high-dose) female (#4819) and one group 5 male were found dead. Two animals were either sacrificed or found dead in the toxicokinetic study groups 3 and 5.

Two females, #4784 from group 2 and #4805 from group 3 were reported as missing at scheduled necropsy.

Body Weights: No statistically significant differences in body weight among various groups were

reported.

Food Consumption: In all dose groups and in both sexes, food consumption frequently increased.

Clinical Observations: All observations were related to skin. One female in group 3 and 2 females in group 5 exhibited eschar at the treated sites during the third month of the study. During the same period three group 5 males had slight erythema at one or two observation periods. One of these males also had eschar.

Hematology:

At scheduled sacrifice of the high-dose (5.0 mg/kg TMG) males, a slight decrease in erythrocyte counts, hematocrit and hemoglobin concentration was reported. A significant dose-related increase in leucocyte numbers was observed in groups 4 and 5. In the recovery animals only normal values have been reported. In the females no unusual values were noted. In the recovery females, platelet counts were "unusually" high in 1 of 2 animals evaluated.

Clinical Chemistry:

A statistically significant dose-related decrease in serum cholesterol was reported in the males of the drug-treated groups. Lower triglyceride and T4 concentrations were also reported in these males. Only decreased T4 concentrations were noted in the females.

Organ Weights: A significant dose-related decrease in absolute and relative testes weights in males of groups 4 and 5 were reported. The relative testes weights in groups 4 and 5 were 25% and 33% less than the vehicle gel control value, respectively. The recovery animals did not show this decrease.

Among the female animals, a significant decrease in the absolute weight of the ovaries was reported in the high-dose (gr 5) females. The relative ovary weight (group 5) was decreased by 36% as

compared to the vehicle gel control group. Again, the recovery animals did not have any decrease in ovarian weights.

Gross Pathology: Foci at the application sites were observed in 2 group 5 (5 mg/kg tretinoin) males at scheduled sacrifice, and in 1 group 1 (vehicle gel) male at recovery sacrifice. Other treatment-related toxicity reported was enlargement of lymph nodes. This adverse finding was also seen in the dead animals, and in 1 vehicle control recovery animal.

Histopathology: Evaluation was performed on all tissues (from groups 1. 2 and 5) normally examined in a general toxicity study; Also were examined spleen, thymus, mandibular lymph nodes, and application skin sites from groups 3 and 4 and recovery animals in groups 2 and 5, any gross lesions from any group.

Among the group 1 (vehicle gel) and 2 (Microsponge gel) animals, one group 2 male had mild hyperkeratosis at the application sites. One group 1 male, 2 group 2 males, and 1 group 1 female had mild lymphoid hyperplasia of lymph nodes.

Among the drug-treated groups, there was a treatment-related incidence of minimal to mild hyperkeratosis, acanthosis, and parakeratosis in both sexes. Minimal to moderate lymphoid hyperplasia and lymphoid/hematopoietic changes of the spleen and/or thymus were also seen in these animals. The incidence of these lesions appears to be dose-related, In the 5 mg/kg dose groups, dermatitis and microabscess were also reported.

Among the recovery animals, Similar skin and lymph node lesions were observed but at a reduced rate, usually one to three animals in each group being affected. Lymphoid hyperplasia and thymocyte depletion were seen in all group 5 animals.

No microscopic changes in testes or ovaries were reported.

13. Toxicokinetic Data (ADME Studies Ref. #D6 and Toxicity Studies Ref. #T24).

Plasma samples from the toxicokinetic groups of animals from 3-month dermal toxicity study were analyzed for tretinoin (tRA) and it's metabolites, 4-oxo- 13-cis- retinoic acid (13-cis-RA) and 4-oxo-13-cis-RA, by HPLC-UV assay. The sensitivity of measurements was 5-1000 ng/ml of mouse plasma using 0.5 ml of sample. The analysis was conducted at the CEDRA Laboratories.

The plasma concentrations are presented in the table below:

Concentrations of tRA and Active Metabolites in Plasma of Mice at 4 Hours After the First Application of a 3 Month Dermal Toxicity Study of RWJ-8203-000 TMG 0.1%

Group (Dose) mg/kg/day	tRA ng/ml	13-*cis*-RA ng/ml	"Positive" samples[a]
II (0.0)	----	----	
III (0.5)	----	----	
IV (2.0)			
V (5.0)			

[a] No. of animals with quantifiable levels (≥5 ng/ml) of: tRA/13-*cis*-RA, respectively (n = 5/group).
[b] Concentrations for individual mice.
[c] mean (SD) concentrations for animals with "positive" samples.

In all predose and control samples, no tRA or it's metabolites were detected.

In the low-dose group (0.2 mg/kg) , plasma concentrations of tRA and/or metabolites were not measurable. The concentrations of tRA averaged 40.1 and 140.7 ng/ml, respectively, in the mid (2.0 mg/kg) and high-dose (5.0 mg/kg) groups at 4.0 hour after the first dose. These levels are about 10 times the levels reported in the same species when the animals were restrained to prevent oral ingestion through licking (see review of APS Study #BO 245S; Ref. #D4).

14. A 4-Week Dermal Range-Finding Study in Dogs with TMG lB, 0.1% (APS Study #BO 233S dated 10/18/93. It is a non-GLP study. Lot #10342-1. Ref. #T25.

Lab Performing Study:

Material tested: Tretinoin 0.1% microsponge gel (lot #21201), and the vehicle microsponge gel (lot #10341-1).

Species: Beagle dog

Age and Weight: Approx. 6 months of age, males weighed 9.1-9.8 kg, females weighed 7.2-7.8 kg

Number of Animals/Group: 4 (2/sex)

Dose Groups and Treatments:

Group No.	Treatment	Tretinoin Dose Level (mg/kg)	Dose Volume (mL/kg)	Animal Numbers	
				Males	Females
1	Microsponge Gel	0	1.0	30, 31	38, 39
2	Tretinoin Microsponge Gel	0.2	0.2	32, 33	40, 41
3	Tretinoin Microsponge Gel	0.5	0.5	34, 35	42, 43
4	Tretinoin Microsponge Gel	1.0	1.0	36, 37	44, 45

Procedure: The test compounds were administered topically to dorsal skin from the cervical area to the tail of animals, once/day, 5 days/week for 4 weeks. Animals were fitted with Elizabethan collars to prevent oral ingestion. The dosing site was clipped once a week.

Results:

Mortality: None

Body Weights: No significant group differences

Food Consumption: Normal

Clinical Observations: No unusual findings reported

Dermal Observations: Dermal erythema was seen in 0/4, 3/4, 1/4 and 2/4 animals, and edema was reported in 0/4, 2/4, 2/4 and 2/4 animals in control, low, mid and high doses, respectively.

Hematology: No unusual findings

Clinical Chemistry: Normal

Gross Necropsy:

Lymph node enlargement was the single most noticeable adverse finding that occurred sporadically in all groups. The incidence rates were 0/2, 2/2, 1/2, and 0/2 males, and 1/2, 1/2, 0/2 and 1/2 females given 0, 0.2, 0.5 and 1.0 mg/kg test article per day, respectively. However, there was no dose-response relationship. Scabs at the treatment site was seen in one high dose dog. Small kidney was found in one high dose dog (not reported in the Summary Table 8).

Organ Weights and Histopathology: Not performed

Reviewer's Note: This was a dose-range finding study on the basis of which the same doses were used in the definitive study.

15. A Three-Month Dermal Toxicity Study of RWJ-8205-000 (Tretinoin) 0.1% Microsponge Gel (TMG lB, 0.1%) in Dogs . APS Study #BO 236S. (A GLP Study). Ref. # T26

Lab Performing Study:

Materials Tested: Vehicle gel (lot #30402), microsponge gel (lot #s 30307, 30706), TMG lB, 0.1% (lot #21201).

Species: Beagle dog

Age and Weights: 7-8 months old weighing 9.0-11.9 kg males and 6.5-9.5 kg females

Dose Groups:

Group #	Treatment	Dose Level (mg/kg)	Dose Weight (g/kg)	Number of Animals	
				13 Week Toxicity	4 Week Recovery
1	Vehicle Gel	0	1.0	4M/4F	
2	Microsponge Gel	0	1.0	4M/4F	2M/2F
3	Tretinoin Microsponge Gel	0.2	0.2	4M/4F	
4	Tretinoin Microsponge Gel	0.5	0.5	4M/4F	
5	Tretinoin Microsponge Gel	1.0	1.0	4M/4F	2M/2F

Procedure: Test procedure was similar to the dose-range finding study presented in Study # 14 above. 100 µl of the material was applied topically to clipped skin of the dorsum of animals once daily, five days per week, for 13 weeks. Four animals (2/sex) each from group 2 and 5 were allowed to recover for 4 weeks. The animals wore collars to prevent oral ingestion.

The application sites were washed once a week during the first 3 weeks of the study when the washing was stopped due to irritation. Several dogs from groups 3, 4 and 5 were severely affected, and were not dosed on days 18 and 19.

Results:

Mortality: None were reported.

Body Weights: Normal body weight gains were reported in all groups.

Food Consumption: No statistically significant group differences were reported.

Clinical Observations: No significant findings reported.

Skin Observations: Severe erythema and edema, erosions and ulcers were observed in 3 males and 4 females of group 5 , and in 2 group 3 dogs. In general, slight to moderate erythema and

A group 1 (vehicle gel) female had a possible mammary tumor. This finding was not related to drug-treatment.

16. Primary Dermal Irritation Study with a Vehicle. APS Study # BO 147S (lot #10208). Ref. #T27. A GLP Study.

Lab Performing Study:

Material Tested: TMG 1A Vehicle (contains Microsponge) (lot #10208)

Species: New Zealand White rabbit (male and female)

Supplier:

No. of Animals/Group: 6

Dose Volume: 0.5 ml

Methods: The test material was applied to abraded and intact skin (clipped) of the dorsal area of the trunk of each animal under occlusion. After 24 hours the patches and any residual test material were removed. Irritation (erythema and edema) was scored at 24, 48 and 72 hours after the application of the test material.

Results: 0.5 ml of TMG 1A Vehicle when applied on intact and abraded skin of rabbits produced slight to well-defined erythema and very slight to slight edema during a 72-hour observation period. The Primary Skin Irritation Score was 2.63 indicating that the material was not a primary irritant.

17. Primary Dermal irritation Study with a Vehicle. APS Study # BO 185S (lot #20108); ref: # T28. A GLP Study.

eschar formation were reported in all groups 4 and 5 males and females, and the duration increased with increasing doses. All group 3 dogs had slight erythema at the application sites at several observations. The irritation was believed to be due to washing of the application sites which was discontinued after the third week.

Physical Examinations: Findings other than in the skin sites were considered incidental and spontaneous.

Ophthalmology: No abnormal findings.

Cardiac Functions: Normal

Hematology: At terminal sacrifice reticulocyte counts decreased significantly in groups 2 through 5 as compared to group 1 (vehicle gel).

Clinical Chemistry: Normal in all female dogs. In the males, sporadic decreases in serum sodium and chloride concentrations, and in albumin, phosphorous and globulin concentrations at week 6 have been reported.

Urinalysis: Within normal limits.

Organ Weights: No significant group differences were noted.

Gross Pathology: Skin application site foci were observed in several 0.2 mg/kg and 0.5 mg/kg dogs. Other findings were considered incidental and spontaneous.

Histopathology: Treatment and dose-related microscopic changes were reported at the application sites on the skin. These lesions included acanthosis, hyperkeratosis, parakeratosis, stratum corneum pustules and inflammation. Stratum corneum pustules were seen as infiltrates of leukocytes in the dermis.

T26. A GLP Study.

Lab Performing Study:

Material Tested: TMG lB vehicle, lot #20108 (contains microsponge).

Species: New Zealand White rabbits

Supplier:

No. of Animals/Group: 6

Dose Volume: 0.5 ml

Methods: Same as in Study #16.

Results: No skin reactions other than very slight erythema (scored by the Draize method) were noted. The Primary Irritation score was calculated to be 0.29 indicating that the material was not a primary irritant.

18. Primary Dermal Irritation Study with TMG lA, 0.025% Gel (lot # 10102). APS Study #BO 147S. Ref. # T29. A GLP study.

Laboratory Performing Study:

Material Tested: Tretinoin Microsponge Gel, 0.025% (TMG lA; lot #10102)

Species: New Zealand White rabbit

No. of Animals/Group: 6 (both sexes). Each animal had an intact and an abraded skin area

Methods: Same as in Study #16.The dose volume was 0.5 ml.

Results: The test material produced slight to well-defined erythema and very slight to slight edema during the 72-hour observation period. The calculated Primary Irritation score was 3.37. Thus the formulation was not considered to be a primary irritant.

19. Primary Dermal Irritation Study with TMG lA, 0.05% Gel (lot #10103). APS Study #BO 147S. Ref. #T30. A GLP study.

This study was performed by the same laboratory and was similar in all respect to Study #16 except the test material which was TMG lA, 0.05% gel.

The results showed a primary irritation score of 2.59. The test material was not considered to be a primary irritant.

20. Primary Dermal Irritation Study with tretinoin Microsponge Gel, 0.025% (TMG lB, Gel, 0.025%; lot #20105). APS Study #BO 185S. Ref. #T31. A GLP study.

The study was performed by the same testing laboratory and with a similar protocol as in Study #16 except that a new formulation, TMG lB, 0.025%, was used.

A primary irritation score was reported to be 1.88. Therefore, the test material was not considered to be a primary irritant.

21. Primary Dermal Irritation with Tretinoin Microsponge Gel, 0.05% (TMG lB Gel, 0.05%; lot #20106). APS Study #BO 185S. Ref. #T32. A GLP study.

This study was performed by the same testing laboratory and by similar methods as in Study #16 except that the test material used was TMG lB, 0.05% Gel.

The reported primary irritation score was 1.63. The material, therefore, was not considered to be a primary irritant.

22. Primary Dermal Irritation Study with Tretinoin Microsponge Gel, 0.10% (TMG lB, 0.05%; lot #20107). APS Study #BO 185S. Ref. #T33.

This study was performed by the same testing laboratory and by similar methods as in Study #16 except that the test material was the TMG lB, 0.05% gel formulation.

The results with a primary irritation score of 0.63 demonstrated that the test material was not a primary irritant.

23. Primary Dermal Irritation Study with Tretinoin Microsponge Gel, 0.10% (TMG lA, 0.10%; lot #10104). APS Study No. BO 147S. Ref. # T34. A GLP study.

This again is a study similar in all respect to Study #16 except the test material which, in this case, was TMG lA, 0.10% Gel.

The primary irritation score was reported to be 3.75 which would indicate that the formulation has potential for severe irritation. Based on the score, it was not considered a primary irritant.

24. Primary dermal Irritation Study with Tretinoin Microsponge Gel (lot #30601) (TMG lC, 0.1% Gel). APS Study #BO 265S. Ref. #T35. A GLP study.

Again only the test material was different in this otherwise similar to No. 16 study.

The primary irritation score was 1.29. The material was not considered to be a primary irritant.

Reviewer's Note: This report is unsatisfactory. The material has been identified variously as a gel, a cream, an yellow cream, and at one place as a gel followed by the statement "yellow cream". Nowhere, the concentration of the active has been provided. The values quoted here were obtained from an additional list of studies with the lot numbers of the drug used, provided later by the Sponsor at my request.

25. Primary Dermal Irritation Study with Retin-A Cream, 0.1% (lot #20K122). APS Study #BO 147S. Ref. #T36. A GLP study.

This study was performed by by a method similar to that used in Study #16. The test material was the marketed Retin-A^{R} Cream, 0.1%.

At 24 and 48 hours, all animals had well-defined erythema at both intact and abraded skin sites. All animals had slight edema at treatment sites.

At 72 hours, 5/6 animals had well-defined erythema at both abraded and intact skin application sites. Slight to very slight edema was reported in some animals. No edema at the intact site was reported in one animal.

The primary irritation score was determined to be 3.92. Thus, the material was not a primary irritant, although it had potential to cause severe irritation.

26. Primary Eye Irritation Studies

All such studies have been performed by the Several different formulations have been tested by the same methods in the rabbit. All these studies (References 37 - 46) are reviewed together here.

Materials Tested:

A. Tretinoin mcrosponge gel (TMG lA gel vehicle; lot # 10208). APS study #BO 142S. Ref. # T37.

B. Tretinoin microsponge gel (TMG lB gel vehicle; lot #20108). APS study #BO 183S. Ref. # T38.

C. Retin-A cream, 0.1% (lot #20K122). APS study #BO 142S. Ref. #T39.

D. Tretinoin microsponge gel, 0.1% (TMG lA, 0.1% gel; lot #10104). APS study #BO

142S. Ref. #T40.

E. Tretinoin microsponge gel, 0.05% (TMG lA gel, 0.05%; lot #10103). APS study #BO 142S. Ref. # T41.

F. Tretinoin microsponge gel, 0.025% (TMG lA gel, 0.025%; lot #10102). APS study #BO 142S. Ref. # T42.

G. Tretinoin microsponge gel, 0.025% (TMG lB gel, 0.025%; lot #20105). APS study #BO 183S. Ref. # T43.

H. Tretinoin microsponge gel, 0.05% (TMG lB gel, 0.05%; lot #20106). APS study #BO 183S. Ref. # T44.

I. Tretinoin microsponge gel, 0.1% (TMG lB gel 0.1%; lot #20107). APS study #BO 183S. Ref. # T45.

J. Tretinoin microsponge gel, 0.1% gel (TMG lC gel, 0.1%; lot #30601). APS study #BO 266S. Ref. # T46

Species: New Zealand White rabbit (male or female)

Number of Animals/Group: 6

Supplier:

Route of Administration: Instilled into the conjunctival sac of the test eye of each rabbit. The eye used has not been specified as to the left or the right one.

Dose Level and Frequency: 0.1 ml, single application

Procedure: All animals' eyes were examined for damage by fluorescein before administration of the drug. The contralateral eye that did not get the drug was the control. All treated eyes remained unwashed for the duration of the study. The eyes were examined for irritation of the cornea, iris and conjunctivae at 24, 48 and 72 hours after treatment.

Results: All results are summarized in the following Table 1:

Study	Material Tested	Lot #	Avg.Irrit. Score at 24 hrs	Avg.Irrit. Score at 72 hrs	Observations and conclusions
A	TMG lA gel vehicle (T37)	10208	0.7	0	Minimal conjunctival redness in 2/6 animals. There was no corneal or iris involvement. It was not a primary irritant.
B	TMG lB gel vehicle (T38)	20108	0	0	minimal conjunctival redness in 1/6 animal cleared by 72 hrs. No corneal or iris involvement. Not a primary irritant.
C	Retin-A cream, 0.1% (T39)	20K122	3	0	Positive conjunctival irritation in 2/6 animals. No corneal or iris involvement. Inconclusive
D	TMG lA gel, 0.1% (T40)	10104	NA	NA	Minimal conjunctival irritation in 3/6 animals. No iritis or corneal involvement noted. Not a primary irritant.
E	TMG lA gel, 0.05% (T41)	10103	1.7	0	Minimal conjunctival irritation in 5/6 animals cleared by day 4. Not considered a positive reaction. No cornea or iris involvement. Not a primary ocular irritant.
F	TMG lA gel, 0.025% (T42)	10102	1.7	0	Minimal conjunctival irritation in 5/6 animals cleared by 72 hrs. No corneal or iris involvement. Not a primary ocular irritant.
G	TMG lB gel, 0.025% (T43)	20105	2.3	0	Similar results as in F above
H	TMG lB gel, 0.05% (T44)	20106	1.7	0.3	Minimal conjunctival irritation in 3/6 animals cleared by day 4. No corneal or iris involvement. Not a primary eye irritant.
I	TMG lB gel, 0.1% (T45)	20107	1	0	Results similar to that in F above
J	TMG l gel, 0.1% (T46)	30601	3.3	0.7	Minimal conjunctival irritation in all 6 animals cleared by day 4. No iritis or corneal involvement. Not a primary irritant.

The clinical formulation is TMG l gel, 0.1%

Apparently, the Sponsor had tested a whole series of concentrations in different vehicles to select one that the Sponsor considers suitable for marketing.

None of the formulation tested was considered to be a primary eye irritant. The clinical formulation caused only slight conjunctival redness that lasted for 72 hours. No iritis or corneal lesions were seen.

27. Segment II Developmental Toxicity Study (Embryo-Fetal Toxicity and Teratogenic Potential) of RWJ-8203-00 (APS 0.1% Tretinoin Microsponge Gel, lot #21201) in Rats. APS Study #BO 251S. Ref. #T47. A GLP Study.

Lab Performing Study:

Materials Tested: APS 0.1% tretinoin microsponge gel, also named TMG lB Gel 0.1% (lot # 21201) and vehicle (lot #30307)

Species and Strain: Crl:CD BR VAF/Plus rat

Weight: Females - 202-267 g; males - 507 - 1113 g

Supplier:

Number of Animals/Group: 31 (pregnant females); 25 for C-sectioning, 6 for blood collection

Dose Levels: 0 (control), 0.2 (low dose), 0.5 (mid dose) or 1.0 (high dose) mg/kg/day

Route of Administration: Percutaneous, once/day

Methods: The test material or the vehicle was applied on the clipped backs of pregnant rats under occlusion for 24 hours at the end of which the patches were removed, the sites were washed, and the next dose was applied. The treatment was continued for days 6 through 15 of pregnancy. Blood samples were collected on days 6 and 15 both before and after treatments.

On day 21 of pregnancy the fetuses were delivered by C-section and the dams were sacrificed

for pregnancy parameters evaluation.

Results:

Mortality: One group 2 rat died during bleeding procedure.

Clinical Observations: Exophthalmos, corneal opacity and hemorrhagic eyes were caused by the bleeding procedure (orbital sinus). Transient skin lesions on the mouth or the forepaw in two group 4 animals were noted. None of these observations were considered treatment-related.

Skin Reactions: One or more skin reactions like erythema, desquamation, edema and/or fissuring were reported in every rat receiving the APS formulation. The onset and severity were generally dose-dependent. Fissuring was reported in only one group 3 rat.

Maternal Body and Uterine Weights: Decreased weight gains in all drug-treated groups during the study period was reported. Reduced body weight compared to controls was reported for groups 3 and 4 animals. Gravid and empty uterine weights were comparable among the various groups.

Food Consumption: Reduced consumption was reported for the 3 drug-treated groups during the treatment period as compared to the control group.

Reproduction Parameters (maternal observations):

These are presented on page 31A. All parameters were similar for all the groups including the control group. No. dams had a litter consisting of only resorbed fetuses. Also no dead fetuses were reported.

Reproductive parameters (litter observations):

PROTOCOL 1501-003: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE GEL) ADMINISTERED PERCUTANEOUSLY TO Crl:CD®BR VAF/Plus® PRESUMED PREGNANT RATS (SPONSOR'S STUDY NUMBER: B02518)

CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(VEHICLE)	II 0.2	III 0.5	IV 1.0
RATS TESTED	N	31	31	31	31
INCLUDED IN ANALYSES b	N	25	25	25	25
PREGNANT	N(%)	20(80.0)	22(88.0)	17(68.0)	21(84.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	20	22	17	21
CORPORA LUTEA	MEAN±S.D.	17.2 ± 3.0	17.2 ± 2.0	17.7 ± 3.0	18.2 ± 3.3
IMPLANTATIONS	MEAN±S.D.	14.5 ± 2.3	14.3 ± 2.5	14.5 ± 2.6	14.5 ± 2.8
LITTER SIZES	MEAN±S.D.	13.8 ± 2.3	13.8 ± 3.0	13.6 ± 2.8	14.0 ± 2.8
LIVE FETUSES	N	275	304	231	293
	MEAN±S.D.	13.8 ± 2.3	13.8 ± 3.0	13.6 ± 2.8	14.0 ± 2.8
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.8 ± 0.8	0.5 ± 1.0	0.9 ± 1.5	0.5 ± 0.7
EARLY RESORPTIONS	N	14	11	16	10
	MEAN±S.D.	0.7 ± 0.9	0.5 ± 1.0	0.9 ± 1.5	0.5 ± 0.7
LATE RESORPTIONS	N	1	0	0	1
	MEAN±S.D.	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.2
DAMS WITH ANY RESORPTIONS	N(%)	11(55.0)	6(27.3)	8(47.0)	8(38.1)
DAMS WITH ALL CONCEPTUSES RESORBED	N	0	0	0	0
DAMS WITH VIABLE FETUSES	N(%)	20(100.0)	22(100.0)	17(100.0)	21(100.0)

a. Dosage occurred on days 6 through 15 of gestation.
b. Excludes rats which were assigned to blood collection and were sacrificed on day 15 of the study.

PROTOCOL 1501-003: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE GEL) ADMINISTERED PERCUTANEOUSLY TO Crl:CD®BR VAF/Plus® PRESUMED PREGNANT RATS (SPONSOR'S STUDY NUMBER: 802515)

TABLE 7 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(VEHICLE)	II 0.2	III 0.5	IV 1.0
LITTERS WITH ONE OR MORE LIVE FETUSES	N	20	22	17	21
IMPLANTATIONS	MEAN±S.D.	14.5 ± 2.3	14.3 ± 2.5	14.5 ± 2.6	14.5 ± 2.8
LIVE FETUSES	N	275	304	231	293
	MEAN±S.D.	13.8 ± 2.3	13.8 ± 3.0	13.6 ± 2.8	14.0 ± 2.8
LIVE MALE FETUSES	N	124	145	120	149
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	45.2 ± 11.1	48.2 ± 13.3	51.8 ± 11.7	51.5 ± 19.4
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	4.98 ± 0.52	5.00 ± 0.20 [21]b	4.84 ± 0.37	4.89 ± 0.31
MALE FETUSES	MEAN±S.D.	5.10 ± 0.54	5.12 ± 0.25 [21]b	4.94 ± 0.40	5.01 ± 0.35
FEMALE FETUSES	MEAN±S.D.	4.87 ± 0.51	4.89 ± 0.20 [21]b	4.73 ± 0.41	4.76 ± 0.32 [20]c
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	5.0 ± 5.7	4.7 ± 11.4	6.3 ± 10.0	3.9 ± 5.8

[ ] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on days 6 through 15 of gestation.

b. Excludes values for dam [redacted], which appeared to have an incorrectly identified mating date (based on fetal body weights).

c. Litter [redacted] had no female fetuses.

These are presented on page 31B. Mean number of implantations, percent resorbed, the number of live fetuses and the male/female ratios were similar in all treated groups, and did not significantly differ from the control values.

Fetal observations (alterations):

a) Fetal Gross External alterations: One control group fetus had micrognathia.

b) Soft Tissue Alterations: Only variations (generally reversible) were reported. One group 4 fetus had slightly dilated pelvis of one kidney, and one group 3 fetus had moderate dilation of the lateral ventricle of the brain.

Fetal Skeletal Alterations:

a) Malformations: The control fetus with micrognathia was confirmed to have a short mandible. A group 3 fetus had interrelated vertebral-rib malformations.

b) Variations: Incomplete ossification in vertebrae, ribs and sternal centers have been reported. Wavy ribs and extra ribs have been noted in a few fetuses from all groups. There were no statistically significant or 'biologically important" differences among the four dose groups (including controls) in the litter averages for number of ossification sites per fetus for the hyoid, vertebrae, forelimbs or hindlimbs.

Conclusions: . No adverse effects on embryo-fetal development was seen at 1.0 mg/kg dose level, the highest tested in this study. The NOEL for developmental toxicity was >1.0 mg/kg in the rat.

28. Segment II Developmental Toxicity Study (Embryo-Fetal Toxicity and Teratogenic Potential) of RWJ-8203-000 (APS 0.1% Tretinoin Microsponge Gel) in Rabbits. Study #BO

252S. Ref. #T48. (Also (D9). A GLP study.

Lab Performing Study:

Materials Tested: APS 0.1% tretinoin microsponge gel; also named TMG lB 0.1% Gel. Lot #21201, and the Vehicle (lot #30307). Ref. #T48. A GLP study.

Species: New Zealand White pregnant rabbits (artificially inseminated)

Age and Weight: 10 months old weighing 2.79 - 4.20 kg

Supplier:

Number of Animals/Group: 15 (females)

Dose Levels: 0 (control, Group 1), 0.2 (low dose, Group 2), 0.5 (mid dose, Group 3) or 1.0 (high dose, Group 4) mg/kg/day

Note: The highest dose level was based on the maximum volume that could be applied uniformly to cover 10% of the body surface.

Route of Administration: Percutaneous

Frequency: Once a day

Methods: The appropriate doses of test materials were applied on the shaved backs of the dams from day 7 through 19 of gestation. No occlusive bandages or wraps were used to cover the application sites. The animals were made to wear Elizabethan collar from gestation day 2 through day 20 of gestation to prevent oral ingestion. Blood samples were collected from the first 6 dams of each group at various time intervals. The rabbits were sacrificed on day 29 of presumed gestation for analysis of reproduction parameters.

<u>Results</u>

Mortality: One group 2 doe died on day 21 of gestation of unknown cause. The animal was

suffering from severe skin irritation and convulsions before death.

Abortions: One group 1 and one group 2 dams aborted on day 23 and day 21, respectively. Minimal to slight skin irritation was noted in these animals. Gross necropsy did not reveal any lesions.

Skin reactions: Erythema, atonia and desquamation were reported in does from all groups including the control group. Additionally, edema was noted in the drug-treated animals. Microscopic examination of skin sites revealed epidermal hyperplasia, hyperkeratosis and dermal inflammation. The severity of these findings was dose dependent.

Clinical Observations: Localized alopecia, lacrimation, neck or back lesions, convulsions and red perioral substance were reported in animals from all groups. The vehicle contains the "Microsponge" which might have some adverse effects when given to pregnant rabbits.

Gross Necropsy: Parovarian cyst in one low and one high dose dam, cyst in uterine horn (left or right) in one control and one high dose dam, gastric trichobezoar in one high dose animal, and mottled and distended gallbladder in one high dose doe have been reported.

The doe 22561 (1.0 mpk) with a cyst in the right uterine horn had a unilateral pregnancy. The doe 22562 (1.0 mpk) had a gastric trichobezoar and experienced weight loss and reduced food consumption. This doe had 8 live fetuses three of which had external alterations (subcutaneous hemorrhage in the hindlimbs).

Maternal Body Weights and Uterine Weights: There was decreased body weight gain in the high dose group as compared to other groups. When the doe with gastric trichobezoar was excluded from the body weight analysis no significant group differences remained.

Uterine weights were comparable among the four groups.

Food Consumption: This was very variable and tended to be reduced in the high dose group.

Blood Analysis: The Table on page 35A shows the results. Generally the concentrations of tretinoin and its metabolites (13-cis-RA, all-trans-4-oxo-RA and 13-cis-4-oxo-tRA) were below the lower limit of detection for these compounds (<5 ng/ml). The endogenous levels in rabbits are also in this range. Measurable concentrations of tretinoin and/or cis-retinoic acid were seen in groups 3 and 4 at 24 hours after the 1st and 13th dose. No drug was detected after the 12th dose. This finding led the Sponsor to speculate that there was sporadic oral ingestion which produced detectable serum concentrations.

The Sponsor also pointed out that "*none of the animals in which blood was taken was one in which developmental toxicity was observed*".

Reproductive Parameters (maternal):

These are shown on page 35B. These observations were based on 11, 14, 14 and 11 surviving pregnant dams in the control, 0.2, 0.5 and 1.0 mg/kg/day dose groups, respectively. One control and two group 3 does had only one live fetus. One control animal had only resorbed conceptuses (four). These and dead and aborted animals were excluded from analysis.

The litter averages of the maternal reproductive parameters were comparable among the four dose groups.

Reproductive Parameters (litter observations):

These are presented on page 35C

As can be seen, none of the parameters evaluated was significantly different among the four dose groups.

Fetal Alterations:

Concentration of Tretinoin (RA) and Its Metabolites
In Individual Rabbits After Dermal Administration of 0.1% APS Microsponge Gel
(APS Protocol B-0252S)

Group	Dose (mg/kg/day)	Day	Time (hr)	RA[a,b] (ng/mL)	CIS-RA[a,c] (ng/mL)	OXO-RA[a,d] (ng/mL)	CIS-OXO-RA[a,e] (ng/mL)
I	0.00	GD-7*		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
II	0.20	GD-7		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
III	0.50	GD-7				-	-
		GD-19				-	-
		GD-19				-	-
		GD-19				-	-
IV	1.00	GD-7					
		GD-19					
		GD-19					
		GD-19					

* GD = Gestational Day. GD-7 = 1st dose; GD-19 = 13th (last) dose.

[a] (-) Lower limit of quantitation (LLOQ) for RA and metabolites is 5 ng/mL. No value indicates all samples in that group were below 5 ng/mL. Blood was sampled from 6 study animals/group.

[b] All-trans-retinoic acid

[c] 13-Cis-retinoic acid

[d] All-trans-4-oxo-retinoic acid

[e] 13-Cis-4-oxo-retinoic acid

[f] n=1

[g] Mean ± standard deviation (n=4)

PROTOCOL 1501-004: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0252S)

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(VEHICLE)	II 0.2	III 0.5	IV 1.0
RABBITS TESTED	N	18	18	18	18
PREGNANT	N(%)	14(77.8)	16(88.9)	16(88.9)	11(61.1)
ABORTED	N(%)	1(7.1)	1(6.2)	0(0.0)	0(0.0)
FOUND DEAD	N(%)	0(0.0)	1(6.2)	0(0.0)	0(0.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	11b,c	14	14d,e	11
CORPORA LUTEA	MEAN±S.D.	10.8 ± 1.7	12.1 ± 2.8	11.1 ± 2.0	12.4 ± 2.3
IMPLANTATIONS	MEAN±S.D.	8.3 ± 1.8	8.4 ± 2.7	7.5 ± 2.3	8.8 ± 2.5
LITTER SIZES	MEAN±S.D.	8.0 ± 2.0	7.4 ± 2.5	5.8 ± 2.3	8.5 ± 2.6
LIVE FETUSES	N	88	104	82	94
	MEAN±S.D.	8.0 ± 2.0	7.4 ± 2.5	5.8 ± 2.3	8.5 ± 2.6
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.3 ± 0.6	0.9 ± 1.3	1.6 ± 2.4	0.3 ± 0.5
EARLY RESORPTIONS	N	3	11	17	1
	MEAN±S.D.	0.3 ± 0.6	0.8 ± 1.2	1.2 ± 2.4	0.1 ± 0.3
LATE RESORPTIONS	N	0	2	6	2
	MEAN±S.D.	0.0 ± 0.0	0.1 ± 0.5	0.4 ± 1.2	0.2 ± 0.4
DOES WITH ANY RESORPTIONS	N(%)	2(18.2)	6(42.8)	6(42.8)	3(27.3)
DOES WITH VIABLE FETUSES	N(%)	11(100.0)	14(100.0)	14(100.0)	11(100.0)

a. Dosage occurred on days 7 through 19 of gestation.
b. Excludes values for doe which had a litter consisting of one live fetus and eight early resorptions.
c. Excludes values for doe which had a litter consisting of four early resorptions.
d. Excludes values for doe which had a litter consisting of one live fetus and six early resorptions.
e. Excludes values for doe which had a litter consisting of one live fetus.

PROTOCOL 1501-004: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0252S)

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(VEHICLE)	II 0.2	III 0.5	IV 1.0
LITTERS WITH ONE OR MORE LIVE FETUSES	N	12	14	16	11
INCLUDED IN ANALYSES	N	11b	14	14c,d	11
IMPLANTATIONS	MEAN±S.D.	8.3 ± 1.8	8.4 ± 2.7	7.5 ± 2.3	8.8 ± 2.5
LIVE FETUSES	N	88	104	82	94
	MEAN±S.D.	8.0 ± 2.0	7.4 ± 2.5	5.8 ± 2.3	8.5 ± 2.6
LIVE MALE FETUSES	N	38	61	37	50
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	46.6 ± 24.4	59.4 ± 21.1	46.7 ± 15.0	52.7 ± 21.9
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	45.26 ± 4.11	45.34 ± 6.06	47.61 ± 4.74	42.29 ± 8.06
MALE FETUSES	MEAN±S.D.	46.86 ± 4.00	46.40 ± 7.08	47.99 ± 5.36	42.53 ± 8.85 [10]e
FEMALE FETUSES	MEAN±S.D.	43.28 ± 3.14 [10]f	43.18 ± 6.26 [13]g	46.99 ± 4.92	41.41 ± 8.21
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	3.5 ± 8.0	9.7 ± 13.3	18.4 ± 25.1	3.5 ± 6.2

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 19 of gestation.
b. Excludes values for litter which consisted of one live fetus and eight early resorptions.
c. Excludes values for litter which consisted of one live fetus and six early resorptions.
d. Excludes values for litter which consisted of one live fetus.
e. Litter had no male fetuses.
f. Litter had no female fetuses.
g. Litter had no female fetuses.

No statistically significant differences among the four dose groups in the total incidences of litters or fetuses with any alteration observed were found. The mean percentage of fetuses with any alteration showed a dose-related increase but, there was no statistically significant difference among the various groups.

However, significant differences were observed among the groups when specific malformations such as domed head, hydrocephaly, cleft palate and flexed paws were examined. The incidence of these malformations are presented on page 36A, 36B and 36C. An increased incidence of the lateral and/or third ventricles in the brain was reported. Alterations associated with marked and extreme dilation of the lateral ventricles have been identified as hydrocephaly (domed head). The reported litter incidences (%) of domed head are: 0, 6.2 and 27.3, respectively, in the low, mid and high dose groups. The fetal incidences in the same groups were 0, 1.2 and 5.3% respectively. The incidence in the high dose group was statistically significantly different from other groups. If one considers dilation of all severity then the incidence rate increases in the mid and high dose groups, and the low dose group shows one fetus with the brain involvement.

The incidence rates at 0.2 (mid dose) and 1.0 (high dose) mg/kg/day groups are well above the historical control incidences reported for the Research Laboratories who conducted this study. The presence of a clear dose response suggest that hydrocephaly observed in the mid and high dose groups were associated with the drug. The NOEL for this effect in the present study was 0.2 mg/kg/day i.e. 20 times the proposed clinical dose.

Note: It appears that the drug, even though was given by percutaneous route, is teratogenic in rabbits when given at doses of 0.5 mg/kg/day and above. The no-effect level for

PROTOCOL 1501-004: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0252S)

TABLE 11 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(VEHICLE)	II 0.2	III 0.5	IV 1.0
Litters Evaluated	N	12	14	16	11
Fetuses Evaluated	N	89	104	84	94
Live Fetuses	N	89	104	84	94
Dead Fetuses	N	0	0	0	0
Late Resorption b	N	0	0	1	1
HEAD:					
Domed					
Litter Incidence	N(%)	0	0	1(6.2)	3(27.3)**
Fetal Incidence	N(%)	0	0	1(1.2)c	5(5.3)d**
PALATE:					
Cleft					
Litter Incidence	N(%)	0	0	1(6.2)	0
Fetal Incidence	N(%)	0	0	1(1.2)c	0
FORELIMBS:					
Paws, Flexed					
Litter Incidence	N(%)	0	1(7.1)	1(6.2)	1(9.1)
Fetal Incidence	N(%)	0	2(1.9)	1(1.2)c	1(1.1)d
HINDLIMBS:					
Rotated Towards the Back					
Litter Incidence	N(%)	0	0	0	1(9.1)
Fetal Incidence	N(%)	0	0	0	1(1.1)d
Subcutaneous Hemorrhage Distal Portion					
Litter Incidence	N(%)	0	0	0	1(9.1)
Fetal Incidence	N(%)	0	0	0	3(3.2)**

a. Dosage occurred on days 7 through 19 of gestation.
b. Late resorptions were excluded from all statistical analyses. Observations for these specimens are cited on Table 22.
c. Fetus also had other gross external alterations.
d. Fetus also had other gross external alterations.
** Significantly different from the vehicle control group value (P≤0.01).

PROTOCOL 1501-004: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0252S)

TABLE 12 (PAGE 1): FETAL SOFT TISSUE ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(VEHICLE)	II 0.2	III 0.5	IV 1.0
Litters Evaluated	N	12	14	16	11
Fetuses Evaluated	N	89	104	84	94
Live Fetuses	N	89	104	84	94
Dead Fetuses	N	0	0	0	0
Late Resorption b	N	0	0	1	1
BRAIN SUMMARIZATION:					
Includes Lateral and/or Third Ventricles, Slight, Moderate, Marked and/or Extreme Dilation; Hemorrhagic					
Litter Incidence	N(%)	0	1(7.1)	3(18.8)	3(27.3)
Fetal Incidence	N(%)	0	1(1.0)c	3(3.6)*	6(6.4)**
BRAIN:					
Lateral Ventricles, Slight to Moderate Dilation					
Litter Incidence	N(%)	0	1(7.1)	1(6.2)	1(9.1)
Fetal Incidence	N(%)	0	1(1.0)c,d	1(1.2)	1(1.1)
Lateral Ventricles, Extreme Dilation (Hydrocephaly)					
Litter Incidence	N(%)	0	0	0	1(9.1)
Fetal Incidence	N(%)	0	0	0	1(1.1)
Lateral and Third Ventricles, Marked Dilation (Hydrocephaly)					
Litter Incidence	N(%)	0	0	0	1(9.1)
Fetal Incidence	N(%)	0	0	0	1(1.1)

PROTOCOL 1501-004: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0252S)

TABLE 12 (PAGE 2): FETAL SOFT TISSUE ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(VEHICLE)	II 0.2	III 0.5	IV 1.0
Litters Evaluated	N	12	14	16	11
Fetuses Evaluated	N	89	104	84	94
Live Fetuses	N	89	104	84	94
Dead Fetuses	N	0	0	0	0
Late Resorption b	N	0	0	1	1
BRAIN (CONTINUED):					
Lateral and Third Ventricles, Extreme Dilation (Hydrocephaly)					
Litter Incidence	N(%)	0	0	2(12.5)	1(9.1)
Fetal Incidence	N(%)	0	0	2(2.4)	1(1.1)
Hemorrhagic					
Litter Incidence	N(%)	0	0	0	2(18.2)**
Fetal Incidence	N(%)	0	0	0	2(2.1)
EYE:					
Circumcorneal Hemorrhage					
Litter Incidence	N(%)	1(8.3)	1(7.1)	0	1(9.1)
Fetal Incidence	N(%)	1(1.1)	1(1.0)	0	1(1.1)
LUNGS:					
Intermediate Lobe, Agenesis					
Litter Incidence	N(%)	2(16.7)	4(28.6)	1(6.2)	1(9.1)
Fetal Incidence	N(%)	3(3.4)	7(6.7)	3(3.6)	1(1.1)

teratogenicity *appears to be 0.2 mg/kg/day in the rabbit when given by dermal route.*

29. Segment II Developmental Toxicity Study (Embryo-Fetal Toxicity and Teratogenicity Potential) of RWJ 8203-000 (APS 0.1% Tretinoin Microsponge Gel) in Rabbits. APS Study #BO 289S. Ref. #T49. A GLP study.

Lab Performing Study:

Materials Tested: APS 0.1% tretinoin microsponge gel also named TMG lB 0.1% Gel (lot #30901) and the vehicle (lot #30902).

Species: NZ White rabbits, pregnant females (mated at Breeder's facility)

Age and Weight: 6-7 months old weighing 1.84 to 4.72 kg

Number of Animals/Group: 20

Dose Levels: 0 (control), 0 (vehicle), 0.5 or 1.0 mg/kg/day

Route: Percutaneous

Duration of Treatment: 6 hours/day for 13 days

Skin Condition: Intact

Dose Volume: 0.5 ml (groups 2 & 3) or 1.0 ml (groups 4 & 5)

Methods: The dose (drug formulation or the vehicle) was applied topically as a single daily application from day 7 through 19 of gestation to the clipped back of each rabbit except those in group 1 which were untreated controls. All groups 1 through 4 rabbits were placed in stocks during 6 hours of treatment period following which Elizabethan collars were put on them for 18 hours i.e. until the next dosing. The collars were worn by the animals until gestation day 22. The group 5 rabbits continually wore rabbits from the day of arrival to day

22 of gestation. The treatment sites were very carefully washed before application of the next dose. The fur around the site was examined for any residual microsponge with a magnifying lens, and if any was detected, further washing was carried out. The sites were examined for irritation every day. The dead, sacrificed and aborted animals were necropsied on the day the event occurred.

All surviving animals were sacrificed on day 29 of gestation.

Results:

This study was submitted previously on 3/21/94 to IND and had been reviewed (see attached Pharmacology Review, dated 7/15/94 for details of the study). It is again reviewed here briefly to point out the differences observed in the results when compared to the first rabbit teratogenicity study. This is a pivotal study.

Mortality, Abortions and Premature Deliveries: The Table 2 below shows the results.

Table 2

GROUP Dose (mg/kg/day)		I 0(Con.) 6 Hours	II 0(Veh.) 6 Hours	III 0.5 6 Hours	IV 1.0 6 Hours	V 1.0 24 Hours
Mortality	N(%)	4(20)	2(10)	3(15)	1(5)	0
Gestation Day (GD) Found Dead	N-GD	1-8 1-14	1-10	1-16 1-22[a] 1-27	1-29	0
Gestation Day (GD) Moribund/Sacrificed	N-GD	1-15 1-26	1-13	0	0	0
Abortion	N(%)	0	1(5)	2(10)	2(10)	1(5)
Gestation Day (GD) Abortion Occurred	N-GD	0	1-27	1-22[a] 1-24	1-21 1-23	1-24
Premature Delivery Gestation Day 29	N(%)	1(5)	0	0	0	0

a. Doe [redacted] aborted and died on day 22 of gestation.

The primary and secondary cause of death were the stock and the collars. Highest deaths were

in the sham control group.

Skin Reactions: erythema and desquamation of grades 1 and 2 were reported in almost all drug and vehicle treated dams. None of the sham control animals were affected. Treatment-related microscopic changes included acanthosis, hyperkeratosis and diffuse superficial dermal inflammation that occurred in a dose-dependent manner.

Clinical observations: Observed mostly in dead or moribund sacrificed animals and included dried or mucoid feces, ataxia, impaired or lost righting reflex, decreased motor activity, tonic convulsions, emaciation, dehydration and labored breathing. These were not considered treatment related because they occurred only sporadically.

Necropsy Observations: Parovarian cysts, mottled and/or raised areas in the lungs, pink to dark red lungs and abdominal cavity filled with clear fluid and splenic changes occurred sporadically in does that survived to day 29 sacrifice.

Reproduction Parameters - Maternal:

The results are shown in the table on page 39A. Exclusion of values from does that resorbed all conceptuses or had litters of three or less live fetuses did not alter the results significantly.

Reproductive Parameters - Fetal

These results are presented in the table on page 39B.

None of the maternal or fetal parameters was affected by the treatment. All values were within the historical control values of the Sponsor's laboratory.

Fetal Alterations:

These are shown on page 39C.

The number of fetuses with *any* alteration were significantly increased in groups 2 (30.3%) 3

PROTOCOL 1501-006: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE® GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0289S)

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(CONTROL)	II 0(VEHICLE)	III 0.5	IV 1.0	V 1.0(24 HOUR)
RABBITS TESTED	N	20	20	20	20	20
PREGNANT	N(%)	19(95.0)	19(95.0)	20(100.0)	18(90.0)	19(95.0)
FOUND DEAD/ MORIBUND SACRIFICED	N(%)	4(21.0)	2(10.5)	3(15.0)b	1(5.6)	0(0.0)
ABORTED	N(%)	0(0.0)	1(5.3)	2(10.0)b	2(11.1)	1(5.3)
PREMATURELY DELIVERED	N(%)	1(5.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION c	N	15	16	16	15	18
CORPORA LUTEA	MEAN±S.D.	10.4 ± 2.4	10.7 ± 1.7	9.9 ± 1.6	11.1 ± 2.2	10.7 ± 2.6
IMPLANTATIONS	MEAN±S.D.	8.6 ± 1.9	9.4 ± 2.1	8.3 ± 2.2	9.5 ± 1.8	8.5 ± 2.5
LITTER SIZES	MEAN±S.D.	8.2 ± 1.7	8.2 ± 3.1	6.8 ± 3.2	8.9 ± 2.1	8.0 ± 2.5
LIVE FETUSES	N	123	132	109	134	144
	MEAN±S.D.	8.2 ± 1.7	8.2 ± 3.1	6.8 ± 3.2	8.9 ± 2.1	8.0 ± 2.5
DEAD FETUSES	N	0	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.4 ± 0.6	1.2 ± 2.7	1.5 ± 2.6	0.5 ± 1.1	0.5 ± 1.2
EARLY RESORPTIONS	N	4	16	20	1	2
	MEAN±S.D.	0.3 ± 0.6	1.0 ± 2.8	1.2 ± 2.2	0.1 ± 0.2	0.1 ± 0.3
LATE RESORPTIONS	N	2	3	4	7	7
	MEAN±S.D.	0.1 ± 0.4	0.2 ± 0.4	0.2 ± 0.6	0.5 ± 1.1	0.4 ± 1.0
DOES WITH ANY RESORPTIONS	N(%)	5(33.3)	7(43.8)	7(43.8)	5(33.3)	4(22.2)
DOES WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	1(6.2)	1(6.2)	0(0.0)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	15(100.0)	15(93.8)	15(93.8)	15(100.0)	18(100.0)

a. Dosage occurred on days 7 through 19 of gestation.
b. Doe [redacted] aborted before it died.
c. Excludes values for does that died, were moribund sacrificed, aborted or prematurely delivered.

PROTOCOL 1501-006: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE® GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0289S)

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(CONTROL)	II 0(VEHICLE)	III 0.5	IV 1.0	V 1.0(24 HOUR)
LITTERS WITH ONE OR MORE LIVE FETUSES b	N	15	15	15	15	18
IMPLANTATIONS	MEAN±S.D.	8.6 ± 1.9	9.3 ± 2.1	8.5 ± 2.2	9.5 ± 1.8	8.5 ± 2.5
LIVE FETUSES	N	123	132	109	134	144
	MEAN±S.D.	8.2 ± 1.7	8.8 ± 2.3	7.3 ± 2.8	8.9 ± 2.1	8.0 ± 2.5
LIVE MALE FETUSES	N	62	73	56	60	73
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	51.3 ± 16.7	55.8 ± 20.9	53.0 ± 25.5	43.4 ± 12.2	51.4 ± 21.3
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	40.29 ± 6.62	40.66 ± 4.03	40.18 ± 4.57	41.86 ± 4.64	42.58 ± 5.50
MALE FETUSES	MEAN±S.D.	40.88 ± 6.43	40.74 ± 4.32	40.50 ± 3.55	42.49 ± 5.24	43.30 ± 5.41 [17]c
FEMALE FETUSES	MEAN±S.D.	40.01 ± 6.86	41.00 ± 4.83 [14]d	40.05 ± 6.20 [14]d	41.42 ± 4.63	42.38 ± 5.67 [17]d
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	4.2 ± 6.6	6.1 ± 10.3	12.5 ± 24.6	5.8 ± 10.9	5.8 ± 13.6

[ ] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on days 7 through 19 of gestation.

b. Excludes values for does that died, were moribund sacrificed, aborted or prematurely delivered.

c. Litter [redacted] had no male fetuses.

d. Litters [redacted] had no female fetuses.

PROTOCOL 1501-006: DEVELOPMENTAL TOXICITY (EMBRYO-FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF RWJ-8203-000 (APS 0.1% TRETINOIN MICROSPONGE® GEL) ADMINISTERED PERCUTANEOUSLY TO NEW ZEALAND WHITE RABBITS (SPONSOR'S STUDY NUMBER: B0289S)

TABLE 10 (PAGE 1): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0(CONTROL)	II 0(VEHICLE)	III 0.5	IV 1.0	V 1.0/24 HRS.
Litters Evaluated	N	15	15	15	15	18
Fetuses Evaluated	N	123	132	109	134	144
Live Fetuses	N	123	132	109	134	144
Dead Fetuses	N	0	0	0	0	0
Late Resorptions b	N	0	1	0	0	1
Litters with Fetuses with any Alteration Observed	N(%)	13(86.7)	14(93.3)	14(93.3)	13(86.7)	17(94.4)
Fetuses with any Alteration Observed	N(%)	22(17.9)	40(30.3)**	38(34.9)**	24(17.9)	40(27.8)**
% Fetuses with any Alteration/ Litter	$\bar{X}$ ± S.D.	18.10 ± 11.06	29.75 ± 21.21	38.99 ± 27.51	17.83 ± 11.02	29.56 ± 15.56

a. Dosage occurred on days 7 through 19 of gestation.
b. Late resorptions are excluded from all averages and statistical analyses. Observations for these conceptuses are cited on Table 22.
** Significantly different from the control group value (P≤0.01).

(34.9%) and 5 (27.8%) as compared to sham controls (17.9%). The results were not considered significant because of absence of dose dependency. Also to be noted that the incidences in the highest dose groups (4 and 5) were lower than in the vehicle group.

Fetal Malformations:

Group 1: None

Group 2: One fetus had a rib malformation consisting of an extra left rib fused to the 6th left rib. This fetus had also variation in sternal ossification.

Group 3: No malformed fetuses.

Group 4: No malformed fetuses.

Group 5: Two fetuses from different litters were malformed, one with microphthalmia and small eye sockets, and the other had no tail and related malformations of the lumber and caudal vertebrae (fused). This fetus also had ossification variation in cervical vertebrae.

Fetal Variations:

Gross External: Flexed or rotated paw(s) were reported in two fetuses from different group 1 litters, and one in group 2 fetuses. In a group 4 doe that died on day 29, three fetuses had flexed paws. The Sponsor stated that "these variations are generally classified as deformations attributable to in utero compression."

Soft Tissue: No variations were reported in group 4 fetuses (high dose - 6 hours). One group 3 and two group 5 fetuses had hemorrhagic brain or circumcorneal hemorrhage in the eye. These were attributed to trauma during processing.

Skeletal: Nothing significant or dose-related was described.

Conclusions: All malformations and variations described in this report appear to be unrelated

to the drug treatment because of the following reasons: 1) The incidences were sporadic, 2) there was no dose dependency and 3) all incidence rates were within the historical control values for the laboratory.

Thus, the Sponsor's claim that the NOEL for developmental toxicity in the study was 1.0 mg/kg/day is acceptable. The NOEL for skin irritation was 0.5 mg/kg/day.

29. In Vitro Skin Penetration Studies Using Cell. APS Report #RDR-001. Ref #T50.

Lab Performing Study: The Sponsor

Materials Tested: TMG 1A, TMG 1B and TMG 1C Gels, 0.1% (Tretinoin microsponge gels, 0.1%) Lot numbers are shown in the result section.

Methods: The study was performed to demonstrate equivalency of drug release (percutaneous penetration) in vitro from the three formulations - TMG 1A 0.1%, TMG 1B 0.1% and TMG 1C, 0.1% gels.

The lower chamber of a standard diffusion cell apparatus was filled with receptor phase medium (a % isopropyl alcohol with % BHT). An artificial membrane (Gelman Super 450, 0.45 µm pore size) was mounted on the cell. A measured amount of the test material was placed on the membrane uniformly, and the cell temperature was maintained at 34° C by circulating water. At preset time intervals, the receptor solution was removed (for tretinoin determination) and was replaced with fresh fluid.

Results:

The table 3 on page 42 shows the formulations with their respective lot numbers and the study numbers where these were used.

The release rates of tretinoin from all three formulations were similar indicating that the

bioavailability of tretinoin are similar for the three formulations. Therefore, dermal preclinical studies performed with one formulation to assess systemic toxicity may be valid for the other two formulations.

Table 3

Experiment	Formulation	APS Lot No.*	Batch Size	Manufacturing Site	Partial List of Nonclinical/Clinical Studies Lot Used for (APS Study No.)
a)	TMG IA, 0.1%	10203	10 Kg	APS, Redwood City	B0145S, B0178S
	TMG IB, 0.1%	21201	2200 Kg	PRI/Ortho-McNeil, Raritan	B0222E, B0223E, B0225S, B0232S, B0233S, B0235S, B0236S, B0251S, B0252S
	TMG IC, 0.1%	30601	10 Kg	APS, Redwood City	B0265S, B0266S, B0267S
b)	TMG IB, 0.1%	21201	2200 Kg	PRI/Ortho-McNeil, Raritan	B0222E, B0223E, B0225S, B0235S, B0236S, B0251S, B0252S
	TMG IC, 0.1%	30703	2200 Kg	PRI/Ortho-McNeil, Raritan	B0285S, B0286S, B0287S, B0288S

iii. Studies on Acrylates Copolymer and the Gel Vehicle

30. Acute Oral Toxicity of Acrylates Copolymer in Rats. APS Study #BO 229S; lot #E-140-06-13-L36B. Ref. #T51.

Lab Performing Study:

Species: Sprague Dawley rats

Dose Level and Route of Admn.: 5g/kg orally

Duration of Observation: 14 days.

Results: All animals appeared normal. The LD_{50} was greater than 5g/kg.

31. Primary Dermal Irritation Study with Acrylates Copolymer in Rabbit. APS Study #BO 231S; lot #E140-06-13-L36B. Ref. #T52.

Lab performing Study:

Species: NZ White rabbit

Methods and Results: Methods were similar to those described earlier in this review. The Primary Irritation Score based on the 24 and 72 hour readings was 0.0.

32. Delayed Contact Hypersensitivity Test in Guinea Pigs. APS study #BO 277S. Ref. #T53

Lab Performing Study:

Material Tested: Acrylate copolymer, lot #E140-06-13-L79AB

Species: Young adult guinea pigs, Hartley derived; males and females

Weight Range: 300 - 500 gms

Supplier:

Number of Animals/Group: 20 (10/sex). 6 (3/sex) for positive control group

Methods:

a. Dosage Selection: A 100% concentration, and 75%, 50% or 25% concentrations (w/w) in corn oil were used to determine the highest non-irritating and mildly irritating concentrations of the test material. 0.5 gm of a test material was placed on clipped back of a guinea pig under occlusion for 6 hours. Erythema was scored at 24, 48 and 72 hours.

Based on the results, the 100% concentration was used during the induction and the challenge phases.

b. Induction phase: This consisted of application of a 0.5 gm of test material under occlusion for 6 hours, every week for three weeks. Positive and naive control groups were also included.

c. Challenge: After a rest period of two weeks, the animals were challenged with either a 100% concentration test material or

Results:

The test material was not a sensitizer even at 100% concentration. The positive control showed the expected irritation.

33. Primary Eye Irritation Test of TMG 1A Vehicle in Rabbits. APS Study #BO 142S. Lot #10208. Ref. #T54.

Methods: All methods were similar to other acute eye irritation tests reviewed earlier.

Results:

A minimal conjunctival irritation in 2/6 rabbits was reported at 24-hour reading. All signs of irritation disappeared within 48 hours. No corneal or iris involvement was seen. The average irritation score was 0.7 at 24 hours and zero at 48 and 72 hours. The material was not a primary eye irritant.

34. Primary Eye irritation Test with TMG lB Vehicle in Rabbits. APS Study #BO 183S. Lot #20108. Ref. #T55.

This study was performed by the The methods were similar to other ocular studies in this review.

Results:

Minimal conjunctival redness which cleared by 72 hours was reported in 1/6 animal. No corneal or iris involvement was seen. The material was considered to be nonirritant in this rabbit eye test.

35. Primary Eye Irritation Test with Acrylate Copolymer in Rabbits. APS Study #BO 230S. Lot #E-140-06-13-L36B. Ref. #T56.

The study was performed by the by methods similar to other ocular studies reviewed in this document.

Results:

Minimal conjunctival redness in 4/6 rabbits was reported. All eyes cleared by 72 hours. The material was not considered to be a primary eye irritant.

36. Health and Environmental Effects Profile for Methyl Methacrylate.

A report prepared by the US EPA. Ref. No. T61.

The conclusion was that "an Acceptable Daily Intake (ADD) , defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for methyl methacrylate is 5.3 mg/day for oral exposure.

Carcinogenicity: Two reports by and one report by Borzelleca et al. indicated that methyl methacrylate was not a carcinogen in Wistar rat (drinking water) or Fischer rat (inhalation). IARC review (1979) cited a study by Oppenheimer et al. (1955) who painted 10 Wistar rats on the back of the neck with methyl methacrylate 3 times/week for 4 months and then observed the animals for the remainder of their lifespan. "No local tumors were observed."

Mutagenicity: Ames' S. typhimurium test for mutagenicity was uniformly negative. In bone marrow cytogenicity tests after inhalation exposure, methyl methacrylate at 1000 and 9000 ppm was mutagenic, but not at 100 ppm (409 mg/m^3).

In bone marrow micronucleus test and in a dominant lethal assay negative results were obtained.

Poss et al. (1979) reported that methyl methacrylate was mutagenic in a forward bacterial mutation assay, using S. typhimurium strain TM677 in the presence of S9.

Teratogenicity: In a rat (Sprague-Dawley) teratogenicity study, a group of 5 pregnant rats were given i.p. doses of methyl methacrylate on gestation days 5, 10 and 15. The incidences of gross abnormalities of fetuses were 2.3% at 0.1328 mg/kg, 8.0% at 0.2656 mg/kg, and

16.7% at 0.4427 mg/kg dose levels. The most common abnormality was hemangiomas, but the specific incidence was not reported.

In a retrospective epidemiologic study of male workers in a plastic manufacturing plant in the death from colorectal cancer was greater than the expected mortality from such cancer. However, analysis of data could not establish any causal relationship. Further analysis is in progress.

37. *In Vitro* Skin Penetration of APS Microsponge Gel. APS Study #BO 293S. Lot #40308. Ref. #T71.

Lab Performing Study:

Materials Tested: As described in the report:

X) Tretinoin MICROSPONGE Gel vehicle with placebo tretinoin (MICROSPONGE polymer containing tritium labeled ethylene glycol dimethacrylate (^{3}H-EGDMA). Lot #40308)

Y) Tretinoin MICROSPONGE Gel vehicle with placebo tretinoin (MICROSPONGE CONTAINING TRITIUM labeled methyl methacrylate (^{3}H-MMA). Lot #40309)

Z) Tretinoin MICROSPONGE Gel vehicle with ^{3}H-MMA/EGDMA (MICROSPONGE polymer. Lot #40310)

Methods:

Transdermal penetration was measured by the method described by Yeung et al. (1984), in

Transdermal Delivery of Drugs Vol II, Kidonius and Berner, Eds, CRC Press, Boca Raton, Fla.

Excised full-thickness human skin was affixed to the bottom of the donor chamber with the epidermal side facing the top of the donor chamber, and was then mounted on the receptor chamber. The material was then placed on the epidermal surface, and phosphate buffer, pH 7.4 was used as the receptor solution.

Results:

APS microsponge polymer particles did not penetrate through the skin samples as evidenced by the absence of radioactivity in the receptor solutions, absence of any significant amount of radioactivity in the dermis compartment, and from autoradiography which showed that microsponges and microsponge-derived radioactivity were confined to the surface of the stratum corneum. Three percent of the applied dose was recovered from the epidermal compartment.

Some monomer penetration was observed with tritium-labeled EGDMA (6% of the applied dose in 24 hours) , but not with MMA. The flux for EGDMA was estimated to be 0.036 $\mu g/cm^2/hr$.

It was also shown that when there was measurable percutaneous permeation, the material could be quantified in both the dermal and epidermal compartments.

38. Ames Mutagenicity Test with Acrylate Copolymer. APS study #BO 165S. Lot #E104-02-12-L01AA. Ref. #T79

Lab Performing Study:

Material Tested: Acrylate copolymer (Assay #915484)

Methods: In a dose range-finding study, it was found that 5000 μg/plate resulted in some precipitation but not toxicity. Therefore, 5000 μg/plate was used as the maximum dose. The test was performed using Salmonella typhimurium tester strains TA97, TA-100, TA 1535, TA 1537 AND TA 1538 in the presence and absence of microsomal enzymes prepared from aroclor-induced rat livers.

Results:

No positive response was observed with any of the tester strains with or without the presence of aroclor-induced rat liver microsomal enzymes. No significant toxicity was reported, although some precipitation was observed.

39. References T80 - T90 are R.W. Johnson's toxicity studies on their retinoic acid formulations. All such studies have been reviewed previously in connection with the respective NDAs or INDs.

40. ADME Studies

a. Absorption and Pharmacokinetics:

i. Tretinoin Microsponge Gel 0.1% with ^{3}H-labeled RWJ 8203-000 (tretinoin)

Lab Performing Study:

Species: i) Male CD-1 mice (APS Study #BO 245S), ii) male Sprague-Dawley rats (APS Study #BO 247S), iii) male New Zealand White rabbits (APS Study #BO 248S) and iv) male Beagle dog (APS Study #BO 246S).

Methods:

Groups of animals were administered topically TMG IB 0.1% Gel on the shaved back with occlusion except mice in which the treatment sites were not occluded. Blood was collected at 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72 hours following drug treatment. In rat study, last blood collection was at 24 hours post-treatment. Total radioactivity was determined in each sample and was expressed as ng.eq/ml. In all species only male animals were used. Thirty two mice, 9 rats, 4 rabbits and 4 dogs per group were utilized. Dose levels were 1, 2 or 5 mg/kg in the mice and rats, and 0.2, 0.5 or 1.0 mg/kg in the rabbit and dog studies. Rats, rabbits and dogs were also made to wear Elizabethan collar.

Results:

i. Mice (Ref #D4).

Dose Groups:

Group No.	Treatment	Dose Level mg [^{3}H]Tretinoin per kg	Dose Level (g(gel)/kg)	Number of Animals
1	[^{3}H]RWJ-8203-000 0.1% Gel	1	1	32M
2	[^{3}H]RWJ-8203-000 0.1% Gel	2	2	32M
3	[^{3}H]RWJ-8203-000 0.1% Gel	5	5	32M

These doses are approximately 100 to 500 times the proposed human clinical dose of 0.01 mg/kg.

Results:

At all three dose levels C_{max} was reached at 4-hour post-dose, and were 475, 568 and 1840 ng-eq/ml at the low, mid and high doses, respectively. These values are about 10 times higher than those reported for restrained mice (see Appendix D results below).

The plasma concentration declined until 12 hours post dose, and remained about constant until 24 hours (the last sampling time). At all dose levels at any particular time point, the total mean

radioactivity in plasma or blood, expressed as percentage of administered dose, was less than 2.5%. The total percutaneous absorption of radioactivity over a period of 24 hours was approximately 6% at all dose levels.

The plasma concentrations of total radioactivity (ng-eq. of the drug) are shown in the table below.

Mean (SD) Concentrations of Radioactivity in Plasma of Male Mice			
	Dose of tRA (mg/kg)		
Concentration (ng-eq./ml)	1.0	2.0	5.0
C_{4hr}	475*	568 (350)	1840 (410)
C_{24hr}	107 (14)	163 (27)	601 (517)
* n=1 (insufficient sample for analysis from 3 mice)			

Radioactivity was measurable in plasma at half hour after administration of 1 and 5 mg/kg doses, and rapidly reached maximum (C_{max}) at 4 hours in a dose-dependent manner. The observed C_{max} values are about 10 - 100 fold higher than those values obtained in the rat, rabbit and dog reported later in this review. Apparently, there was some oral ingestion because the mice were not restricted in any way. Also, the application sites were not occluded.

In support of this possibility, APS had a pilot drug metabolism study performed in mice (Study No. A 94-04) by the and has been submitted as Appendix D to APS study #BO 235S (3-month toxicity study) as well as

Reference D5 in the ADME Section reviewed below.

Determination of Total Plasma Radioactivity in Mice Following Topical Administration of 0.1% Tretinoin Microsponge Gel. (RWJ Study #DMP A94-04. APS Ref. #D5.)

In this study tretinoin gel. 0.1% (lot no. 30803) was applied topically to the clipped back of female CD-1 mice. One group of animals wore Elizabethan collar, and a second group was anesthetized with pentobarbital. A control group of animals remained unrestricted in their cages. Total radioactivity expressed as nanogram equivalent tretinoin per ml was determined in plasma samples collected at 3 or 4 hours post dose from these animals.

Mean ± SD of tretinoin concentrations in the control (unrestricted group), the group with the collars, and the anesthetized group were 384.1 (±334.3), 33.6 (±22.7) and 3.4 (±2.1), respectively.

These results are consistent with the Sponsor's explanation for observed high blood levels of tretinoin from dermal application in mice were due to oral ingestion.

ii. Rat (Ref. #D7)

The mean plasma concentrations of tretinoin (ng.eq) are shown in the table below.

Mean (SD) ng-eq. Concentrations of Tretinoin in Plasma of Male Rats			
	Dose of tretinoin (mg/kg)		
Concentration (ng-eq./ml)	1.0	2.0	5.0
C_{4hr}	5(3)	9(1)	16(1)
C_{24hr}	66(86)	31(9)	34(15)

Dr. Mildred Christian, President of Argus International, Inc., where these studies were performed, as a Consultant to the Sponsor has made a rather exhaustive review of hydrocephaly and other malformations in rabbits using in-house and published data. She has made a rather strong case for oral ingestion as the cause for the adverse findings in the first rabbit study. The toxicokinetic data also support this hypothesis. Accepting the results of the first rabbit study as equivocal, pregnancy category C may be assigned to this drug product.

In Section IV. Appendix 1 (NDA Vol. 1.13, page 05 - 00325) the Sponsor has submitted a request for waiver of carcinogenicity and photocarcinogenicity studies citing existing data for tretinoin. This database was also submitted as amendments (#s 29 and 30) to the IND (dated 11/15/94 and 12/19/94, respectively). In a pre-NDA meeting held on November 3, 1992 at FDA, it was decided that the Sponsor could use the same database available for Renova, and would accept similar labeling as that of Renova with respect to Photocarcinogenicity. The carcinogenicity issue was to be handled later.

Although, tretinoin itself is not a primary carcinogen, the possible presence of monomers (MMA and EGDMA) was the complicating factor. It was decided that the Sponsor will submit waiver request with justification, which on examination if unsatisfactory, we reserved the right to ask for phase IV dermal carcinogenicity study.

The safety of the acrylates copolymer has been evaluated in the NDA Vol. 1.12. page 05-00281. All the Multidose studies referred to in this section are the same studies which tested

Detectable plasma radioactivity was reported at all dose levels at 4 hours post dose that plateaued to a fairly constant level by 24 hours. Although there was a dose related increase in plasma radioactivity, the changes may not be meaningful because of great inter-animal variability.

At all three dose levels, total mean radioactivity in blood, expressed as percentage of dose, was less than 0.3% at any time point indicating low level of systemic availability from a dermal application of 0.1% tretinoin microsponge gel to rats.

iii. Rabbit (Ref. #D8).

The results of plasma concentrations are shown in the table below:

Mean (SD) Concentrations of Radioactivity (ng.eq. tretinoin) in Plasma of Rabbits			
	Dose of Tretinoin (mg/kg)		
Concentration (ng-eq./ml)	0.2	0.5	1.0
C_{4hr}	1 (2)	5 (2)	5 (2)
C_{24hr}	3 (4)	6 (1)	7 (4)
C_{48hr}	5 (5)	8 (1)	13 (11)
C_{72hr}	7 (8)	11 (4)	15 (14)

Slight increases in plasma concentrations with increasing dose and with time (measured up to 72 hours) are evident, with a plateau seen between 4 and 24 hours, but large variability is also seen.

The maximum mean systemic availability was less than 0.2% of the applied dose.

For toxicokinetic results see the Segment II reproduction studies.

IV.Dog (Ref. #D 11)

The mean plasma concentrations of radioactivity (ng.eq. t-RA) are shown in the table below.

Mean (SD) Radioactivity Concentrations in Plasma of Dogs			
	Dose of tretinoin (mg/kg)		
Concentration (ng-eq./ml)	0.2	0.5	1.0
C_{24hr}	1 (3)	BLQ	1 (3)
C_{48hr}	1 (1)	0 (1)	12 (19)
C_{72hr}	6 (9)	1 (1)	7 (6)
BLQ: all values less than twice background. Values less than twice background treated as zero for calculation of mean (SD).			

In contrast to mice, rat or rabbit, radioactivity was not detected in the plasma of dog before 24 hours post-dose. Also, plasma concentrations did not increase with increasing doses in a consistent manner.

The maximum mean systemic availability was less than 0.3% of the total applied dose.

These experiments showed that the relative dermal absorption of tretinoin from TMG 0.1% gel was in the order: rodents>dogs≈rabbits.

Note: The Sponsor has reported that the relative dermal penetration of tretinoin "from the TMG 0.1% increases in the order: rodents > rabbits > dogs." This statement is not correct.

41. Toxicokinetic Studies (from the two rabbit developmental studies presented earlier)

A. Segment II Reproduction Study in Rabbits (APS Study No. BO 252S; Ref. #D9 & T48)

The study has already been reviewed earlier (item #28) in this review. Only the toxicokinetics portion is discussed here.

Methods: Blood samples were collected from the first 6 rabbits in each dose group at various time points (see the results table). The analysis was done at the

by a reverse phase gradient HPLC method. The lower limit of quantitation (LLOQ) was established as 5 ng/ml.

Results

These are shown in the table on page 55A. (This is the same table as the one on p35A).

Blood samples were collected at 4 hr and 24 hr postdose based on a separate study (APS Study #BO 248S; Ref. #D8) that utilized tritiated APS 0.1% gel (item # 38).

In the current study, the concentrations of tretinoin and its metabolites were generally below 5 ng/ml, the reported range of endogeneous concentrations in rabbits. When measurable concentrations were detected in a few animals, the results were not consistent. Thus, in one animal tretinoin was detected in plasma 24 hr after the first and thirteenth dose but not after the twelfth dose, suggesting sporadic oral ingestion.

It is to be noted that the t-RA concentration of 15.2 ng-eq./ml found after the first dose of 1 mg/kg, is more than twice the mean value of 7 ng-eq./ml for total plasma radioactivity at 24 hours obtained after a single application of ^{3}H-t-RA (see review of single dose rabbit study reported earlier. Item #28). This lends support to the possibility of sporadic oral ingestion by

Concentration of Tretinoin (RA) and Its Metabolites
In Individual Rabbits After Dermal Administration of 0.1% APS Microsponge Gel
(APS Protocol B-0252S)

Group	Dose (mg/kg/day)	Day	Time (hr)	RA[a,b] (ng/mL)	CIS-RA[a,c] (ng/mL)	OXO-RA[a,d] (ng/mL)	CIS-OXO-RA[a,e] (ng/mL)
I	0.00	GD-7*		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
II	0.20	GD-7		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
		GD-19		-	-	-	-
III	0.50	GD-7				-	-
		GD-19				-	-
		GD-19				-	-
		GD-19				-	-
IV	1.00	GD-7					
		GD-19					
		GD-19					
		GD-19					

* GD = Gestational Day. GD-7 = 1st dose; GD-19 = 13th (last) dose.

[a] (-) Lower limit of quantitation (LLOQ) for RA and metabolites is 5 ng/mL. No value indicates all samples in that group were below 5 ng/mL. Blood was sampled from 6 study animals/group.

[b] All-trans-retinoic acid

[c] 13-Cis-retinoic acid

[d] All-trans-4-oxo-retinoic acid

[e] 13-Cis-4-oxo-retinoic acid

[f] n=1

[g] Mean ± standard deviation (n=4)

the animals wearing collar alone as opposed to collar and occlusive dressings.

A no-effect dose level in this study was 0.2 mg/kg/day.

B. A Second Segment II Reproduction Study in Rabbits (APS Study No. BO289S; Ref. #D10, T49; Item #29.

Methods:

This study also has already been reviewed (see item #29). The NOEL for developmental toxicity was reported to be 1.0 mg/kg.

Following collections of pretreatment blood samples from rabbits on GD7 post-dose samples were taken at 2, 4 and 24 hours after the final application on GD19, and then again on GD29 (during terminal sacrifice) from all animals. The analysis was done by the same method as in A above.

Results

These are presented on the next page (p 56A).

Mean pretreatment (endogenous) concentrations of tretinoin ranged from below 5 ng/ml (LLOQ) to 7.32 ng/ml. Measurable concentration was present in 15/80 does.

In the majority of the treated dams plasma retinoic acid concentrations were below LLOQ. When quantifiable, there was no dose-dependency for the plasma concentrations of t-retinoic acid. The highest mean concentration reported was 31.0 ng/ml in group IV animals at 4 hours post-dose. However, there was one dam in this group with a high value of 188.0 ng/ml. The Sponsor stated that "in light of extreme measures taken to avoid oral ingestion" the high value "indicates that the possibility of oral ingestion may still have been present."

No developmental abnormality was seen in this doe.

TABLE 1

Tretinoin Concentrations in Rabbits Above 5 ng/mL After Dermal Administration of 0.1% APS Microsponge Gel (Argus Protocol No. 1501-006)

Group	Dose (mg/kg/day)	No. of Animals on Study	Day	Time (hr)	Mean[a] (ng/mL)	S.D.[b]	No. of Animals[a]
I	0.00	20	GD-7*		5.67	0.06	3
			GD-19		5.54	0.58	4
					7.32	2.41	5
					BQL[c]	N/A[e]	17
			GD-29		BQL	N/A	16
III	0.50	20	GD-7		7.28	3.05	6
			GD-19		ND[d]	ND	ND
					7.93	4.12	6
					7.76	4.45	3
			GD-29		6.00	N/A	2
IV	1.00	20	GD-7		5.80	0.76	3
			GD-19		ND	ND	ND
					30.95	63.68	8
					12.6	14.64	5
			GD-29		BQL	N/A	17
V	1.00	20	GD-7		6.10	1.10	3
			GD-19		6.92	1.24	7
					7.33	1.87	7
					10.8	N/A	1
			GD-29		5.04	N/A	1

* GD=Gestational Day. GD-7=1st dose; GD-19=13th (last) dose.
[a] Animals with measurable concentrations of tretinion, i.e. above BQL of 5 ng/mL; all other animals had concentrations of tretinoin below 5 ng/mL.
[b] S.D. = Standard deviation
[c] BQL = Below the lower limit of quantitation, i.e. 5 ng/mL
[d] ND = Not determined
[e] N/A = Not applicable

Reviewer's Note: The most sensitive period to retinoic acid's developmental effects is the very early organogenesis period. The blood sample from the animal with 188.0 ng/ml try plasma concentration was collected on GD19. Thus, the absence of any fetal malformations is not surprising.

None of the pretreatment samples had any quantifiable amount of active metabolites (4-oxo-try, 13-cis-RA, and 4-oxo-13-cis-RA). Among the treated animals, 2 group IV and 3 group V dams had measurable plasma concentration of 13-cis-RA, and 2 group V dams had quantifiable amount of 13-cis-4-0xo-RA.

Reviewer's Note: Oral ingestion as well as enhanced percutaneous absorption due to washing procedures after each treatment may have caused the high plasma concentrations observed in some animals.

42. Limited Tissue Distribution Report #DMR 1404 RWJ). Ref. #D32.

This report was generated by from single administration of ^{3}H-tretinoin to Long-Evans Rats. the study was performed in connection with the drug "Retin-A" and "Renova".

For male rats, the highest concentration of radioactivity was in the body fat (9.1% of the administered dose at 4 hours) which was followed by liver (7.5%), plasma (3.8%) and bone marrow (1.3%.).

At 72 hours, 51% of the radioactivity was excreted via feces whereas 12% was excreted

through urine.

The mean apparent elimination half-lives of radioactivity were 21.7 hours for male plasma, 19.1 for female plasma, 32.4 hours for male bone marrow, 12.7 hours for testes and 37.4 hours for ovaries. No unusual accumulation in any of the tissues examined was reported.

43. Reference Number D44 describes the method validation for the determination of retinoic acid and it's metabolites in plasma samples from rat, mice, rabbit, dog and humans, done by the

The method was validated at a concentration range of 5-1000 ng/ml of mouse plasma using 0.5 ml of sample.

44. Safety Evaluation Of MMA and EGDMA (NDA 20-475, Vol. 12, p.05-00281).

IND amendments 28 through 31 were assigned to Dr. Sheevers and then reassigned to me again. In these amendments, the Sponsor had submitted their safety evaluation of the two monomers, MMA and EGDMA, used in the synthesis of Microsponge copolymer. These data have again been submitted in the NDA and are briefly addressed.

Transdermal penetration across excised human skin was studied *in vitro* for tritium-labeled Microsponge, MMA and EGDMA. There was no significant transdermal penetration of either the Microsponge or MMA when measured either by radioactivity or autoradiography.

When 35 mg of a gel was applied to 7 cm^2 of skin, about 7% of the applied dose was absorbed over 24 hours.

It has been reported in the literature that MMA on prolonged topical application or given in

been reported to be mutagenic and teratogenic. No information is available on the carcinogenic activity of EGDMA. According to manufacturing specifications, the maximum EGDMA concentration in TMG 0.1% gel is 1.85 ppm. Assuming a 5% absorption in a 50 kg man, Dr. Hill (a Consultant to the Sponsor) has shown that the potential exposure is over 3 billionth of the i.p. LD_{50} in rat (2800 mg/kg). This indeed is a very low level of exposure

45. Miscellaneous

The Sponsor has submitted numerous publications on pharmacology and toxicology of retinoids in general, and on all-trans-retinoic acid in particular. A few of these studies relevant to dermal application of try (not the NDA formulation) are very briefly reviewed.

a. Pharmacokinetics of Tretinoin Following Cutaneous Application, Brode, E. et al., Arzneim. Forsch., 24, No. 3, p1188(1974).

Tritium-labeled tretinoin in a gel base was applied to the shaved back of male SD rats as single or multiple (8 daily) dose. The rate of percutaneous absorption was about constant between 10 and 24 hours after single application, and the maximum penetration amounted to 5-6% of the applied dose in 24 hours. Multiple application slightly increased the 24-hour penetration (6-7% of the dose). In man, only a maximum of 0.5% of the applied dose was found to be absorbed in a 24 hour period after the drug application.

b. Systemic Absorption of Retinoic Acid, Franz, T. J. and Lehman, P. A., J. Toxicol.-Cut. & Ocular Toxicol. 8(4), 517 (1989-1990).

Retin-A cream (0.05%) was mixed with C^{14}-labeled tretinoin, and was applied topically on

the shaved backs of Rhesus monkeys (6) for 24 hours (no occlusion), and the urinary excretion of radioactivity was followed over a period of 7 days. One group of monkeys was pretreated for 2 weeks with try to induce irritation before application of the radioactive drug. Two groups of humans, one with normal skin and the other pretreated with try to induce irritation (slight erythema and scaling), were treated on the face with Retin-A cream for 10 hours. The urinary excretion of radioactivity was then followed.

The tretinoin absorption in the monkey was reported to be 9.6% and 48.3% of the dose in the normal and pretreated animals, respectively. In humans, the corresponding values were 5.3% and 7.2% for normal and dermatitic skin, respectively.

Reviewer's Note: It appears that monkey is not a suitable model for percutaneous absorption of trans-retinoic acid in human, or oral ingestion occurred in the dermatitic monkeys.

c. Embryotoxicity and Teratogenicity of Topical Retinoic Acid. Heinz Nau, Skin Pharmacol., 6(suppl 1), 35 (1993).

In this review article, the Author has evaluated the teratogenic risk of topical all-trans-retinoic acid (tretinoin). Several difficulties with the interpretation of the results obtained after topical application of tretinoin have been pointed out. These are:

1) Maternal toxicity due to gross skin irritation and other lesions which may cause induction of supernumerary ribs or fetal weight loss.

2) The severe dermal lesions caused by topical tretinoin may greatly increase percutaneous absorption with consequent systemic toxicity. Franz and Lehman (J. Toxicol. 8:517, 1990) has

shown in monkey that the absorption of try through the dermatitic skin was 5-fold higher than through normal skin. A four fold increase has been reported in the rat. In contrast, no such differential absorption was seen in humans.

3) Oral intake through licking or ingestion of feces may contribute to systemic exposure.

4) Considerable species variation in dermal absorption is known to exist. Mouse, rat and rabbit skins are more permeable than human skin. Therefore, dermal absorption studies in rodents will overestimate the human systemic exposure from such applications.

Because of these reasons, a direct evaluation of "the embryotoxic potential of topical all-trans-retinoic acid is difficult." A teratologic risk assessment is severely limited by dose limitation due to maternal toxicity.

The following human risk assessment for topical all-*trans*-retinoic acid has been made by the Authors. "If a daily dose of 20 g of 0.05% preparation (10 mg of all-*trans*-retinoic acid) is applied to the human skin for therapeutic or cosmetic purposes, and a systemic bioavailability of 10% is assumed (probably overestimated), then 1 mg of all-*trans*-retinoic acid is expected to reach the central circulation daily. Assuming a body weight of 65 kg, the daily absorbed dose would be 0.015 mg/kg. This dose is about 30-fold lower than the lowest teratogenic dose of 13-*cis*-retinoic acid reported to result in a teratogenic response in the human." In support of such conclusions a publication by Franz et al. (J. Invest Dermatol, 100:490A, 1993) has been quoted. When 150 mg of a 0.025% tretinoin gel was applied to 50 cm^2 of the face of 8 normal volunteers for 27 days followed by a day 28 application of a tritiated tretinoin gel, 4.3% of the last dose as measured by radioactivity was absorbed. Plasma levels peaked at 34

pg equivalents/ml at 10 hr after the last application. This value is, at least, 30-fold below endogenous plasma concentrations found in man.

Reviewer's Note: More of such reasonings is discussed in the evaluation section.

Evaluation:

The drug product for this application is Tretinoin Microsponge^{R} Gel, 0.1% or TMG, 0.1% Gel. The active ingredient in this product is a retinoid called tretinoin which is also variously known as trans-retinoic acid, all-trans-retinoic acid or vitamin A acid and is usually abbreviated as t-RA, trans-RA or ATRA. The proposed indication is for the treatment of acne vulgaris.

The efficacy of tretinoin in the treatment of acne is well established. Retin-A Cream with 0.1% tretinoin have been in the market for topical treatment of acne vulgaris for over 25 years. It is also available as gel, and solution, and at lower concentrations. One of it's cis isomers, 13-cis-retinoic acid has been approved for the oral treatment of severe recalcitrant cystic acne.

Several factors such as seborrhea, follicular hyperkeratinization, androgens, bacterial colonization and cutaneous inflammation have been implicated in the pathogenesis of acne. Increased rate of sebum production is believed to be one of the most important factor. Although the exact mechanisms of action is unknown, it is generally thought that the inhibition of sebaceous glands and keratinization by retinoic acids are responsible for their

therapeutic effects in acne.

Retinoids affect many aspects of cell differentiation and proliferation in the skin primarily due to changes in gene expression. It is now hypothesized that such changes are mediated through the interaction of retinoids with a family of nuclear receptors, RARs and RXRs. A number of genes have been shown to have specific binding sites for these receptors on DNA, termed retinoic acid response elements (RAREs). This strongly suggests that interactions of ligand-bound receptors with RAREs directly modify the rate of transcription of target genes. The presence of one of the subtypes of these receptors, gamma-RAR predominantly in skin suggests that this receptor is an important mediator of cutaneous effects of tretinoin (Giguere, V. Retinoic Acid Receptors and Cellular Retinoid Binding Proteins: Complex Interplay in Retinoid Signaling. Endocrine Rev.15(1):61, 1994).

The drug product (TMG 0.1% Gel) is a novel formulation in which the active moiety tretinoin has been incorporated into porous acrylates copolymer microspheres (Microsponge) in an aqueous gel without using any oils or organic solvents. "Like a true sponge, each MICROSPONGE (copolymer of methyl methacrylate and ethyleneglycol dimethacrylate) particle consists of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface." The Sponsor claims that tretinoin is entrapped on the surface and within the MICROSPONGE polymer.

At various stages of development, minor changes in the formulation were made. These

formulations have been called TMG 1A, 0.1% Gel (original IND), TMG 1B, 0.1% Gel (used for all pivotal preclinical studies) and TMG 1C 0.1% Gel (the clinical formulations to be marketed). These formulations are shown in the Appendix 1. The NDA formulation (TMG IC 0.1% Gel) differs from the other two in having added and replacement of

Both *in vitro* release studies (chemistry section) and clinical cumulative irritation studies indicated that the minor formulation changes had no significant effect on the release or pharmacologic effect (irritation) of tretinoin. Each of the three TMG formulations were mild dermal irritant, being more irritant than the vehicle but less than the marketed Retin-A.

No pharmacology studies have been performed with the TMG formulations. On the other hand, hundreds of scientific publications are available on the pharmacologic and toxicologic effects of tretinoin, the active ingredient. These studies have been reviewed in connection with the various INDs and NDAs for this active ingredient. The most recent review of these data have been made in connection of NDA 19,963 (Renova).

A series of acute oral (5g/kg) toxicity studies was performed in rats with TMG 1A, 1B and 1C 0.1% Gel and Retin-A Cream 0.1%. All formulations were considered nontoxic.

Because of the extensive toxicity data on tretinoin, available in the literature and in-house, it was decided that two 3-month toxicity studies in two species, one non-rodent, would be sufficient to establish preclinical safety of the drug product. Accordingly, the Sponsor has performed two such studies in mice and dogs following 4-week dermal range-finding studies in these species. Typical retinoid-induced toxicities were seen in the studies.

In mice, primary toxic effects seen were dermal irritation of various degrees, and

lymphoid/hematopoietic changes such as increased number of circulating leucocytes in males, and lymphoid hyperplasia in the spleen and lymph nodes, and thymocyte depletion of the thymus. Dermal lesions included minimal to moderate hyperkeratosis, acanthosis, parakeratosis, dermatitis and microabscesses of the stratum corneum. Testes and ovary weights were decreased significantly as compared to controls, but no microscopic changes were reported. These changes were not seen in the dog.

In dog, skin lesions were milder and were mostly reversible. Microscopic lesions at the treatment site skin included minimal to moderate acanthosis, hyperkeratosis, and stratum corneum pustules in a few animals.

One of the most significant toxicities of retinoic acids is embryotoxicity and teratogenicity when administered systemically. Although it is generally assumed that topical tretinoin is not teratogenic, the Sponsor was asked to perform segment II reproductive studies in two animal species because of a new formulation containing a new polymer (Microsponge^{R}).

The rat study did not produce any terata. In rabbits, however, dermally applied tretinoin induced hydrocephaly and cleft palate in fetuses at high doses in spite of use of Elizabethan collars (24 hrs/day) to prevent oral ingestion.

The Sponsor, therefore, repeated the rabbit study taking extra precautions to prevent oral ingestion. In this second rabbit study, topical tretinoin was not teratogenic at doses 50 and 100 times the clinical dose of 0.01 mg/kg (500 mg TMG 0.1% to a 50 kg human).

The sponsor's explanation for such contradictory results is oral ingestion by animals.

These developmental studies have been extensively reviewed and evaluated in detail in connection with the review of IND for this Application (see appendix 2).

the safety of the drug product. Groups of animals that received the copolymer vehicle only were included in these studies.

The copolymer "Microsponge" was not a primary skin or eye irritant, and was not a sensitizer in guinea pigs. In subchronic (90-day) dermal studies, it was only mildly irritant in rabbits and nonirritant in dogs. ~~The copolymer was not a primary ocular or dermal irritant, and it was not a sensitizer in guinea pigs~~. In 3-month studies, it was a mild skin irritant in rabbit and was not an irritant in dog. The copolymer with the possible monomer contaminant was not a mutagen in Ames test for mutagenicity. In addition, the two 3-month dermal toxicity studies did not produce any significant toxicity.

The possible maximum systemic absorption of the monomer EGDMA is miniscule. It is not a mutagen in the Ames test, negative in *in vitro* cell transformation assay. At high concentrations, however (>750 μg/ml), it gave positive response with metabolic activation in the cell transformation study. In comparison, the possible maximum concentration of EGDMA in plasma of a 50 kg person has been calculated to be 0.000002 μg/ml. Thus, a large margin of safety exists for the proposed use of the Microsponge. As reported earlier (NDA 20-481, Vol. 1.13, p.136-137 and Vol. 1.19, p. 334-409), microsponge (with <25 ppm EGDMA) itself was negative in micronucleus assay.

A variety of copolymers produced from EGDMA are already present in many commonly used products such as cosmetics, contact lenses and artificial replacement organs. (Patty's Industrial Hygiene and Toxicology, 3rd. Ed. Vol 2A, p.2298).

Based on the above reasoning, it is concluded that a carcinogenicity study of the new drug product containing Microsponge is not necessary. (i.e., at this time).

5/5/96

Discrepancies and deficiencies:

Although these are mostly minor, they did cause difficulties and confusions resulting in slowing down the review process.

a. Several studies have been submitted in more than one place without properly explaining and identifying the studies. Thus in Vol. 1.16 of this Application a 3-month toxicity study in mice has been variously identified as Ref. #T24, BDL Ref, #43404 or APS Study #BO 235S. In the Toxicokinetic Section, a reference has been made to some data (RWJ Study # DMP 94-04) in Attachment 2. Actual data was present in Appendix D to this Attachment.

b. The same Appendix D (actually a separate study) has also been submitted in Vol. 1.23 as Ref. #D4, APS Study #BO 245S. The RWJ Study has again been submitted as Appendix D, although it has been titled as "Appendix to Study APS BO 235S." To make things more confusing, the Attachment 2 has been identified both as APS Study No. BO 235S (Vol. 1.16, p 05-01789) and as APS Study No. BO 245S (Vol. 1.16, p 05-01790).The complete 3-Mo study has again been submitted as Ref. #D6 in the ADME Section with APS Study #BO 245S (Ref. #D4) as an attachment 2.

b. The two rabbit teratogenicity studies have also been submitted twice, once as toxicology studies (Ref. #s T48 and T49), and again as ADME studies with Ref. #s D9 and D10.

c. Formulation nomenclature is very confusing. For example, t-retinoic acid 0.1% gel has been used to describe both the drug product and the vehicle. Similarly, vehicle meant both with and without the presence of Microsponge.

Recommendations:

1. The Sponsor must identify clearly each formulation used in the preclinical studies as to it's composition, and must clearly explain which vehicle was being tested.

2. Since in one of the three studies quoted, a contaminant (EGDMA) was mutagenic, the material should be tested in an expanded battery of mutagenicity tests. If the product gives positive results, a dermal carcinogenicity bioassay may be required to be performed. All these studies may be conducted as phase IV studies.

3. With extensive revision of the preclinical section of the labeling, I find this Application approvable.

Syed N. Alam, Ph.D.
Pharmacologist

cc:

HFD-540/DD/Concur/Wilkin 11/11/95

HFD-340/

HFD-502/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/SPharm/Jacobs

HFD-540/MO/Toombs

HFD-540/Micro/via Sheldon

HFD-540/Chem/Rejali

HFD-540/CSO/Holmes

HFD-540/f/t init by AJacobs 11/16/95

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

NDA 20-475 (Labeling amendment, dated 10/24/96)

Drug Name: Nuretin^{R} (Tretinoin Microsponge Gel, 0.1%)

NOV 15 1996

Category: retinoid

Indication: Acne vulgaris

Sponsor: Advanced Polymer Systems, Redwood City, CA

Number of Vols.: One

Date CDER Received: 10/29/96

Date Assigned: 11/8/96

Date Review Started: 11/8/96

Date 1st Draft Completed: 11/8/96

Date Review Accepted by Supervisor:

Related Submissions: IND

Review Objective: To determine if the revised labeling has addressed adequately the pharmacology recommendations.

Comments: The examination of the revised labeling indicates that the Sponsor has adequately addressed the potential chronic toxicities of the components of the microsponge used in the drug. The following change should be inserted: Under Tab C on page 13, the last line should read:

Regulatory recommendation:

I find this revised labeling satisfactory and approvable for the drug application, except as

indicated above under the Comments Section.

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 11/15/96

HFD-540/TL/Concur/Jacobs 11/8/96

cc:
NDA 20-475

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/SPharm/Jacobs

HFD-540/MO/Huene

HFD-540/Chem/Pappas

HFD-540/CSO/Cintron

Review and Evaluation of the Pharmacology and Toxicology Sections of the Proposed Labeling
Division of Dermatologic and Ophthalmologic Drug Products (HFD-540)

January 24, 1996

NDA: 20-475 (Original Submission, dated 2/6/95)

Drug Name: Nuretin^{R}

Sponsor: Advanced Polymer Systems, Redwood City, CA

The following comments should be forwarded to the Sponsor to make the necessary changes in the labeling to be acceptable to Pharmacology.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

1. The Sponsor has mentioned the negative results of a carcinogenicity study performed only with the active ingredient, tretinoin. Nothing has been mentioned about the present drug formulation. Specifically, the Sponsor should address the mutagenicity and carcinogenicity potential of the monomers, used to manufacture Microsponge^{R}. The extremely low levels of these monomers in the final product (Microsponge^{R}) indicating insignificant human risk under the usage condition may be mentioned.

2. Pregnancy: Teratogenic Effects. Pregnancy Category C:

The Sponsor's claim that

must be modified. In one of

the two teratology studies performed in rabbits with Nuretin^R (Ref. #T48), a dose-related increase in the incidence of hydrocephaly (domed head) was seen in the fetuses of the treated groups. This fact should be inserted in the labeling contrasting the findings with the second rabbit study where no such effects were observed. The NOEL dose in the first rabbit study should be compared with the proposed clinical dose. Also different lengths of treatment period (24 hrs vs. 6 hrs) in the two rabbit studies should be pointed out.

In the same paragraph, the last sentence should read:

3. Irritation potential: The Medical Officer has already addressed this aspect of the labeling.

4. In a 3-month dermal toxicity study in mice (Ref. #T24), significant decreases in the absolute testes and ovary weights, in the absence of any significant body weight loss, have been reported. No significant histopathology was observed and the effect was absent in the dog. These facts should be included in the labeling under a separate section on preclinical toxicity studies. Doses used should be compared with the proposed clinical dose.

Syed N. Alam, Ph.D.
Pharmacologist

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

cc:
HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/SPharm/Jacobs

HFD-540/MO/ Huene

HFD-540/Chem/ via DeCamp

HFD-540/CSO/ Kozma-Fornaro

HFD-540/f/t init by AJacobs A.J. 1/24/96

Statistical Review and Evaluation

JAN 2 1996

NDA:	20-475
Name of Drug:	NURETIN™, Tretinoin MICROSPONGE® Gel, 0.1%,
Drug Class:	3S
Applicant:	Advanced Polymer Systems Inc. Redwood City, CA
Indication:	Acne Vulgaris
Documents Reviewed:	Volumes 1,53-73 and Volume 1 of the CANDA and two data diskettes
Medical Officer:	Dr. Phyllis A.Huene, HFD-540

Introduction

Topical tretinoin (trans-retinoic acid) products, at concentrations from 0.01% to 0.1%, have been marketed in the U.S. since 1971 for the treatment of acne vulgaris, under the brand-name RETIN-A®. While generally effective, these products are often irritating to the skin. It is the sponsor's claim that their formulation: Tretinoin MICROSPONGE® Gel, 0.1%, i.e., NURETIN™, is both as effective as, and, potentially less irritating than, the standard, direct application of Tretinoin.

The sponsor proposes to use tretinoin with the sponsor's patented acrylate copolymer porous micro spheres (i.e., micro sponge) for the treatment of acne vulgaris. The sponsor describes each micro sphere as consisting of a myriad of interconnecting voids within a noncollapsible structure having a large porous surface. Tretinoin is trapped on the surface of and within the micro sponge polymer. The resulting gel, Tretinoin MICROSPONGE® Gel, 0.1%, i.e., TMG 0.1%, presumably reduces cutaneous dose, and hence irritation.

Treatment Formulations:

Three different formulations of Tretinoin Microsponge Gel 0.1% have been used in the various phase I to III studies, denoted by the sponsor as TMG IA 0.1%, TMG IB 0.1%, and TMG IC 0.1%. The composition of these formulations was as follows:

Table 1. Treatment Formulations

	TMG IA 0.1%	TMG IB 0.1%	TMG IC 0.1%
1% Tretinoin in acrylates copolymer			
Water			
Carbomer 934P			
Glycerin			
Propylene glycol			
PPG-20 methyl glucose ether distearate			
Cyclomethicone and dimethicone copolyol			
Trolamine			
Butylated hydroxytoluene			
Disodium edetate			
Benzyl alcohol			
Sorbic acid			

It is the sponsor's claim that these three formulations are all fundamentally the same. Note that formulation IB was used in the clinical efficacy studies BO222E and BO223E that are the primary source this report. However, formulation IC is the version proposed for marketing. Looking at the constituents, it is apparent that these formulations are very similar. However for reasons of good science this reviewer would have preferred that the formulation marketed be the same as the formulation tested. The sponsor claims that a series of *in vitro* drug release studies, and other studies, verified that the differences between these formulations were indeed minor. The Medical Officer expressed the opinion these formulations should be clinically equivalent with respect to therapeutic value. It is beyond the expertise of this reviewer to substantively comment further on those claims.

Phase I studies:

Several different tolerance studies were performed, using the various TMG 0.1% formulations. From the brief descriptions it does appear that there is some statistically significant evidence that these formulations are less irritating than direct application of tretinoin. However, as detailed reports and data sets were not available to this reviewer, they will be ignored. This report will focus on the clinical efficacy studies, or more exactly, a subset of these studies.

Methods and Results

1. Methods

This report primarily concerns the analysis of two studies, denoted by the sponsor as B0222E and B0223E, comparing the efficacy and safety of Tretinoin MICROSPONGE® Gel, 0.1% (formulation IB) to its vehicle. These studies were U.S., multicenter, double-blinded, vehicles controlled, randomized trials following the virtually the same protocol. Both studies had a treatment period of twelve weeks, divided into five consecutive periods after baseline. That is, measurements were taken at weeks 2, 4, 7, 10, and 12. Both studies were conducted at three centers in the United States. Subjects were randomly assigned to medication, again, in both studies, TMG 0.1% formulation IB or its vehicle. Patients were required to have 20-250 total facial acne lesions, of which between 10-200 were comedones and between 10-50 were inflammatory lesions, with no more than two cysts. Subjects were also required to have a Cunliffe Visual Acne Score of at least 1.0 on a scale of (0.0 none to 8.0 most severe). Patients were excluded at baseline if they had a measure of moderate or greater on any of the erythema, peeling, burning/stinging, or itching scales described in the Safety section below.

At each visit the various facial lesions, papules, pustules, cysts, and comedones, were counted. The sponsor proposed that the primary efficacy criteria be the percent change from baseline to week twelve in total lesion count, total inflammatory lesion count (papules, pustules, and cysts), total noninflammatory lesion count (comedones), along with the investigator's global assessment of treatment response when the patient exited the study.

1. Study B0222E involved tretinoin MICROSPONGE® gel, 0.1% (TMG 0.1%, or Nuretin™), versus its vehicle for the treatment of acne vulgaris. There were three investigators, and, initially 178 subjects, 88 in the TMG 0.10% group and 90 in the vehicle group. Subjects ranged in age from 11 to 39 years. In the TMG 0.10% group the age ranged from 11 to 38 years with a mean age of 19 years, 42 (48%) were female, and 84 (95%) were Caucasian. In the vehicle group the age ranged from 11 to 39 years with a mean age of 19 years, 46 (51%) were female, and 88 (98%) were Caucasian.

2. Study B0223E was a virtually identical study of TMG 0.1%. There were three investigators, and, initially 169 subjects, 84 in the TMG 0.10% group and 85 in the vehicle group. Subjects ranged in age from 11 to 40 years. The TMG 0.10% group age ranged from 11 to 40 years with a mean age of 18 years, 36 (43%) were female, and 76 (90%) were Caucasian. The vehicle group age ranged from 11 to 37 years with a mean age of 18 years, 34 (40%) were female, and 77 (91%) were Caucasian.

In both studies, subjects were to apply the medication once daily in the evening during the 12-week study period. Since the outcome measures are virtually identical, the results from both studies are presented in parallel.

3. Other studies:

TMG IB was also investigated at three independent sites in the U.S. The results for the TMG 0.1% treatment were largely consistent with the B0223E study, while the results from a single center, Argentine studies were consistent with the B0222E study. While these studies do tend to support the conclusions here, from a discussion with the Medical Officer, it was felt that a detailed review of them was unnecessary.

2. Efficacy

a. Subject Population:

The subject populations from studies B0222E and B0223E used in this review consist of all subjects with data after baseline, from all subjects randomized to treatment. This is the Intent-to-Treat population, except the subjects who are measured solely at baseline, and at no follow-up visit, are excluded. Some definitions of intent-to-treat (ITT) include the baseline subjects. The reference population used by the sponsor, and by the Medical Officer in her report, was all valid observations, i.e., subjects without protocol violations, etc. As an alternative view of the data, the Medical Officer agreed with using this intent-to-treat population, rather than the valid subjects population as in her report. Deletion of the subjects with protocol violations does not have a major impact upon the main conclusions.

b. Physicians' Global Evaluation:

This was defined as the physicians' overall rating of treatment efficacy using the scale Excellent, Good, Fair, No Change, and Poor. These evaluations were performed at the end of the twelfth week or at the time of early discontinuation from the study:

Table 2. Physicians' Assessments of Overall Efficacy

Study:	B0222E				B0223E			
Treatment:	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
	n	%	n	%	n	%	n	%
Excellent	29	34.1	8	9.3	20	25.6	6	7.6
Good	25	29.4	19	22.1	23	29.5	19	24.1
Fair	10	11.8	20	23.3	18	23.1	21	26.6
No Change	11	12.9	26	30.2	12	15.4	21	26.6
Poor	10	11.8	13	15.1	5	6.4	12	15.2
Total n	85		86		78		79	
CMH p-value	0.000				0.000			

The Cochran-Mantel-Hanzel (CMH) statistics were computed using integer or trend scores, simply 1 (Excellent) to 5 (Poor). The p-value is from a test of mean differences in these scores across treatment groups. For both studies, stratifying on investigator, the TMG 0.1% treatment group means are statistically significantly better than the corresponding vehicle means.

Reviewer Conclusion:

In terms of the physician's global assessments of treatment efficacy Tretinoin MICROSPONGE® Gel, 0.1% *is statistically significantly superior to its vehicle at the end of the study (p=0.000 in both studies).*

b. Inflammatory Lesions:

The total of inflammatory lesions is the sum of papules, pustules, and cysts. These were counted at each of the six scheduled visits, i.e., at baseline, and weeks 2, 4, 7, 10, and 12. The response variable used by the sponsor and requested by the Medical Officer was the percent change from baseline, i.e., the ratio of change in inflammatory lesion count to the actual baseline count. By definition, the decrease from baseline is the change in inflammatory lesion counts used in the numerator. This means that a decrease in counts from baseline will have a positive percent change, while an increase in counts will correspond to negative percent change.

The following table displays the number of subjects, the F-ratio's for various effects, and the corresponding p-values for the response variable: inflammatory lesion percent change from baseline. These are computed from a simple two-way analysis of variance (ANOVA).

Table 3. Percent Decrease from Baseline Count of Inflammatory Lesions
ANOVA Table: F-ratios and p-values

		Treatment Differences		Investigator Differences		Interaction	
Study/ Week	Overall n	F ratio	p-value	F ratio	p-value	F ratio	p-value
B0222E							
Week= 2	173	1.1	.2922	25.1	.0000	1.6	.2044
Week= 4	168	0.7	.4183	27.6	.0000	1.1	.3194
Week= 7	166	4.4	.0369	12.0	.0000	0.4	.6992
Week= 10	162	13.8	.0003	11.0	.0000	2.2	.1091
Week= 12	160	8.1	.0051	4.9	.0089	1.1	.3262
LOCF*	173	8.7	.0037	7.2	.0010	1.1	.3392
B0223E							
Week= 2	158	10.3	.0016	2.6	.0771	2.4	.0941
Week= 4	159	0.0	.9388	2.5	.0824	0.4	.6495
Week= 7	149	1.9	.1752	9.5	.0001	1.0	.3577
Week= 10	142	0.3	.5708	5.5	.0051	2.9	.0599
Week= 12	146	0.5	.4951	2.9	.0575	0.1	.8985
LOCF*	164	1.3	.2562	2.5	.0848	0.2	.8491

*LOCF denotes a last observation carried forward analysis

The LOCF analysis above refers to each subject's last value after the baseline. Thus if a subject dropped out, say after week seven but before week 10, his last observation is at week seven. A subject who completed all twelve weeks of the study has his last observation at the 12th week. For each subject, the last such measured value is the LOCF response.

We are primarily interested in treatment differences. In the table above, the presence of treatment by investigator interaction would suggest "relatively large" differences in treatment effect across investigators. Note that each p-value above corresponds to a statistical test. As a rough guide note that if there were absolutely no "true" interaction at each time point, if the tests on interaction were independent, just from random variation we would expect at least one p-value below .10. This is close to the two actually observed. So adjusting for this multiplicity of tests performed, there seems to be no particularly strong evidence of such interaction here. However, if one interprets the individual interactions by investigating the values of the treatment by investigator least squares means, it appears that in the B0223E study, the week two possible interaction appears to be quantitative. That is, there seems to be a greater difference between Tretinoin MICROSPONGE® Gel, 0.1% and its vehicle in the center associated with investigator 2578 than in the other centers. At the 10th week in the same center, there is a qualitative interaction, where investigator 2578 has a smaller decrease in lesions the TMG 0.1% group than in the vehicle group. The other two centers show a greater decrease in the TMG 0.1% group. By the tenth week, in both studies, the percent change is greater in the TMG 0.1% group than in the vehicle group. However, it is statistically significantly better only in the B0222E study. Results are similar for the LOCF responses.

The statistically significant investigator differences may reflect different patient populations among the investigators. As noted later, there are statistically significant age differences among investigators in both studies. There is some age effect, i.e., the reduction tends to be somewhat higher in older subjects. This generalizes to noninflammatory lesions, i.e., in general, all relative change measure of lesion counts, for either treatment, including vehicle, seem to slightly increase with age. However the effect is only statistically significant in the vehicle group in the B0222E study, and in the TMG 0.1% group in the B0223E study. Tests of equality in slope across treatment groups were statistically nonsignificant in both studies. This suggests that while there is some statistical evidence for an age effect, it also appears that it is fairly homogeneous across investigators. In particular, age effects hardly explain the large investigator differences. There was some question about whether these investigator effects may have changed over time. Although not shown here, a mixed model repeated measures analysis, over the five time points, assuming an exchangeable covariance structure was also performed (using SAS® PROC MIXED). It indicated neither study had a statistically significant investigator by treatment by time period interaction. On the other hand, in the B0223E study, the investigator by time period interaction was statistically significant. That suggests that while the investigator effects may not be homogeneous over time, at least in the B0223E study, there is no strong evidence of a particular bias favoring either treatment.

The following table displays so called "least squares means," at each measured time

point, of these percent change from baseline in inflammatory lesion counts. Again, a positive number denotes a decrease in overall lesion counts, a negative number, an increase. All means are adjusted for unequal group sizes across investigator and treatment. Located between each treatment group least squares mean percent change in the table is the corresponding difference across treatment groups of these mean percent changes. The F-tests for treatment above are actually tests that this difference is zero. Also included are estimated standard errors of the means and differences, and the p-value of the test of no treatment differences between Nuretin and vehicle at that time point in the study. Further, in the following table, it may be useful to note that in the B0222E study Nuretin shows statistically significant superiority to its vehicle at the seventh week and at all following time points. In the B0223E study, this Nuretin treatment seemed somewhat less efficacious, while the vehicle treatment was much more efficacious than in the B0222E study.

Table 4. Percent Decrease from Baseline Count of Inflammatory Lesions: Least Squares Means and Differences, with (Standard Errors), and P-values of the Test of No Difference Between Treatments.

	B0222E			B0223E		
	TMG 0.1% LSM (SE)	Difference LSM (SE)	Vehicle LSM (SE)	TMG 0.1% LSM (SE)	Difference LSM (SE)	Vehicle LSM (SE)
Week= 2	8.2 (5.0)	7.4 (7.0) .2922	0.9 (4.9)	-4.3 (4.7)	-21.4 (6.7) .0016	17.1 (4.7)
Week= 4	16.2 (4.6)	5.2 (6.4) .4183	10.9 (4.5)	11.5 (4.7)	-0.5 (6.4) .9388	12.0 (4.3)
Week= 7	28.3 (6.7)	19.6 (9.3) .0369	8.7 (6.5)	17.0 (4.8)	-9.2 (6.7) .1752	26.2 (4.7)
Week= 10	40.4 (5.8)	30.1 (8.1) .0003	10.4 (5.7)	28.4 (5.3)	4.3 (7.5) .5708	24.1 (5.3)
Week= 12	36.4 (5.9)	23.9 (8.4) .0051	12.5 (5.9)	27.2 (5.6)	5.6 (8.1) .4951	21.7 (5.9)
LOCF*	33.3 (5.7)	23.7 (8.0) .0037	9.6 (5.6)	27.5 (4.8)	7.7 (6.7) .2562	19.8 (4.7)

*LOCF denotes a last observation carried forward analysis

Thus in study B0222E at the second week we estimate percent decrease in the Nuretin group as 8.2% and as 0.9% in the vehicle group. The simple difference is 7.4%, with standard error 7.0%. In study B0223E at the second week we estimate the percent decrease in the Nuretin group as -4.3%. Note this corresponds to an increase of 4.3% from baseline in inflammatory lesions. The Nuretin group in both studies showed increases over time in percent reduction from baseline, however, again the Nuretin treatment was statistically significantly superior only in the B0222E study.

One problem with the above analysis is using the percent reduction in inflammatory lesions as a response. The distribution of percent reduction in inflammatory lesions does not closely follow a so-called normal (bell-shaped) curve. It is actually somewhat uniform over the range of observed values. This may, to some extent, invalidate the computations

of standard errors and the p-values associated with the F-ratios above. By comparison, for both studies the distribution of the absolute lesion counts is roughly lognormal. Thus p-values computed from the analysis of variance on the logs of the lesion counts should be somewhat more accurate than the p-values based on the percent change from baseline. Still, the tests that form an analysis of variance are fairly robust to distributional misspecification, particularly with relatively equal group sizes as here, so the ANOVA using percent change should also be interpretable.

Taking this alternate approach that might be statistically more attractive, consider analyzing the logarithms of the inflammatory lesion counts. These logarithms are approximately normally distributed. The following table is derived from ANOVAs of the logarithm of the number of inflammatory lesions (actually the number + 0.5, to cover the case of possible zero counts). Terms for investigator, treatment, and interaction are entered in the model. To make the analysis more consistent with the results using the change from baseline, the baseline measure is entered as a single covariate at all time points after baseline. As above, F-ratio's and p-values are provided for both studies.

Table 5. Log Counts of Inflammatory Lesions ANOVA Table: F-ratios and p-values

		Treatment Differences		Investigator Differences		Interaction	
Study/ Week	Overall n	F ratio	p-value	F ratio	p-value	F ratio	p-value
B0222E							
Baseline	178	1.1	.2962	11.9	.0000	2.2	.1116
Week= 2	173	0.1	.7083	34.8	.0000	2.1	.1250
Week= 4	168	0.2	.6597	31.1	.0000	1.0	.3842
Week= 7	166	2.5	.1161	22.1	.0000	0.2	.8591
Week= 10	162	11.2	.0010	17.1	.0000	0.7	.4977
Week= 12	160	8.9	.0034	9.8	.0001	0.1	.9436
LOCF*	173	10.2	.0017	11.4	.0000	0.1	.9143
B0223E							
Baseline	169	0.2	.6904	29.6	.0000	0.3	.7564
Week= 2	158	11.4	.0009	4.3	.0146	3.8	.0241
Week= 4	159	0.1	.7962	4.6	.0120	0.4	.6605
Week= 7	149	2.4	.1201	12.1	.0000	2.3	.1019
Week= 10	142	0.8	.3813	4.2	.0162	3.3	.0416
Week= 12	146	1.4	.2393	5.5	.0049	0.1	.8894
LOCF*	164	2.7	.0997	4.7	.0107	0.4	.6861

*LOCF denotes a last observation carried forward analysis

Results are fairly similar to those using percent change from baseline in total inflammatory lesions as the response. Again, in the B0222E study, this time by the 10th week there are statistically significant differences between the Tretinoin MICROSPONGE® Gel, 0.1%, treatment group and its vehicle. In the B0223E study the increase in lesions in the Tretinoin MICROSPONGE® Gel, 0.1%, treatment group at the second week is now statistically significant. That is, at the second week, the TMG 0.1% group has a statistically significant greater number of inflammatory lesions than the vehicle group (actually significantly more log(# lesions + 0.5)). None of the treatment by investigator interactions were statistically significant in the B0222E study. In the B0223E study at the

second week the investigator by treatment interaction is quantitative, i.e., for all investigators, the TMG 0.1% (Nuretin) groups show higher log inflammatory lesion count means than in the vehicle group. However the amount by which the Nuretin group exceeds the vehicle group varies across investigator. The interaction at the 10th week is qualitative. For one investigator, 2578, the Nuretin group mean inflammatory lesion counts are higher than the vehicle group, while for the other two investigators, the Nuretin means are lower.

The following table displays the least squares means of these inflammatory lesion counts, transformed back to the original units. As before, all means are adjusted for unequal group sizes across investigator and treatment. In addition, the means after the baseline are adjusted for each individual's baseline inflammatory lesion count (i.e., the baseline count is included as a covariate). Actually, adjusting for the baseline severity only increases precision. Conclusions drawn from including the baseline value as a covariate are virtually the same as those from not including it. As above, between each treatment group least squares mean in the table is the corresponding difference across treatment groups of these mean counts. In this table, it may be useful to note that in the B0222E study Nuretin shows statistically significant superiority to its vehicle at the tenth week and at all following time points. In the B0223E study, the Tretinoin MICROSPONGE® Gel, 0.1%, treatment seemed somewhat less efficacious, while the vehicle treatment was statistically much more efficacious than in the B0222E study.

Table 6. Inflammatory Lesions Count: Least Squares Means and Differences, with 95% Confidence Intervals, and P-values of the Test of No Difference Between Treatments.

	B0222E			B0223E		
	Overall n	TMG 0.1% LSM (CI)	Vehicle LSM (CI)	Overall n	TMG 0.1% LSM (CI)	Vehicle LSM (CI)
		Difference/p-value			Difference/p-value	
Baseline	178	21.7 (19.7,23.9)	20.2 (18.4,22.2)	169	18.7 (17.1,20.6)	19.2 (17.5,21.1)
		-1.5 (-4.3, 1.4)			0.5 (-2.0, 3.0)	
		.2962			.6904	
Week= 2	173	17.1 (15.5,18.9)	17.6 (15.9,19.4)	158	18.0 (16.2,19.9)	14.1 (12.7,15.6)
		0.5 (-2.0, 2.9)			-3.9 (-6.2,-1.6)	
		.7083			.0009	
Week= 4	168	15.6 (13.8,17.5)	15.0 (13.4,16.8)	159	15.7 (14.2,17.3)	15.4 (14.1,16.9)
		-0.6 (-3.1, 2.0)			-0.3 (-2.4, 1.8)	
		.6597			.7962	
Week= 7	166	12.3 (10.6,14.2)	14.4 (12.5,16.7)	149	14.1 (12.6,15.8)	12.5 (11.2,13.9)
		2.2 (-0.6, 4.9)			-1.6 (-3.7, 0.5)	
		.1161			.1201	
Week=10	162	10.3 (8.9,11.9)	14.4 (12.5,16.5)	142	11.4 (9.9,13.2)	12.5 (10.8,14.5)
		4.1 (1.6, 6.6)			1.1 (-1.4, 3.6)	
		.0010			.3813	
Week=12	160	10.0 (8.4,11.8)	14.3 (12.1,16.9)	146	11.6 (10.0,13.5)	13.2 (11.3,15.4)
		4.3 (1.4, 7.3)			1.6 (-1.1, 4.3)	
		.0034			.2393	
LOCF*	173	10.6 (9.0,12.5)	15.3 (13.1,17.9)	164	11.9 (10.5,13.5)	13.8 (12.2,15.7)
		4.7 (1.7, 7.7)			1.9 (-0.4, 4.2)	
		.0017			.0997	

*LOCF denotes a last observation carried forward analysis

Thus, in study B0222E at the second week, we estimate a mean inflammatory lesion count of 17.1 in the Nuretin group and 17.6 in the vehicle group. The simple difference is 0.5. Because these have been transformed back to the original units, standard errors are no longer constant across possible true values of the mean. Hence, confidence limits are not symmetric about the mean estimates. Thus, instead of simple standard errors, 95% confidence limits are supplied above. At week ten in the B0222E study we would estimate the difference in lesion count as 4.3 with a 95% confidence interval: (1.4,7.3). In the B0223E study the corresponding difference is estimated as 1.9, with confidence interval
(-1.1,4.3).

Reviewer Conclusion:

In the B0222E study there is statistically significant evidence of efficacy relative to vehicle. For example, in this study the LOCF analysis has p≤ .0017. However, in the B0223E study there is no such evidence. Note that the p≤.0997 in the LOCF analysis corresponds to the case where the reduction in lesions is greater in the vehicle group than in the TMG 0.1% group. Consequently this reviewer would claim that TMG 0.1% gel has not shown itself to be unequivocally superior to its vehicle in terms of reducing inflammatory lesions.

c. Noninflammatory Lesions:

The total of noninflammatory lesions is the sum of comedones, open and closed. Again, the actual response variable used by the sponsor was the percent change from baseline, i.e., the ratio of change to the baseline value. So, again, a decrease in counts will have a positive percent change, while an increase in counts will correspond to negative percent change.

The following table displays the number of subjects, the F-ratio's for various effects, and the corresponding p-values for the noninflammatory lesion percent change from baseline computed from a simple two-way analysis of variance (ANOVA).

Table 7. Percent Decrease from Baseline Count of Noninflammatory Lesions
ANOVA Table: F-ratios and p-values

Study / Week	Overall n	Treatment Differences F ratio	Treatment Differences p-value	Investigator Differences F ratio	Investigator Differences p-value	Interaction F ratio	Interaction p-value
B0222E							
Week= 2	173	6.3	.0134	23.4	.0000	0.5	.6182
Week= 4	168	4.3	.0407	27.6	.0000	1.4	.2591
Week= 7	166	18.6	.0000	34.0	.0000	1.6	.2020
Week= 10	162	30.9	.0000	31.1	.0000	3.3	.0389
Week= 12	160	18.0	.0000	27.9	.0000	2.9	.0558
LOCF*	173	16.6	.0001	32.4	.0000	3.3	.0403
B0223E							
Week= 2	158	10.6	.0014	2.3	.1011	3.7	.0263
Week= 4	159	7.4	.0073	1.4	.2503	2.3	.1075
Week= 7	149	11.6	.0009	0.8	.4298	3.5	.0320
Week= 10	142	26.0	.0000	1.0	.3682	6.4	.0023
Week= 12	146	14.0	.0003	3.1	.0502	3.7	.0275
LOCF*	164	15.7	.0001	3.1	.0467	3.2	.0438

*LOCF denotes a last observation carried forward analysis

Again, we are primarily interested in treatment differences. For both studies, starting at the second week, the TMG 0.1% group shows a statistically significant greater percent decrease in noninflammatory lesions. Before relying on this simple result one needs to note that there are several statistically significant interactions in both studies. These interactions generally signify a situation where treatment effects vary by investigator. However, simply comparing the F-ratios it is clear that the interaction effect is of less statistical importance than the simple treatment differences (i.e., F-ratios for interaction are much smaller than F-ratios for treatment). At the second week in the B0223E study, one investigator had overall increases in lesions in both groups, but the increase was slightly larger in the TMG group. For the other two investigators the TMG 0.1% group showed a decrease in lesion count, while the vehicle group showed an increase. All other interactions are quantitative, from the seventh week of the B0223E study and the tenth week of the B0222E study. The estimated difference in percent decrease varied as much as between 10% -50% among investigators. That is, for one investigator the difference between TMG and its vehicle might be as low as 10%, for others as high as 50%. Still in all remaining cases, as measured by percent reduction in noninflammatory lesions, the TMG group was uniformly better than its corresponding vehicle.

Again, the statistically significant investigator differences may reflect different patient populations among the investigators. This may explain the presence of the interactions. Although these differences among investigators seem to change somewhat with time, a repeated measures analysis seemed to show no significant drug by investigator by time interaction. This analysis, not reported here, was performed with SAS

PROC MIXED assuming an exchangeable covariance structure. Thus, there does not seem to be a large general bias in favor of one treatment or the other because of time differences.

The following table displays least squares means at each measured time point, of these percent change from baseline in noninflammatory lesion counts. Again, a positive number denotes a decrease in lesion counts, a negative number an increase. Located between each treatment group least squares mean percent change in the table is the corresponding difference across treatment groups of these mean percent changes. As before, the estimated standard errors of the means and differences, and the p-value of the test of no treatment differences is also included. In the following table, it may be useful to note that TMG 0.1% shows a statistically significant reduction in proportion of lesions versus its vehicle in both studies.

Table 8. Percent Decrease from Baseline Count of Noninflammatory Lesions: Least Squares Means and Differences, with (Standard Errors), and P-values of the Test of No Difference Between Treatments.

	B0222E			B0223E		
	TMG 0.1% LSM (SE)	Difference LSM (SE)	Vehicle LSM (SE)	TMG 0.1% LSM (SE)	Difference LSM (SE)	Vehicle LSM (SE)
Week= 2	15.9 (4.0)	14.2 (5.7) .0134	1.7 (4.0)	15.9 (4.6)	21.2 (6.5) .0014	-5.4 (4.6)
Week= 4	20.1 (4.4)	12.6 (6.1) .0407	7.6 (4.2)	14.5 (6.4)	23.8 (8.7) .0073	-9.2 (5.9)
Week= 7	39.3 (3.9)	23.2 (5.4) .0000	16.1 (3.7)	22.3 (8.1)	38.1 (11.2) .0009	-15.8 (7.8)
Week= 10	46.3 (4.3)	33.8 (6.1) .0000	12.5 (4.3)	37.8 (6.9)	49.8 (9.8) .0000	-12.0 (6.9)
Week= 12	47.0 (5.1)	30.5 (7.2) .0000	16.5 (5.1)	34.2 (8.2)	44.4 (11.9) .0003	-10.2 (8.6)
LOCF*	43.6 (4.9)	28.2 (6.9) .0001	15.4 (4.8)	33.1 (7.0)	39.2 (9.9) .0001	-6.1 (7.0)

*LOCF denotes a last observation carried forward analysis

Thus we would estimate the percent decrease from baseline with Nuretin treatment as 34-47% at the 12th week versus a 10% increase to 16% decrease with the vehicle.

Again, the distribution of absolute counts is approximately lognormal. So an alternative, statistically somewhat better approach is to analyze the logarithms of the noninflammatory lesion counts. The following table is derived from ANOVAs of the logarithm of the number of noninflammatory lesions (again, actually number + .5, in case of possible zero counts). As before, terms for investigator, treatment, and interaction are entered into the model. Again, to make the analysis more consistent with the results using the percent change from baseline, the baseline measure is entered as a single covariate at all time points after baseline. As above, F-ratio's and p-values are provided for both studies.

Table 9. Log Counts of Noninflammatory Lesions ANOVA: F-ratios and p-values

Study/ Week	Overall n	Treatment F ratio	Treatment p-value	Investigator Differences F ratio	Investigator Differences p-value	Interaction Differences F ratio	Interaction Differences p-value
B0222E							
Baseline	178	0.8	.3700	0.4	.6483	0.6	.5705
Week= 2	173	10.0	.0018	29.9	.0000	0.2	.7826
Week= 4	168	6.3	.0132	38.5	.0000	0.9	.4156
Week= 7	166	25.7	.0000	43.5	.0000	0.2	.8395
Week= 10	162	44.8	.0000	40.8	.0000	1.0	.3635
Week= 12	160	35.2	.0000	48.1	.0000	0.5	.6384
LOCF*	173	33.7	.0000	53.3	.0000	0.6	.5461
B0223E							
Baseline	169	0.2	.6848	4.4	.0141	1.1	.3232
Week= 2	158	10.8	.0013	5.3	.0059	3.0	.0529
Week= 4	159	6.7	.0108	1.4	.2494	2.8	.0651
Week= 7	149	9.9	.0021	0.4	.6389	3.0	.0523
Week= 10	142	16.1	.0001	1.1	.3299	3.7	.0262
Week= 12	146	15.5	.0001	0.4	.6416	4.2	.0174
LOCF*	164	18.1	.0000	0.8	.4710	3.4	.0362

*LOCF denotes a last observation carried forward analysis

Again, we are primarily interested in treatment differences. For both studies, starting at the second week, the TMG 0.1% group shows statistically significant lower noninflammatory lesion counts. However, before interpreting this simple result one needs to note that there are a number of statistically significant interactions in both studies. First simply comparing the F-ratio's it is clear that this effect is of less statistical importance than the simple treatment differences. The only qualitative interaction was in the second week of the B0223E study, where one investigator had overall increases in lesions in both groups, but the increase was slightly larger in the TMG 0.1% group. All other interactions are quantitative, where the estimated difference in percent decrease varied as much as between 10% -50% among investigators. That is, for one investigator the difference between TMG and its vehicle might be as low as 10%, for others as high as 50%. Still in all remaining cases, as measured by percent reduction in noninflammatory lesions, the TMG group was uniformly better than its corresponding vehicle.

Again, the statistically significant investigator differences may reflect different patient populations among the investigators. Although these differences among investigators seem to change somewhat with time, a repeated measures analysis seemed to show no significant drug by investigator by time interaction. This analysis, not reported here, was performed with SAS PROC MIXED assuming an exchangeable covariance structure. Again, there is no clear evidence of an overall bias in favor of one treatment or the other as a result of time.

The following table of least squares means at each measured time point is useful to evaluate the effect of treatment.

Table 10. Noninflammatory Lesion Count: Least Squares Means and Differences, with 95% Confidence Intervals, and P-values of the Test of No Difference Between Treatments.

	B0222E			B0223E		
	Overall n	TMG 0.1% LSM (CI)	Vehicle LSM (CI)	Overall n	TMG 0.1% LSM (CI)	Vehicle LSM (CI)
		Difference/p-value			Difference/p-value	
Baseline	178	36.3 (31.8,41.5)	39.5 (34.6,45.1)	169	30.3 (25.8,35.5)	28.9 (24.6,33.9)
		3.2 (-3.9,10.3)			-1.4 (-8.1, 5.3)	
		.3700			.6848	
Week= 2	173	28.5 (26.0,31.2)	34.9 (31.9,38.2)	158	21.9 (19.8,24.2)	27.6 (25.0,30.5)
		6.4 (2.3,10.5)			5.7 (2.2, 9.3)	
		.0018			.0013	
Week= 4	168	26.9 (24.4,29.7)	31.9 (29.0,35.0)	159	22.1 (19.3,25.4)	28.2 (24.8,32.0)
		5.0 (1.0, 8.9)			6.1 (1.4,10.8)	
		.0132			.0108	
Week= 7	166	18.8 (16.7,21.1)	28.4 (25.4,31.8)	149	18.8 (15.7,22.5)	27.8 (23.4,32.9)
		9.7 (5.7,13.6)			8.9 (3.1,14.8)	
		.0000			.0021	
Week= 10	162	15.9 (14.0,18.0)	28.4 (25.2,32.1)	142	15.0 (12.3,18.3)	26.2 (21.6,31.7)
		12.6 (8.6,16.5)			11.1 (5.3,17.0)	
		.0000			.0001	
Week= 12	160	13.9 (12.0,16.2)	26.2 (22.5,30.3)	146	15.3 (12.8,18.3)	25.2 (21.0,30.3)
		12.2 (7.8,16.7)			9.9 (4.6,15.3)	
		.0000			.0001	
LOCF*	173	14.9 (12.8,17.2)	26.9 (23.3,31.0)	164	16.0 (13.7,18.6)	25.1 (21.6,29.1)
		12.0 (7.6,16.5)			9.1 (4.7,13.6)	
		.0000			.0000	

*LOCF denotes a last observation carried forward analysis

The estimated number of noninflammatory lesions in the TMG 0.1% group varied from 15-16 at the 10th week, and from 14-15 at the 12th week. The corresponding vehicle estimates are roughly 26-28 and 25-26 in the vehicle group.

Reviewer Conclusion:

By the second week of treatment, in both studies, the TMG 0.1% group has statistically significantly fewer noninflammatory lesions than it its vehicle group. This superiority to vehicle generally increases over time (See Tables 9 & 10). Note that the LOCF analysis is statistically significant in both studies (p=0.0000 in both studies).

d. Total Lesions:

Total lesions is defined as the sum of inflammatory and noninflammatory lesions. The following table displays results from an ANOVA on the percent change from baseline of these total lesions.

Table 11. Percent Decrease from Baseline Count of Total Lesions ANOVA Table: F-ratios and p-values

		Treatment Differences		Investigator Differences		Interaction	
Study/ Week	Overall n	F ratio	p-value	F ratio	p-value	F ratio	p-value
B0222E							
Week= 2	173	5.6	.0187	51.2	.0000	1.0	.3792
Week= 4	168	3.6	.0605	41.1	.0000	1.5	.2308
Week= 7	166	15.8	.0001	34.5	.0000	1.2	.3082
Week= 10	162	27.1	.0000	29.8	.0000	3.7	.0281
Week= 12	160	16.7	.0001	25.0	.0000	2.9	.0594
LOCF*	173	16.5	.0001	30.2	.0000	3.1	.0472
B0223E							
Week= 2	158	0.9	.3324	4.4	.0138	0.8	.4625
Week= 4	159	5.7	.0187	3.3	.0381	2.0	.1444
Week= 7	149	4.9	.0286	2.0	.1449	1.4	.2481
Week= 10	142	19.3	.0000	1.6	.2109	1.7	.1909
Week= 12	146	9.7	.0023	2.1	.1278	1.4	.2582
LOCF*	164	14.2	.0002	2.5	.0892	1.5	.2277

*LOCF denotes a last observation carried forward analysis

Again, we are primarily interested in treatment differences. For the B0222E study, starting at the second week the TMG 0.1% group shows a statistically significant greater percent decrease in lesions. At the fourth week the difference is no longer statistically significant (though just barely). But after that, treatment statistical significance increases with time, as one would expect with a cumulatively effective treatment. In the B0223E study this superiority is not evident until the fourth week. Again there is no particular evidence of interactions in the B0223E study. In the B0222E study the interactions are all quantitative, primarily due to large differences between TMG 0.1% and vehicle in the center associated with investigator 1912. These are of much less importance than the treatment main effects. The mixed model analysis with an exchangeable covariance structure seems to confirm that there does not seem to be an overall bias in favor of one treatment or the other as a result of time.

Table 12. Percent Decrease from Baseline Count of Total Lesions: Least Squares Means and Differences, with (Standard Errors), and P-values of the Test of No Difference Between Treatments.

	B0222E			B0223E		
	TMG 0.1% LSM (SE)	Difference LSM (SE)	Vehicle LSM (SE)	TMG 0.1% LSM (SE)	Difference LSM (SE)	Vehicle LSM (SE)
Week= 2	14.2 (2.9)	9.6 (4.0) .0187	4.6 (2.8)	9.6 (3.7)	5.1 (5.2) .3324	4.5 (3.7)
Week= 4	19.4 (3.6)	9.4 (4.9) .0605	10.0 (3.4)	15.7 (4.0)	12.8 (5.4) .0187	3.0 (3.6)
Week= 7	35.9 (3.8)	21.0 (5.3) .0001	14.9 (3.7)	21.8 (5.1)	15.8 (7.1) .0286	6.0 (5.0)
Week= 10	43.9 (4.1)	29.8 (5.7) .0000	14.1 (4.0)	35.6 (4.6)	28.6 (6.5) .0000	7.0 (4.6)
Week= 12	43.4 (4.5)	25.7 (6.3) .0001	17.7 (4.4)	33.5 (5.0)	22.6 (7.3) .0023	11.0 (5.2)
LOCF*	40.3 (4.3)	24.6 (6.1) .0001	15.7 (4.2)	32.8 (4.3)	23.1 (6.1) .0002	9.7 (4.3)

*LOCF denotes a last observation carried forward analysis

Note that this suggests that at the end of twelve weeks of treatment with Nuretin, our best estimate of the treatment effect is a reduction of 33-44% in total lesions.

Again as an alternative, statistically better approach, analyze the logarithms of the total lesion counts. The following table summarizes an ANOVA of these log total lesion counts:

Table 13. Log Counts of Total Lesions ANOVA Table: F-ratios and p-values

		Treatment Differences		Investigator Differences		Interaction	
Study/ Week	Overall n	F ratio	p-value	F ratio	p-value	F ratio	p-value
B0222E							
Baseline	178	0.1	.7201	1.6	.2129	0.8	.4661
Week= 2	173	5.7	.0180	59.1	.0000	0.6	.5385
Week= 4	168	3.2	.0766	53.3	.0000	0.8	.4524
Week= 7	166	16.8	.0001	46.9	.0000	0.1	.8922
Week= 10	162	32.3	.0000	40.7	.0000	1.0	.3804
Week= 12	160	28.7	.0000	37.0	.0000	0.5	.6015
LOCF*	173	28.6	.0000	41.8	.0000	0.6	.5396
B0223E							
Baseline	169	0.0	.8808	13.8	.0000	0.8	.4739
Week= 2	158	1.7	.1885	4.2	.0174	0.7	.4894
Week= 4	159	5.6	.0193	4.1	.0192	1.9	.1472
Week= 7	149	7.0	.0093	1.2	.3181	1.5	.2310
Week= 10	142	19.8	.0000	0.2	.7970	1.4	.2534
Week= 12	146	10.7	.0013	1.0	.3648	1.8	.1737
LOCF*	164	14.6	.0002	1.3	.2694	1.5	.2232

*LOCF denotes a last observation carried forward analysis

Except for the decreased effect of interactions in the B0222E study, the results are virtually identical to those for the percent change from baseline. Both studies show highly statistically significant effects from the seventh week. As above, in the B0222E study the week two differences are statistically significant, as are the week four differences in the B0223E study. Neither study displayed any statistically significant interactions, and, though not displayed here, the mild evidence that was apparent from the smaller p-values in the last half of the B0223E study, turned out to associated small quantitative interactions (not displayed here).

Table 14. Total Lesions Count: Least Squares Means and Differences, with 95% Confidence Intervals, and P-values of the Test of No Difference Between Treatments.

	B0222E			B0223E		
	Overall n	TMG 0.1% LSM (CI)	Vehicle LSM (CI)	Overall n	TMG 0.1% LSM (CI)	Vehicle LSM (CI)
		Difference/p-value			Difference/p-value	
Baseline	178	60.5(54.4,67.4)	62.2(56.0,69.1)	169	51.1(45.6,57.3)	51.7(46.2,58.0)
		1.7 (-7.5,10.8)			0.6 (-7.7, 8.9)	
		.7201			.8808	
Week= 2	173	49.0(45.7,52.5)	55.1(51.4,59.0)	158	42.1(38.8,45.6)	45.3(41.8,49.2)
		6.1 (1.0,11.2)			3.3 (-1.7, 8.3)	
		.0180			.1885	
Week= 4	168	45.1(41.4,49.1)	50.1(46.2,54.4)	159	40.0(36.4,43.9)	46.5(42.7,50.7)
		5.0 (-0.6,10.6)			6.5 (1.0,12.0)	
		.0766			.0193	
Week= 7	166	33.5(30.0,37.3)	45.7(41.1,50.7)	149	35.5(31.8,39.8)	43.6(39.2,48.6)
		12.2 (6.2,18.2)			8.1 (1.9,14.2)	
		.0001			.0093	
Week= 10	162	28.3(25.2,31.7)	44.7(39.9,50.0)	142	29.0(25.6,32.8)	42.8(37.8,48.4)
		16.4 (10.4,22.4)			13.8 (7.4,20.2)	
		.0000			.0000	
Week= 12	160	26.0(22.7,29.8)	43.2(37.8,49.4)	146	29.2(25.4,33.5)	40.4(35.0,46.6)
		17.2 (10.5,24.0)			11.2 (4.2,18.2)	
		.0000			.0013	
LOCF*	173	27.7(24.3,31.5)	45.1(39.7,51.2)	164	30.1(26.7,33.8)	41.3(36.7,46.4)
		17.4 (10.6,24.2)			11.2 (5.2,17.2)	
		.0000			.0002	

*LOCF denotes a last observation carried forward analysis

Thus after twelve weeks of treatment, we would estimate a total lesion count of 26-29 in the TMG 0.1% group, versus 40-43 in the vehicle group.

Reviewer Conclusion:

The LOCF comparison of Tretinoin Microsphere Gel, 0.1% to its vehicle was quite statistically significant (p≤.0000 in B0222E study, and p≤.0002 in B0222E study). Thus this reviewer would conclude that for both studies, Tretinoin Microsphere Gel, 0.1% was shown to be statistically significantly better than its vehicle. Further, from Tables 13 and

14 by the 7th week in both studies, the differences between TMG 0.1% and vehicle are statistically significant, with generally increasing statistical significance in both studies.

e. Subgroup Analyses:

e.1. Baseline Demographic Measures:

Though not shown here, as modeled by an ANOVA there were highly statistically significant age differences among investigators in both studies. In study B0222E the least squares mean of age (adjusting for investigator, drug, and interaction) is 21 for investigator 545, 18 for investigator 1012, and 17 for investigator 1980. In study B0223E the least squares mean of age is 16 for investigator 693, 17 for investigator 2141, and 25 for investigator 2578. (Note each LSM has standard error about one year.) However, drug treatment and treatment by investigator interactions were not statistically significant (For treatment: $p \leq 0.5784$ and $p \leq 0.8843$ in B0222E and B0223E respectively, for interaction $p \leq 0.8734$ and $p \leq 1361$ respectively). Thus it seems safe to conclude that age effects are roughly balanced across treatment group. However, there are relatively few young patients in the 2578 study (two subjects less than 16, six less than age 18). Despite the balance over treatment, this has an effect on appropriate tests for subgroups.

For B0222E, loglinear contingency table tests of independence of gender with investigator and treatment group were highly nonsignificant ($p \leq 0.3879$ and $p \leq 0.6421$ respectively). So for this study, gender is generally balanced over treatment group within investigator. In the B0223E study, the gender by investigator term was statistically significant ($p \leq 0.0003$), while the genders by treatment term, and the gender by treatment by investigator interaction were both statistical nonsignificant ($p \leq 0.6946$ and $p \leq 0.4520$ respectively). Note that investigator 2578 in the B0223E study had only two males, versus thirteen females, in the TMG 0.1% group. The vehicle group had eleven males and fourteen females. This unbalanced allocation has an effect on the appropriate tests and least squares means estimates.

Even after pooling all non-Caucasian patients into one race group the data are too sparse for any loglinear statistical modeling of the relationship between race and investigator and treatment. However, in the B0222E study, tests of independence of race with treatment group and investigator were also nonsignificant ($p \leq 0.4100$ and $p \leq 0.3144$ respectively). So again, the statistical evidence suggests that race allocation is generally balanced across treatment groups within investigator in this study. There were insufficient nonwhite patients in the B0223E study for any conclusions.

e.2. Gender

Recall that the physicians' global evaluation of treatment efficacy was recorded at the time the subject left the study. This measure, broken down by gender, is as follows:

Table 15. Physicians' Global Assessment Stratified by Gender

	Male				Female			
	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
B0222E	n	%	n	%	n	%	n	%
Excellent	14	30.4	2	4.7	15	38.5	6	14.0
Good	13	28.3	10	23.3	12	30.8	9	20.9
Fair	7	15.2	8	18.6	3	7.7	12	27.9
No Change	6	13.0	11	25.6	5	12.8	15	34.9
Poor	6	13.0	12	27.9	4	10.3	1	2.3
Total n	46		43		39		43	
CMH p-value		0.000				0.016		
B0223E								
Excellent	10	22.2	2	4.2	10	30.3	4	12.9
Good	14	31.1	13	27.1	9	27.3	6	19.4
Fair	11	24.4	13	27.1	7	21.2	8	25.8
No Change	6	13.3	12	25.0	6	18.2	9	29.0
Poor	4	8.9	8	16.7	1	3.0	4	12.9
Total n	45		48		33		31	
CMH p-value		0.008				0.016		

Note that for both genders and in both studies, the Tretinoin Microsphere Gel 0.1% is statistically significantly better than its vehicle (Table 15).

The ANOVA table broken down by gender for percent change from baseline in inflammatory lesions follows:

Table 16. Percent Decrease from Baseline Count of Inflammatory Lesions Stratified on Gender: F-ratios and p-values

	Males							Females					
Study/		Treatment		Investigator		Interaction			Treatment		Investigator		Interaction	
Week	n	F	p-value	F	p-value	F	p-value	n	F	p-value	F	p-value	F	p-value
B0222E														
Week=2	89	3.2	.0793	13.7	.0000	2.5	.0890	84	0.0	.8632	14.4	.0000	0.1	.9142
Week=4	88	0.8	.3870	11.6	.0000	0.4	.6603	80	0.2	.6933	15.4	.0000	0.6	.5406
Week=7	87	5.7	.0194	7.7	.0009	0.1	.8827	79	0.8	.3694	5.3	.0070	0.2	.8119
Week=10	84	10.7	.0016	7.3	.0013	1.1	.3282	78	4.3	.0418	4.8	.0113	1.2	.2997
Week=12	82	4.6	.0349	1.5	.2288	0.3	.7425	78	4.4	.0402	5.1	.0083	1.0	.3792
LOCF*	89	6.4	.0135	3.1	.0522	0.4	.6474	84	3.2	.0783	6.0	.0037	0.7	.5124
B0223E†														
Week=2	89	0.9	.3506†	2.9	.0941†	0.0	.9303†	65	4.7	.0339	0.3	.7212	0.9	.4039
Week=4	90	0.1	.7329†	1.0	.3317†	0.1	.8027†	65	0.0	.8978	1.5	.2258	2.5	.0945
Week=7	88	0.1	.7560†	4.2	.0439†	0.0	.8418†	59	0.7	.4230	5.1	.0095	1.7	.1915
Week=10	83	4.7	.0338†	12.1	.0008†	0.7	.4163†	59	1.5	.2273	1.1	.3420	1.3	.2872
Week=12	86	0.7	.3991†	4.2	.0446†	0.0	.8630†	59	0.3	.5674	1.3	.2782	0.2	.8258
LOCF*	91	1.4	.2379†	3.3	.0748†	0.0	.9992†	69	0.8	.3864	1.9	.1615	0.2	.8518

*LOCF denotes a last observation carried forward analysis

†Because of the small number of males from investigator 2578, he has been deleted from the analysis for males in study B0223E.

There are only two males in the TMG 0.1% treatment group at the center with investigator 2578 (study B0223E). Both of them later drop out. Least squares means weight cells equally, so, by default, those males are weighted equal to cells with 20 or so cases. To correct for this, least squares means have been redefined, essentially by eliminating those cases. The table of least squares means for percent change from baseline in inflammatory lesions broken down by gender follows:

Table 17. Percent Decrease from Baseline Count of Inflammatory Lesions Stratified on Gender: LS Means and Differences

	Males			Females		
Study/ Week	Treatment (SE)	Investigator (SE)/p-value	Interaction (SE)	Treatment (SE)	Investigator (SE)/p-value	Interaction (SE)
B0222E						
Week=2	6.6 (7.5)	19.1 (10.7) .0793	-12.4 (7.7)	10.3 (6.2)	-1.5 (8.6) .8632	11.8 (5.9)
Week=4	16.1 (5.9)	7.3 (8.4) .3870	8.8 (6.0)	16.9 (7.5)	4.0 (10.2) .6933	12.8 (6.9)
Week=7	24.0 (7.4)	25.3 (10.6) .0194	-1.3 (7.6)	34.1 (12.0)	14.6 (16.2) .3694	19.5 (10.8)
Week=10	34.9 (6.6)	31.7 (9.7) .0016	3.2 (7.1)	47.3 (10.0)	28.2 (13.6) .0418	19.1 (9.2)
Week=12	28.6 (8.4)	27.1 (12.6) .0349	1.5 (9.4)	46.3 (8.4)	23.7 (11.3) .0402	22.6 (7.6)
LOCF*	26.3 (8.2)	29.7 (11.8) .0135	-3.4 (8.4)	41.4 (7.9)	19.3 (10.8) .0783	22.1 (7.5)
B0223E†						
Week=2	-3.8† (5.6)	-7.3 (7.8) .3506	3.5† (5.4)	-3.2 (7.2)	-23.2 (10.7) .0339	20.0 (7.9)
Week=4	4.0† (6.1)	2.9 (8.5) .7329	1.1† (5.9)	16.2 (5.2)	-1.0 (7.4) .8978	17.2 (5.2)
Week=7	8.6† (5.3)	-2.3 (7.5) .7560	11.0† (5.3)	21.9 (6.8)	-7.8 (9.7) .4230	29.7 (6.9)
Week=10	26.6† (5.7)	17.4 (8.1) .0338	9.1† (5.7)	39.4 (6.5)	11.2 (9.2) .2273	28.1 (6.5)
Week=12	22.6† (6.4)	7.8 (9.2) .3991	14.8† (6.6)	36.7 (7.1)	6.0 (10.3) .5674	30.8 (7.5)
LOCF*	23.2† (6.3)	10.5 (8.9) .2379	12.7† (6.2)	36.4 (6.1)	7.8 (8.9) .3864	28.6 (6.5)

*LOCF denotes a last observation carried forward analysis

†Because of the small number of males in the center associated with investigator 2578, he has been deleted from the analysis for males in study B0223E.

Generally, the previous inconsistent study results for the ungrouped data are consistent across genders. That is, in the B0222E differences between treatment groups in both genders are statistically significant or close to statistical significance (see Table 17 above). Contrariwise, in the B0223E study there is no statistically significant difference between the treatment groups for both genders.

The ANOVA table and table of least squares means for percent change from baseline in noninflammatory lesions follow:

Table 18. Percent Decrease from Baseline Count of Noninflammatory Lesions Stratified on Gender: F-ratios and p-values

	Males							Females						
Study/ Week	n	Treatment F	Treatment p-value	Investigator F	Investigator p-value	Interaction F	Interaction p-value	n	Treatment F	Treatment p-value	Investigator F	Investigator p-value	Interaction F	Interaction p-value
B0222E														
Week=2	89	2.5	.1160	14.5	.0000	0.3	.7551	84	2.9	.0914	10.6	.0001	0.3	.7072
Week=4	88	1.1	.3003	15.0	.0000	1.6	.2100	80	3.3	.0720	12.0	.0000	0.1	.8713
Week=7	87	6.8	.0108	24.1	.0000	2.1	.1249	79	13.2	.0005	13.1	.0000	1.2	.3020
Week=10	84	13.0	.0005	24.3	.0000	3.7	.0298	78	17.8	.0001	9.1	.0003	1.8	.1648
Week=12	82	5.3	.0238	16.9	.0000	3.4	.0396	78	23.0	.0000	14.9	.0000	0.6	.5298
LOCF*	89	6.7	.0112	20.3	.0000	3.9	.0234	84	11.9	.0009	14.5	.0000	0.1	.8681
B0223E†														
Week=2	89	0.0	.9599†	5.4	.0228†	0.8	.3883†	65	15.3	.0002	0.3	.7740	2.7	.0745
Week=4	90	0.6	.4474†	0.0	.9493†	0.7	.4017†	65	5.3	.0252	1.6	.2187	1.7	.1974
Week=7	88	1.9	.1718†	2.6	.1105†	1.3	.2583†	59	7.8	.0073	1.0	.3843	4.2	.0210
Week=10	83	6.2	.0150†	2.7	.1021†	2.0	.1583†	59	12.0	.0010	1.3	.2725	4.8	.0126
Week=12	86	3.1	.0832†	3.4	.0704†	0.3	.5977†	59	10.2	.0024	2.5	.0942	6.0	.0044
LOCF*	91	3.8	.0550†	2.9	.0904†	0.2	.6318†	69	8.7	.0045	2.4	.0965	4.4	.0169

*LOCF denotes a last observation carried forward analysis

†Because of the small number of males in the center associated with investigator 2578, he has been deleted from the analysis for males in study B0223E.

Note that for both genders in the B0222E study, the Tretinoin Microsphere Gel, 0.1%, is statistically significantly better than its vehicle. From other analyses of treatment by investigator least squares means evidently interactions are quantitative, and generally ignorable. There are no such significant differences in the B0223E study.

Table 19. Percent Decrease from Baseline of Noninflammatory Lesions Stratified on Gender: LS Means

	Males			Females		
Study/ Week	Treatment (SE)	Investigator (SE)/p-value	Interaction (SE)	Treatment (SE)	Investigator (SE)/p-value	Interaction (SE)
B0222E						
Week=2	20.4 (4.8)	11.0 (7.0) .1160	9.4 (5.0)	11.1 (6.5)	15.4 (9.0) .0914	-4.3 (6.2)
Week=4	17.9 (6.3)	9.4 (9.0) .3003	8.6 (6.4)	22.3 (6.3)	15.5 (8.5) .0720	6.8 (5.7)
Week=7	33.4 (5.4)	20.1 (7.7) .0108	13.2 (5.5)	45.0 (5.4)	26.4 (7.2) .0005	18.6 (4.9)
Week=10	38.7 (5.8)	30.8 (8.5) .0005	7.9 (6.3)	54.1 (6.4)	36.4 (8.6) .0001	17.7 (5.8)
Week=12	36.5 (8.0)	27.9 (12.1) .0238	8.6 (9.0)	58.1 (5.3)	34.6 (7.2) .0000	23.5 (4.9)
LOCF*	36.5 (7.7)	28.6 (11.0) .0112	8.0 (7.9)	50.3 (5.7)	27.0 (7.8) .0009	23.3 (5.4)
B0223E†						
Week=2	5.0†(5.0)	0.3 (6.9) .9599	4.6† (4.8)	20.1 (7.0)	40.4 (10.3) .0002	-20.3 (7.6)
Week=4	4.2†(6.6)	7.1 (9.2) .4474	-2.9† (6.5)	14.6 (10.0)	32.7 (14.2) .0252	-18.1 (10.1)
Week=7	8.3†(9.2)	17.9 (13.0) .1718	-9.6† (9.2)	28.0 (10.2)	40.4 (14.5) .0073	-12.4 (10.3)
Week=10	24.1†(7.1)	25.3 (10.2) .0150	-1.2† (7.2)	44.0 (9.5)	46.6 (13.4) .0010	-2.5 (9.4)
Week=12	28.5†(8.5)	21.3 (12.1) .0832	7.2† (8.7)	41.6 (11.5)	53.5 (16.7) .0024	-11.9 (12.2)
LOCF	29.3†(8.2)	22.5 (11.5) .0550	6.8† (8.1)	38.2 (10.4)	44.7 (15.2) .0045	-6.5 (11.0)

*LOCF denotes a last observation carried forward analysis

†Because of the small number of males in the center associated with investigator 2578, he has been deleted from the analysis for males in study B0223E.

From Table 19 above, in the B0222E study, both gender groups have a statistically significant reduction in noninflammatory lesions, as do the females in the B0223E study. At the 12th week of the study in these groups we would estimate the percent reduction to be 36%, 53%, and 38% respectively. While not testing significantly different at the 12th week, the males in the TMG 0.1% group in the B0223E study actually have a small increase in overall lesion count from baseline, estimated as 7.7%, while the corresponding vehicle group has a decrease. The LOCF results are similar.

Though not displayed here, results for total lesions are almost identical to the results for noninflammatory lesions. In the B0222E study, both gender groups have a statistically significant reduction in total lesions, as do the females in the B0223E study.

e.3. Age

Dividing patients into three age groups, those aged 11-15, those age 16-18, and those aged 19 or more, we get the following distributions of physicians' global evaluation:

Table 20. Physicians' Global Assessment Stratified by Age

Age:	11-15				16-18				19+			
B0222E	TMG	0.10%	Vehicle		TMG	0.10%	Vehicle		TMG	0.10%	Vehicle	
	n	%	n	%	n	%	n	%	n	%	n	%
Excellent	10	31.3	2	5.3	9	42.9	2	10.0	10	31.3	4	14.3
Good	6	18.8	7	18.4	6	28.6	4	20.0	13	40.6	8	28.6
Fair	5	15.6	9	23.7	3	14.3	4	20.0	2	6.3	7	25.0
No Change	6	18.8	12	31.6	1	4.8	5	25.0	4	12.5	9	32.1
Poor	5	15.6	8	21.1	2	9.5	5	25.0	3	9.4	.	.
Total n	32		38		21		20		32		28	
CMH p-value		.013				.005				.151		
B0223E												
Excellent	11	27.5	2	6.9	6	25.0	3	9.7	3	21.4	1	5.3
Good	13	32.5	3	10.3	5	20.8	9	29.0	5	35.7	7	36.8
Fair	7	17.5	10	34.5	7	29.2	8	25.8	4	28.6	3	15.8
No Change	7	17.5	10	34.5	3	12.5	7	22.6	2	14.3	4	21.1
Poor	2	5.0	4	13.8	3	12.5	4	12.9	.	.	4	21.1
Total n	40		29		24		31		14		19	
CMH p-value		.000				.355				.086		

From Table 20 above, note that for both studies, the 11-15 year age group has the TMG 0.1% group significantly better than the vehicle. The same holds true for the 16-18 year age group in the B0222E study. The difference between treatments in the 19+ years age groups in the B0222E study would have been statistically significant, except for the three poor responders. Still, in general, results for the age subgroups seem to be consistent, though not necessarily statistically significant, with the overall results.

The ANOVA table and table of least squares means for percent change from baseline in inflammatory lesions follow. Note that at each time point, the ANOVA from the 11-15 years and 16-18 years age groups are on one line, followed on the next line by the results from the third age group, 19+ years:

In study B0223E, investigator 2578 had only six subjects aged 18 or below. Though allocation to treatment was balanced within this center, the effect of these few subjects on p-values and least squares means is potentially considerable. Therefore, they were deleted from the analysis.

Table 21. Percent Decrease from Baseline Count of Inflammatory Lesions Stratified on Age: F-ratios and p-values

		11-15 / 19+							16-18					
Study/ Week	n	Treatment F	Treatment p-value	Investigator F	Investigator p-value	Interaction F	Interaction p-value	n	Treatment F	Treatment p-value	Investigator F	Investigator p-value	Interaction F	Interaction p-value
B0222E														
Week=2	70	0.9	.3589	10.6	.0001	0.6	.5621	41	6.0	.0192	4.2	.0234	3.9	.0303
	62	1.3	.2623	15.1	.0000	0.3	.7530							
Week=4	67	0.1	.8064	13.3	.0000	0.1	.8906	41	3.1	.0882	3.4	.0441	0.4	.6911
	60	1.1	.3042	13.3	.0000	0.3	.7301							
Week=7	66	3.4	.0700	2.3	.1113	1.0	.3711	41	8.1	.0073	6.9	.0029	1.3	.2949
	59	1.4	.2374	12.7	.0000	0.8	.4713							
Week=10	65	7.3	.0092	3.4	.0386	1.8	.1723	39	17.4	.0002	4.5	.0188	7.2	.0025
	58	0.1	.8218	7.8	.0011	0.2	.7826							
Week=12	65	3.9	.0534	0.9	.4076	0.5	.6003	37	5.6	.0247	1.3	.2876	4.3	.0226
	58	0.1	.7546	14.9	.0000	0.0	.9600							
LOCF	70	3.5	.0678	1.7	.1965	0.4	.6842	41	7.5	.0095	1.2	.3017	4.9	.0132
	62	0.1	.7864	16.4	.0000	0.2	.7970							
B0223E†														
Week=2	68	2.3	.1361†	1.7	.1998†	0.8	.3785†	53	2.7	.1093†	2.4	.1248†	0.6	.4273†
	35	0.1	.7248	3.0	.0671	3.0	.0637							
Week=4	69	0.0	.8424†	0.0	.8720†	0.3	.5740†	54	0.2	.6285†	0.6	.4327†	0.0	.9381†
	34	3.6	.0677	1.7	.2049	1.5	.2454							
Week=7	68	0.0	.8361†	7.0	.0105†	0.3	.5592†	51	0.1	.7820†	0.2	.6993†	2.7	.1098†
	28	0.4	.5451	5.5	.0114	4.4	.0250							
Week=10	64	6.5	.0134†	5.6	.0208†	0.2	.6345†	51	1.7	.2020†	10.5	.0023†	0.2	.6845†
	26	2.1	.1652	1.4	.2797	2.7	.0914							
Week=12	67	2.0	.1596†	2.4	.1274†	2.3	.1358†	52	0.1	.7241†	10.4	.0023†	0.0	.9105†
	25	3.0	.0986	0.5	.6289	3.3	.0608							
LOCF	70	2.6	.1126†	1.8	.1831†	1.9	.1720†	54	0.0	.8716†	8.6	.0051†	0.2	.6846†
	38	5.8	.0221	0.5	.5836	3.9	.0313							

†-Investigator 2578 deleted from 11-15 and 16-18 age groups

In reading Table 21 above, note that we have the ANOVA results for the 11-15 year age group aligned with the results for the 16-18 group. Results for the 19+ years age group appear immediately below the displayed values for the 11-15 age group. The small p-values show interactions at later time points in the 16-18 age group of the B0222E study, as well as some at the 19+ age group in the B0223E study. However, interaction effects are small and generally quantitative. Hence they can be ignored.

One caveat is that there were very few subjects younger than 18 years associated with investigator 2578 in study B0223E. Thus, these few cases are deleted from the analysis above.

From Table 22 below, for each study and each age group the later differences between the TMG 0.1% and vehicle are usually positive, particularly in the B0222E study. Treatment differences tend to be statistically significant in that study, and not statistically significant in the B0223E study.

So, again, from Tables 21 and 22, overall there appears to be generally statistically significant evidence that TMG 0.1% is effective in terms of inflammatory lesions in the B0222E study. However, this is not evident in patients aged more than 19 years, and there is no such clear evidence in the B0223E study.

The ANOVA table and table of least squares means for percent change from baseline in noninflammatory lesions follow:

Table 23. Percent Decrease from Baseline Count of Noninflammatory Lesion Stratified on Age: F-ratios and p-values

	11-15 / 19+							16-18						
Study/ Week	n	Treatment F ratio	Treatment p-value	Investigator F ratio	Investigator p-value	Interaction F ratio	Interaction p-value	n	Treatment F ratio	Treatment p-value	Investigator F ratio	Investigator p-value	Interaction F ratio	Interaction p-value
B0222E														
Week=2	70	0.5	.4881	12.6	.0000	1.1	.3344	41	2.3	.1363	10.9	.0002	3.3	.0484
	62	1.4	.2364	8.0	.0009	0.1	.9308							
Week=4	67	0.0	.8571	10.7	.0001	0.9	.4309	41	2.8	.1041	11.2	.0002	4.2	.0226
	60	0.4	.5441	11.3	.0001	0.1	.9033							
Week=7	66	3.2	.0794	14.1	.0000	0.1	.8627	41	12.7	.0011	15.5	.0000	6.5	.0041
	59	2.6	.1148	12.2	.0000	0.1	.8655							
Week=10	65	8.1	.0062	18.3	.0000	1.2	.3075	39	12.2	.0014	8.4	.0012	6.0	.0060
	58	4.2	.0449	7.1	.0018	0.3	.7791							
Week=12	65	1.4	.2403	15.3	.0000	1.4	.2611	37	10.8	.0026	9.0	.0008	5.0	.0129
	58	4.5	.0391	15.0	.0000	0.4	.6941							
LOCF	70	1.2	.2769	16.7	.0000	1.2	.3068	41	14.3	.0006	9.8	.0004	5.5	.0087
	62	2.6	.1143	14.9	.0000	0.5	.6354							
B0223E†														
Week=2	68	0.7	.4213†	2.7	.1066†	0.3	.5766†	53	0.2	.6828†	3.1	.0864†	1.7	.2016†
	35	4.3	.0479	0.3	.7802	0.7	.5270							
Week=4	69	4.6	.0356†	4.4	.0409†	2.0	.1578†	54	0.3	.5945†	5.4	.0244†	2.6	.1123†
	34	0.4	.5559	4.1	.0270	4.5	.0202							
Week=7	68	3.6	.0642†	3.6	.0627†	0.7	.3915†	51	0.6	.4456†	0.0	.8826†	1.2	.2695†
	28	0.6	.4541	0.1	.8702	1.4	.2582							
Week=10	64	16.2	.0002†	2.9	.0949†	4.4	.0401†	51	0.4	.5310†	0.2	.6362†	0.1	.7142†
	26	2.2	.1520	0.3	.7684	2.1	.1469							
Week=12	67	7.7	.0073†	4.3	.0424†	1.4	.2456†	52	0.0	.8720†	1.0	.3220†	0.0	.8795†
	25	1.0	.3402	0.4	.7055	2.1	.1448							
LOCF	70	9.8	.0026†	4.6	.0352†	1.7	.1932†	54	0.0	.8542†	0.9	.3576†	0.1	.7932†
	38	1.1	.3111	0.4	.6970	1.7	.1911							

†-Investigator 2578 deleted from 11-15 and 16-18 age groups

Just from the p-values in Table 23, there may be some concern about interactions in the 16-18 age group of the B0222E study. Still these are mainly quantitative, and can be ignored.

To investigate treatment effects one would inspect the treatment group least squares means in Table 23 below:

Table 22. Percent Decrease from Baseline Count of Inflammatory Lesion Stratified on Age: F-ratios and p-values

Study/ Week	11-15/19+ Treatment (SE)	11-15/19+ Investigator (SE)/p-value	11-15/19+ Interaction (SE)	16-18 Treatment (SE)	16-18 Investigator (SE)/p-value	16-18 Interaction (SE)
B0222E						
Week=2	1.0 (9.9)	12.6 (13.6)	-11.6 (9.3)	16.9 (8.1)	28.2 (11.5)	-11.3 (8.1)
		.3589			.0192	
	12.3 (8.0)	-12.9 (11.4)	25.2 (8.1)			
		.2623				
Week=4	6.9 (8.4)	2.8 (11.3)	4.1 (7.5)	24.4 (9.4)	23.4 (13.3)	1.0 (9.4)
		.8064			.0882	
	19.7 (8.6)	-12.7 (12.2)	32.3 (8.7)			
		.3042				
Week=7	30.1 (15.0)	37.6 (20.4)	-7.5 (13.8)	32.6 (9.9)	39.8 (14.0)	-7.3 (9.9)
		.0700			.0073	
	24.0 (8.6)	-14.6 (12.2)	38.5 (8.7)			
		.2374				
Week=10	39.2 (11.8)	43.4 (16.1)	-4.2 (10.9)	46.9 (8.6)	52.7 (12.6)	-5.8 (9.3)
		.0092			.0002	
	35.8 (9.4)	3.0 (13.5)	32.7 (9.6)			
		.8218				
Week=12	30.1 (12.9)	34.7 (17.6)	-4.6 (11.9)	42.8 (10.1)	37.2 (15.8)	5.6 (12.1)
		.0534			.0247	
	38.6 (6.9)	3.1 (9.8)	35.5 (7.0)			
		.7546				
LOCF	24.4 (12.0)	30.6 (16.5)	-6.2 (11.3)	42.8 (10.1)	39.3 (14.3)	3.6 (10.1)
		.0678			.0095	
	37.0 (6.9)	2.7 (9.9)	34.3 (7.0)			
		.7864				
B0223E†						
Week=2	-4.2† (6.1)	-13.7 (9.0)	9.5† (6.7)	-2.9† (7.0)	-14.9 (9.1)	12.0† (5.9)
		.1361			.1093	
	6.5 (11.7)	5.5 (15.6)	0.9 (10.3)			
		.7248				
Week=4	5.6† (6.2)	-1.9 (9.3)	7.5† (6.9)	4.4† (7.2)	-4.6 (9.5)	9.1† (6.2)
		.8424			.6285	
	27.3 (12.8)	30.6 (16.1)	-3.3 (9.8)			
		.0677				
Week=7	8.2† (6.4)	2.0 (9.7)	6.2† (7.3)	18.7† (6.3)	-2.3 (8.4)	21.0† (5.5)
		.8361			.7820	
	15.8 (10.8)	-8.5 (13.8)	24.3 (8.5)			
		.5451				
Week=10	30.2† (6.3)	24.6 (9.6)	5.6† (7.3)	31.1† (6.6)	11.6 (8.9)	19.5† (6.0)
		.0134			.2020	
	44.9 (13.0)	24.3 (16.9)	20.6 (10.7)			
		.1652				
Week=12	27.1† (6.6)	14.5 (10.2)	12.6† (7.7)	23.7† (8.2)	-3.9 (11.0)	27.6† (7.3)
		.1596			.7241	
	45.9 (12.3)	27.9 (16.1)	18.0 (10.3)			
		.0986				
LOCF	27.4† (6.5)	15.8 (9.8)	11.6† (7.4)	23.7† (8.3)	-1.8 (11.0)	25.5† (7.2)
		.1126			.8716	
	44.8 (9.9)	31.6 (13.1)	13.3 (8.6)			
		.0221				

†-Investigator 2578 deleted from 11-15 and 16-18 age groups

Table 24. Percent Decrease from Baseline Count of Noninflammatory Lesions Stratified on Age: LS Means

Study/ Week	11-15 / 19+ Treatment (SE)	11-15 / 19+ Investigator (SE)/p-value	11-15 / 19+ Interaction (SE)	16-18 Treatment (SE)	16-18 Investigator (SE)/p-value	16-18 Interaction (SE)
B0222E						
Week=2	10.3 (5.7)	5.5 (7.9) .4881	4.9 (5.4)	26.9 (5.6)	12.0 (7.9) .1363	14.9 (5.6)
	16.2 (10.4)	17.7 (14.8) .2364	-1.5 (10.5)			
Week=4	7.1 (8.4)	2.0 (11.2) .8571	5.0 (7.4)	18.3 (7.3)	17.1 (10.3) .1041	1.2 (7.2)
	26.8 (8.2)	7.2 (11.7) .5441	19.6 (8.4)			
Week=7	27.5 (7.5)	18.0 (10.1) .0794	9.4 (6.8)	43.7 (6.3)	31.6 (8.9) .0011	12.1 (6.3)
	40.6 (6.8)	15.5 (9.7) .1148	25.1 (6.9)			
Week=10	37.3 (7.5)	29.1 (10.3) .0062	8.2 (7.0)	45.8 (7.9)	40.5 (11.6) .0014	5.3 (8.5)
	48.9 (8.8)	25.7 (12.5) .0449	23.2 (8.9)			
Week=12	24.5 (10.1)	16.3 (13.7) .2403	8.2 (9.3)	57.1 (8.9)	45.6 (13.9) .0026	11.5 (10.6)
	49.3 (6.8)	20.6 (9.7) .0391	28.7 (6.9)			
LOCF	22.8 (9.3)	14.1 (12.8) .2769	8.8 (8.8)	57.1 (8.9)	47.4 (12.6) .0006	9.6 (8.9)
	45.5 (7.6)	17.3 (10.8) .1143	28.2 (7.7)			
B0223E†						
Week=2	8.7†(5.3)	6.4 (7.9) .4213	2.2† (5.9)	2.7† (7.9)	4.2 (10.3) .6828	-1.5† (6.7)
	29.1 (13.6)	37.3 (18.0) .0479	-8.1 (11.9)			
Week=4	4.8†(8.4)	27.1 (12.6) .0356	-22.3†(9.4)	9.8† (6.7)	4.8 (8.9) .5945	5.0† (5.8)
	-20 (19.0)	-14.3 (24.0) .5559	-5.5 (14.7)			
Week=7	12.4† (8.9)	25.3 (13.4) .0642	-12.9†(10.1)	16.5† (12.7)	12.9 (16.8) .4456	3.5† (11.1)
	15.4 (25.0)	24.2 (31.8) .4541	-8.8 (19.6)			
Week=10	31.8†(6.1)	37.2 (9.2) .0002	-5.4†(7.0)	24.3† (10.8)	9.2 (14.6) .5310	15.1† (9.8)
	32.3 (23.5)	45.4 (30.5) .1520	-13.1 (19.3)			
Week=12	35.2†(8.6)	36.5 (13.1) .0073	-1.2†(9.9)	24.6† (10.6)	2.3 (14.3) .8720	22.3† (9.5)
	27.9 (30.8)	39.3 (40.2) .3402	-11.4 (25.8)			
LOCF	35.9†(8.4)	39.6 (12.7) .0026	-3.7† (9.5)	24.6† (10.4)	2.5 (13.8) .8542	22.1† (9.0)
	28.7 (23.1)	31.5 (30.6) .3111	-2.7 (20.0)			

†-Investigator 2578 deleted from 11-15 and 16-18 age groups

Note from Table 24 above, both LOCF differences and differences after the 7th week are all positive, i.e., show a smaller decrease in the vehicle group than in the TMG 0.1% group. Thus, though the size of this difference varies considerably, and the differences may or may not be of statistical significance, the general pattern is consistent for each age group in both studies. That is, there tend to be fewer noninflammatory lesions with the TMG 0.1% treatment than with its vehicle.

c.4. Race

In both studies, most patients are white, and the number of nonwhite patients is too small to estimate least squares means. In particular, it is not appropriate to compute least squares means of lesion counts for the race groups. Also, the number of responses in the non-Caucasian groups at the 15th week and 29th week are too sparse for valid statistical inference. Descriptively, patterns are like those below.

Table 25. Physicians' Global Assessment Stratified by Race

	White				Other			
	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
	n	%	n	%	n	%	n	%
B0222E								
Excellent	28	34.6	8	9.5	1	25.0	.	.
Good	24	29.6	18	21.4	1	25.0	1	50.0
Fair	10	12.3	20	23.8	.	.	.	.
No Change	9	11.1	25	29.8	2	50.0	1	50.0
Poor	10	12.3	13	15.5	.	.	.	.
Total n	81		84		4		2	
CMH p-value		0.000						

	White				Other			
	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
	n	%	n	%	n	%	n	%
B0223E								
Excellent	19	25.7	6	8.3	1	25.0	.	.
Good	22	29.7	16	22.2	1	25.0	3	42.9
Fair	17	23.0	21	29.2	1	25.0	.	.
No Change	11	14.9	18	25.0	1	25.0	3	42.9
Poor	5	6.8	11	15.3	.	.	1	14.3
Total n	74		72		4		7	
CMH p-value		0.000						

Although the frequency of non-Caucasians in the study is too low for valid inference, note that in both studies, the non-Caucasian's in the TMG 0.1% group show a small superiority to those in the vehicle group. This at least is consistent with the sponsor's claim of efficacy.

f. Drop-outs

The various reasons for drop-outs in the two studies were categorized as follows (percentages are based on columns):

Table 26. Reasons for Dropping Out of Study

	B0222E						B0223E					
	TMG 0.10%		Vehicle		Total		TMG 0.10%		Vehicle		Total	
Reasons	n	%	n	%	n	%	n	%	n	%	n	%
Adverse Event	6	75%			6	33%	5	50%	3	23%	8	35%
Treatment Failure			5	50%	5	28%						
Protocol Violation	1	13%	1	10%	2	11%			2	15%	2	9%
Personal Reasons			1	10%	1	6%			1	8%	1	4%
Lost to Follow-up	1	13%	3	30%	4	22%	5	50%	6	46%	11	48%
Other									1	8%	1	4%
Total Discontinued	8		10		18		10		13		23	

Note, as with other tables, this table differs somewhat from the tables presented by the sponsor in the printed volumes, but does reflect the data sets on disk. The adverse events associated with drop-outs were almost always related to skin irritation, particularly in the TMG 0.1% group. Except for adverse events and treatment failures, the within study drop-out rates are similar between treatment groups

3. Safety Data

a. Adverse Events

Subjects were interviewed at each return visit for the occurrence of adverse events. Since it was felt that erythema, peeling, burning/stinging, and itching were assessed separately, the investigators were instructed not to record these as adverse events unless they were sufficiently serious to require suspension, or even discontinuation, of treatment.

Table 27. Adverse Events

Body System	Event	B0222E TMG 0.10% # subjects	B0222E TMG 0.10% # events	B0222E Vehicle # subjects	B0222E Vehicle # events	B0223E TMG 0.10% # subjects	B0223E TMG 0.10% # events	B0223E Vehicle # subjects	B0223E Vehicle # events
Skin	Acne	1	1	.	.	.	.	2	2
	Bullous Eruption	1	1	.	.	2	2	.	.
	Dermatitis Contact	1	1	1	1	.	.	.	.
	Naevus	.	.	.	.	.	.	1	1
	Rash	1	1	.	.	.	.	.	.
	Rash Erythematous	.	.	.	.	1	1	.	.
	Seborrhoea	.	.	.	.	1	1	.	.
	Skin Disorder	26	31	4	9	22	31	.	.
	Skin Dry	2	2	.	.	1	1	.	.
	Skin Ulceration	.	.	.	.	.	.	1	2
Muskulo-Skeletal	Bone Disorder	1	1	.	.	.	.	.	.
	Myalgia	.	.	1	1	.	.	1	1
	Tendon Disorder	.	.	.	.	1	1	.	.
Central Nervous System	Depression	.	.	1	1	.	.	.	.
	Headache	6	8	4	8	3	3	1	1
	Insomnia	.	.	1	1	.	.	.	.
	Neuralgia	1	1	.	.	.	.	.	.
	Paraesthesia	1	1	1	1	.	.	.	.
Eye	Conjunctivitis	1	1	.	.	.	.	1	1
Ear	Ear Disorder	1	1	.	.	.	.	1	1
Gastroin-testinal	Diarrhoea	.	.	.	.	1	1	.	.
	Dyspepsia	.	.	2	2	.	.	.	.
	Mouth Dry	1	1	.	.	.	.	.	.
	Nausea	1	1	1	1	1	1	.	.
	Tooth Disorder	.	.	1	1	.	.	.	.

Table 27. (cont.) Adverse Events

Respiratory	Bronchitis	3	3	1	1	.	.	.	.
	Coughing	2	2	2	2	.	.	2	2
	Pharyngitis	2	2	2	2	1	1	.	.
	Pneumonia	.	.	1	1	.	.	.	.
	Rhinitis	8	9	7	8	6	6	6	6
	Sinusitis	1	1	2	2	2	2	3	3
	Upper Respiratory Tract Infection	4	4	4	4	3	3	3	3
Renal	Urinary Tract Infection	1	1	.	.	1	1	.	.
Genitalia	Dysmenorrhoea	1	1	1	1	2	5	1	2
	Epididymitis	.	.	.	.	.	.	1	1
Neoplasm	Breast Neoplasm Benign Female	1	1	.	.	.	.	.	.
General Pain	Allergy	1	1	.	.	.	.	.	.
	Back Pain	2	2	1	1	.	.	.	.
	Influenza-like Symptoms	3	3	5	5	2	2	2	2
	Pain	.	.	3	3	.	.	1	1
Infectious Disease	Herpes Simplex	.	.	.	.	1	1	.	.
	Infection	2	2	.	.	1	1	.	.
	Otitis Media	3	3	2	2	.	.	1	1

Except for the highly statistically significant set of skin disorders, the frequency of various individual adverse events is too sparse for statistical modeling. No other body groups seem to show statistically significant differences between the TMG 0.1% and vehicle treatments.

In the TMG 0.1% group in the B0222E study of the 26 skin events, 18 were of moderate severity, and one was very severe. The corresponding vehicle group had one event of moderate severity and the other event was rated as severe. In the B0223E study of the 22 skin disorders in the TMG 0.1% group, 15 were of moderate severity and 4 were rated as severe.

b. Safety Variables

At baseline (week 0) and each return visit, the physician recorded an assessment of erythema and peeling. These represent the patients' status at that visit. Further scores for burning/stinging and itching were recorded. These two variables represent the overall experience of the subject prior to that visit and after any preceding visits. All variables were recorded on a four point scale: none, mild or slight, moderate, and severe. The CMH test below is a test of equal treatment means.

Table 28. Incidence and Severity of Erythema

Erythema	B0222E				B0223E			
	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
Week=0	n	%	n	%	n	%	n	%
None	75	85.2	78	86.7	75	89.3	73	85.9
Mild	13	14.8	12	13.3	9	10.7	12	14.1
Total	88		90		84		85	
CMH p-value		0.788				0.499		
Week=2	n	%	n	%	n	%	n	%
None	43	50.6	81	92.0	42	54.5	70	86.4
Mild	33	38.8	7	8.0	29	37.7	11	13.6
Moderate	8	9.4	.	.	6	7.8	.	.
Severe	1	1.2	.	.	.	.	.	.
Total	85		88		77		81	
CMH p-value		0.000				0.000		
Week=4	n	%	n	%	n	%	n	%
None	48	59.3	81	93.1	55	72.4	68	81.9
Mild	31	38.3	6	6.9	19	25.0	15	18.1
Moderate	2	2.5	.	.	2	2.6	.	.
Total	81		87		76		83	
CMH p-value		0.000				0.058		
Week=7	n	%	n	%	n	%	n	%
None	52	65.0	78	90.7	56	76.7	71	93.4
Mild	28	35.0	8	9.3	16	21.9	5	6.6
Moderate	.	.	.	.	1	1.4	.	.
Total	80		86		73		76	
CMH p-value		0.000				0.002		
Week=10	n	%	n	%	n	%	n	%
None	55	68.8	74	90.2	57	80.3	68	94.4
Mild	24	30.0	8	9.8	14	19.7	4	5.6
Moderate	1	1.3	.	.	.	.	.	.
Total	80		82		71		72	
CMH p-value		0.001				0.010		
Week=12	n	%	n	%	n	%	n	%
None	57	71.3	74	92.5	65	87.8	67	93.1
Mild	22	27.5	6	7.5	9	12.2	5	6.9
Moderate	1	1.3	.	.	.	.	.	.
Total	80		80		74		72	
CMH p-value		0.000				0.260		

From Table 28 above, note that starting at the second week, in study B0223E, the TMG 0.1% group has statistically significantly worse erythema at all time points. In the B0223E study, there was statistically significantly worse erythema at all weeks except the fourth and twelfth week.

Table 29. Incidence and Severity of Peeling

Peeling	B0222E				B0223E			
	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
Week=0	n	%	n	%	n	%	n	%
None	85	96.6	85	94.4	83	98.8	84	98.8
Slight	3	3.4	5	5.6	1	1.2	1	1.2
Total	88		90		84		85	
CMH p-value	0.478				0.993			
Week=2	n	%	n	%	n	%	n	%
None	35	41.2	84	95.5	35	45.5	77	95.1
Slight	36	42.4	4	4.5	31	40.3	4	4.9
Moderate	13	15.3	.	.	11	14.3	.	.
Severe	1	1.2	.	.	.	.	.	.
Total	85		88		77		81	
CMH p-value	0.000				0.000			
Week=4	n	%	n	%	n	%	n	%
None	47	58.0	81	93.1	52	68.4	80	96.4
Slight	29	35.8	6	6.9	22	28.9	3	3.6
Moderate	5	6.2	.	.	2	2.6	.	.
Total	81		87		76		83	
CMH p-value	0.000				0.000			
Week=7	n	%	n	%	n	%	n	%
None	42	52.5	81	94.2	55	75.3	75	98.7
Slight	30	37.5	5	5.8	18	24.7	1	1.3
Moderate	8	10.0	.	.	.	.	.	.
Total	80		86		73		76	
CMH p-value	0.000				0.000			
Week=10	n	%	n	%	n	%	n	%
None	56	70.0	73	89.0	55	77.5	71	98.6
Slight	23	28.8	9	11.0	15	21.1	1	1.4
Moderate	1	1.3	.	.	1	1.4	.	.
Total	80		82		71		72	
CMH p-value	0.002				0.000			
Week=12	n	%	n	%	n	%	n	%
None	58	72.5	78	97.5	70	94.6	70	97.2
Slight	22	27.5	2	2.5	4	5.4	2	2.8
Total	80		80		74		72	
CMH p-value	0.000				0.414			

Note that starting at the second week, for both studies, the TMG 0.1% group has significantly worse peeling at all time points except the 12th week in the B0223E study.

Table 30. Incidence and Severity of Burning/Stinging

Burning	B0222E				B0223E			
	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
Week=0	n	%	n	%	n	%	n	%
None	86	97.7	90	100%	82	97.6	83	97.6
Slight	2	2.3	.	.	2	2.4	2	2.4
Total	88		90		84		85	
CMH p-value		0.154				0.985		
Week=2	n	%	n	%	n	%	n	%
None	47	55.3	85	96.6	44	57.1	77	95.1
Slight	24	28.2	3	3.4	28	36.4	4	4.9
Moderate	9	10.6	.	.	5	6.5	.	.
Severe	5	5.9	.	.	.	.	.	.
Total	85		88		77		81	
CMH p-value		0.000				0.000		
Week=4	n	%	n	%	n	%	n	%
None	61	75.3	86	98.9	66	86.8	82	98.8
Slight	18	22.2	1	1.1	7	9.2	1	1.2
Moderate	2	2.5	.	.	3	3.9	.	.
Total	81		87		76		83	
CMH p-value		0.000				0.003		
Week=7	n	%	n	%	n	%	n	%
None	67	83.8	82	95.3	71	97.3	76	100%
Slight	9	11.3	3	3.5	1	1.4	.	.
Moderate	4	5.0	.	.	1	1.4	.	.
Severe	.	.	1	1.2	.	.	.	.
Total	80		86		73		76	
CMH p-value		0.043				0.165		
Week=10	n	%	n	%	n	%	n	%
None	65	81.3	81	98.8	71		71	98.6
Slight	15	18.8	1	1.2	.	.	1	1.4
Total	80		82		71		72	
CMH p-value		0.000				0.317		
Week=12	n	%	n	%	n	%	n	%
None	71	88.8	78	97.5	72	97.3	72	100%
Slight	7	8.8	2	2.5	2	2.7	.	.
Moderate	1	1.3	.	.	.	.	.	.
Severe	1	1.3	.	.	.	.	.	.
Total	80		80		74		72	
CMH p-value		0.030				0.161		

In the B0222E study burning/stinging is statistically significantly worse in the TMG 0.1% group than its vehicle at all weeks after the baseline. In the B0223E study the results are more ambiguous.

Table 31. Incidence and Severity of Itching

Itching	B0222E				B0223E			
	TMG 0.10%		Vehicle		TMG 0.10%		Vehicle	
Week=0	n	%	n	%	n	%	n	%
None	81	92.0	79	87.8	79	94.0	79	92.9
Slight	7	8.0	11	12.2	5	6.0	6	7.1
Total	88		90		84		85	
CMH p-value	0.311				0.777			
Week=2	n	%	n	%	n	%	n	%
None	55	64.7	84	95.5	57	74.0	76	93.8
Slight	20	23.5	4	4.5	16	20.8	4	4.9
Moderate	7	8.2	.	.	4	5.2	1	1.2
Severe	3	3.5	.	.	.	.	.	.
Total	85		88		77		81	
CMH p-value	0.000				0.001			
Week=4	n	%	n	%	n	%	n	%
None	72	88.9	85	97.7	66	86.8	82	98.8
Slight	8	9.9	1	1.1	10	13.2	1	1.2
Moderate	1	1.2	1	1.1	.	.	.	.
Total	81		87		76		83	
CMH p-value	0.064				0.003			
Week=7	n	%	n	%	n	%	n	%
None	69	86.3	81	94.2	69	94.5	73	96.1
Slight	7	8.8	5	5.8	4	5.5	3	3.9
Moderate	4	5.0	.	.	.	.	.	.
Total	80		86		73		76	
CMH p-value	0.033				0.628			
Week=10	n	%	n	%	n	%	n	%
None	67	83.8	74	90.2	68	95.8	69	95.8
Slight	12	15.0	8	9.8	2	2.8	3	4.2
Moderate	1	1.3	.	.	1	1.4	.	.
Total	80		82		71		72	
CMH p-value	0.170				0.733			
Week=12	n	%	n	%	n	%	n	%
None	69	86.3	77	96.3	71	95.9	71	98.6
Slight	7	8.8	3	3.8	3	4.1	1	1.4
Moderate	3	3.8	.	.	.	.	.	.
Severe	1	1.3	.	.	.	.	.	.
Total	80		80		74		72	
CMH p-value	0.016				0.307			

Although after baseline itching is virtually always worse in the TMG 0.1% group than in the vehicle group, it is statistically significantly worse at only a few time points in the studies. This suggests that itching is worse in the TMG 0.1% group, but not as extreme as with the erythema or peeling.

Reviewer Conclusions:

The sponsor proposes to use tretinoin within the sponsor's patented acrylates copolymer porous microspheres for the treatment of acne vulgaris. The resulting gel, Tretinoin MICROSPONGE® Gel, 0.1%, i.e., TMG 0.1%, was compared to its vehicle in two U.S., two armed, vehicle controlled, randomized, double-blinded studies, denoted B0222E and B0223E respectively. It should be noted that the formulation of TMG 0.1% used in these clinical trials differs slightly from the formulation proposed for marketing. However, it was the opinion of the Medical Officer that these formulations were clinically equivalent. Still, as a point of science, it is this reviewer's opinion that the formulation tested should be the formulation proposed for marketing.

For patients in both studies, the sponsor proposed that the primary endpoints be chosen as the physician's global evaluation of treatment efficacy, performed at the end of the study or when the subject left the study, as well as inflammatory lesion counts, noninflammatory lesion counts, and total lesion counts. The medical officer amended this to be the global evaluation, plus success in both studies with either the inflammatory lesion count or the noninflammatory lesion count.

Lesion counts were made at baseline, and at weeks 2, 4, 7, 10, and 12. For analysis, these were measured as percent change from baseline, so that a positive number gave the percent decrease from the baseline. The probability distribution of these percent change measures is not very normal, so as a supplemental analysis, the absolute counts were analyzed. These absolute counts are approximately lognormal in distribution, and theoretically provide a better analysis . However, actual results were quite consistent whether one used log counts or percent change from baseline.

For both studies, the physicians' global evaluation was statistically significantly better in the TMG 0.1% treatment group than in its vehicle (CMH mean differences test from Table 2: $p \leq .000$ in both studies). For inflammatory lesions, from Table 4, at the 12th week, in the B0222E study the estimated percent reduction in inflammatory lesions is 36% (Standard Error - SE 6%) in the TMG 0.1% group versus 13% (SE 6%) in the vehicle group (Table 4- test of equal reductions: $p \leq .0051$). On the other hand, at the 12th week in the B0223E study the estimated percent reduction in inflammatory lesions is 27% (SE 6%) in the TMG 0.1% group versus 22% (SE 6%) in the vehicle group (Table 4: $p \leq .4951$). To see what a small difference this is in absolute lesion counts, at 12 weeks in the B0222E the estimated number of inflammatory lesions in the TMG 0.1% group is 10, and in the vehicle group 14 (Table 6 - test of equal counts: $p \leq .0034$). In the B0223E study, at 12 weeks, the estimated number of inflammatory lesions in the TMG 0.1% group is 12, versus 13 for vehicle ($p \leq .2393$). While there is statistically clear evidence of efficacy in reducing inflammatory lesions in the B0222E study, the corresponding results from the B0223E study were more problematical. Results from using the last-observation-carried-forward (LOCF) responses are equivalently ambiguous.

From Table 8, for noninflammatory lesions at the 12th week, in the B0222E study, the estimated percent reduction is 47% (SE 5%) in the TMG 0.1% group versus 17% (SE 5%) in the vehicle group (Table 8 - test of equal reductions: $p \leq .0000$). At the 12th week

in the B0223E study the estimated percent reduction in noninflammatory lesions is 34% (SE 8%) in the TMG 0.1% group versus an increase -10% (SE 9%) in the vehicle group (Table 8: $p \leq .0003$). This corresponds to an estimated lesion count of 14 or 15 in the TMG 0.1% groups, versus 26 to 25 in the vehicle groups (from Table 10). Results for the LOCF response for noninflammatory lesions are equivalent. So both studies seem to provide statistically strong evidence of efficacy in reducing noninflammatory lesions.

Two minor difficulties arose in interpreting the above results:

1. There were a number of significant interactions of treatment and investigator. However, at the later time points these were all quantitative interactions, and do not reflect a reversal of treatment. Further, the impact of these differences is much smaller than the treatment effects.

2. There were many investigator effects, often of the same magnitude as the treatment effects. These were modeled in mixed model/repeated measures analysis. The result seemed to be that while there were strong investigator differences, and often investigator by period interactions, there were no apparent investigator by treatment by time interactions. So the effect of time and investigator is roughly balanced across treatment group.

Thus these potential problems do not seem to particularly modify the conclusion that both treatments show a statistically significant difference between TMG 0.1% and its vehicle in terms of noninflammatory lesions (as well as total lesions).

After removing one investigator with two or fewer males in the TMG 0.1% treatment group, results in gender subgroups were generally consistent with the ungrouped results (see Tables 17 and 19). Similarly (from Tables 22 and 24) for age subgroups 11-15, 16-18, and 19+ results for these subgroups are generally consistent with the ungrouped data (after deleting the same investigator from the age 11-15 and 16-18 groups).

Statistically, the only clear adverse event associated with Tretinoin Microsponge Gel, 0.1%, was irritation to the skin. Some 69% of the subjects in the TMG 0.1% group in the B0222E study displayed erythema at some office visit, versus 26% in the vehicle group. Percentages were less discrepant in the B0223E study, 50% versus 27%. Results were similar for peeling, and burning/stinging. From Table 27, about 30% of the subjects in the TMG 0.1% group in the B0222E study were recorded as having an adverse skin disorder versus 5% in the vehicle group. In B0223E study 26% of the TMG 0.1% subjects had adverse skin disorders recorded versus none in vehicle.

As noted above, according to the medical officer, the sponsor is assumed to have demonstrated efficacy if differences for the physician's global evaluation and either inflammatory lesions or noninflammatory lesions are statistically significant. Since statistical significance has been achieved on both the physician's assessment and on the noninflammatory lesion counts, it is this reviewer's opinion that the sponsor has demonstrated that a twelve-week treatment with Tretinoin MICROSPONGE® Gel, 0.1%, is

effective in the treatment of acne vulgaris, particularly in reducing noninflammatory lesions. This is consistent with their proposed package insert where the postulated mode of action of Tretinoin is primarily to reduce and alleviate comedones. There is evidence that TMG 0.1% is associated with facial irritation, though possibly less than with Tretinoin cream.

See my review

So, it appears that the drug has demonstrated efficacy with the physician's global assessment of efficacy and with noninflammatory lesions. Assuming that the slight difference in formulations is of no importance, and that the adverse events are less than would be expected with Tretinoin cream, this reviewer would recommend approval of Tretinoin MICROSPONGE® Gel, 0.1%, for the treatment of inflammatory lesions associated with acne vulgaris.

Steve Thomson 2 Jan 96

Steve Thomson
Mathematical Statistician, Biometrics IV

Jan 2, '96

concur: R. Srinivasan, Ph.D.
Acting Team Leader, Biometrics IV

1/2/96

concur: Ralph Harkins, Ph.D.
Acting Division Director, Biometrics IV

cc:
Archive NDA: 20-475
HFD-540/Division File
HFD-540/Dr. Wilkin
HFD-540/Dr. Chambers
HFD-540/Dr. Vaughn
HFD-540/Ms. Kozma-Fornaro
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Mr. Thomson
HFD-701/Dr. Anello
HFD-344/Dr. Pierce
This review has 38 pages.
Chron.

\Thomson\WP Text\x 7-2078\January 2, 1996\c:\wpfiles\report6.wp

DIVISION OF DERMATOLOGIC AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-475

REVIEW # 1 **DATE REVIEWED:** 9/11/95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	2/6/95	2/6/95	2/16/95
AMENDMENT	6/29/95	7/3/95	
AMENDMENT	7/17/95	7/18/95	

NAME & ADDRESS OF APPLICANT:
Advanced Polymer Systems Inc (APS)
3696 Haven Avenue, Redwood City, CA 94063
Sergio Nacht, Ph.D., Senior V.P., Science and Technology,
415-366-2626

DRUG PRODUCT NAME
Proprietary: **NURETIN GEL 0.1%** (For marketing by Ortho Dermatological)
Established: Tretinoin microsponge gel (Tretinoin gel is a USP monograph item)
Code Name/#:
Chem.Type/Ther.Class: 5-S

PHARMACOL. CATEGORY: For acne treatment

DOSAGE FORM: Gel; whether Nuretin product should be classified as a gel or suspension was discussed between FDA/USP personnel on 10/13/92; Nuretin is supplied in 2, 20 and 45 gm. tubes.

STRENGTHS: 0.1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
Tretinoin USP; (all-E) 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid; all-*trans* Retinoic acid (TRA); $C_{20}H_{28}O_2$; Mol. wt. 300.4; CAS# 302-79-4.

RELATED DOCUMENTS:
IND
DMF
DMF
DMF

DMF
DMF
DMFs

REMARKS:

The applicant believes that Nuretin gel is not an antimicrobial drug for acne, and the microbiological review should be limited to the USP preservative effectiveness test. Acne disease is characterized by inflammation of pilosebaceous skin glands, localization of Propionibacterium acnes, keratinization, and an increased rate of sebum production. Regarding the safety question, the applicant has responded in the following manner. Microsponge material used for Nuretin gel is similar to the Polytrap material used in cosmetic products. Microsponge material is a copolymer of and it contains about ppm monomers. However, these monomer levels are diluted to about ppm in Nuretin gel. These monomers are known sensitizers (nail products) but harmless at ppm. Tretinoin microsponge has tretinoin filled open pores, and therefore Nuretin gel has less irritancy. However, *FDA Consumer* (Nov. 78) had stated that tretinoin may increase the risk of skin cancer, and acne drug tretinoin does not mix with sun. During clinical research, Nuretin gels were prepared at a 15 kg. batch size at the R&D site. Early investigational formulations had % benzyl alcohol and failed the USP antimicrobial effectiveness test. Subsequently, Nuretin gel was reformulated with % benzyl alcohol (see IND amendments 3 and 8 dated 2/14/92 and 11/25/92). One pivotal clinical study has shown its efficacy (n=122; 0, 0.025, and 0.1% tretinoin gels). Another pivotal clinical study has shown less irritancy compared to Retin-A 0.1% Cream. Batches of 2,200 kg. size Nuretin gels were prepared at Ortho Dermatological, and released on the basis of positive TLC identity, NLT % assay, LT % photoisomers plus autoxidation products, and compliance with the USP antimicrobial effectiveness test.

The applicant has requested an expiry date of 18 months at RT for Nuretin gel prepared with % overage. Satisfactory stability data and executed batch records were submitted by the applicant for 4 x 2,200 kg. Nuretin gel batches (PE-844, 845, 849 and 850). According to the scientific literature, tretinoin is unstable due to photoisomerization, decarboxylation, and polymerization reactions. Photoisomerization reactions have produced 13-*cis* retinoic acid (CRA), 9,13-di-*cis* isomer, 5-alpha-epoxy 5,6-dihydro retinoic acid (ERA), and 4-oxo retinoic acid (ORA).

Decarboxylation reaction has produced an adduct (decomposition product plus retinoic acid). Polymerization has occurred in the presence of water.

CONCLUSIONS & RECOMMENDATIONS:

CMC sections for Nuretin gel are adequate and APPROVABLE.

cc:
Orig. NDA 20-475
HFD-540/Division File
HFD-007/Maturu
HFD-540/DeCamp
HFD-540/Kozma-Fornaro

filename: N 20-475
SATISFACTORY

P. Maturu, Primary Review Chemist

Wilson W. DeCamp, Ph.D. 5/7/96
W. DeCamp, Supervisory Chemist

DIVISION OF DERMATOLOGIC AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-475

REVIEW # 2 **DATE REVIEWED:** 2/4/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	2-6-95	2-6-95	2-16-95
AMENDMENT	6-29-95	7-3-95	
AMENDMENT	7-17-95	7-18-95	
AMENDMENT	1-2-96	1-4-96	

NAME & ADDRESS OF APPLICANT:
Advanced Polymer Systems Inc (APS)
3696 Haven Avenue, Redwood City, CA 94063
Sergio Nacht, Ph.D., Senior V.P., Science and Technology,
415-366-2626

DRUG PRODUCT NAME
Proprietary: **NURETIN GEL 0.1%** (For marketing by Ortho Dermatological)
Established: Tretinoin microsponge gel (Tretinoin gel is a USP monograph item)
Code Name/#:
Chem.Type/Ther.Class: 5-S

PHARMACOL. CATEGORY: For acne treatment

DOSAGE FORM: Gel; whether Nuretin product should be classified as a gel or suspension was discussed between FDA/USP personnel on 10/13/92; Nuretin is supplied in 2, 20 and 45 gm. tubes.

STRENGTHS: 0.1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
Tretinoin USP; (all-E) 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid; all-*trans* Retinoic acid (TRA); $C_{20}H_{28}O_2$; Mol. wt. 300.4; CAS# 302-79-4.

RELATED DOCUMENTS:
IND
DMF
DMF

DMF
DMF
DMF
DMFs

REMARKS:

Reference is made to Chemist review #1 dated 9/11/95 for all information regarding chemistry, manufacturing and controls (CMC) for the subject New Drug Application. Chemist review #1 found the NDA approvable from a CMC standpoint. However, the approvability state for this NDA depends on the findings of the Establishment Inspections reports (EERs) for the facilities stated in the NDA (pg.13) and the Environmental Assessment review and FONSI (pg.15), which chemist review #1 failed to indicate. In this regard, Chemist review # 2 was drafted to summarize this information as follows:

1. Establishment Inspections: Acceptable for all facilities except Advanced Polymer System, Redwood City, CA. facilities; see below.

(a)

(preparation of Tretinoin USP bulk drug; see DMF EER requested via CIRTS on 6/30/95 (EER ID 8400). Inspection of these facilities was completed on 7/6/95. **Memo dated 1/29/96 from the Office of Compliance found these facilities acceptable.**

(b)

(for the preparation of Tretinoin USP bulk drug; see DMF EER requested via CIRTS on 6/30/95 (EER ID 8400). Inspection of these facilities was completed on 7/6/95. **Memo dated 1/29/96 from the Office of Compliance found these facilities acceptable.**

(c) Advanced Polymer Systems (APS), 301 Laser Lane, Lafayette, LA 70507 (preparation of Tretinoin Microsponge 1.05%; DMF EER requested via CIRTS on 6/30/95 (EER ID 8400). Inspection of these facilities was completed on 1/26/96. **Memo dated 1/29/96 from the Office of Compliance found these facilities acceptable.**

Note: The facilities at APS, Lafayette, LA was inspected by the New Orleans District Office on 8/1,3,7,10,14,21, & 23/95. These facilities were found unacceptable from GMP standpoint. In this regard, a Form 483 was issued to APS on 8/23/95 for deviations in GMPs as follows:

* Failure to evaluate and document non-process and process related errors.

* Failure to document the passivation operation performed on manufacturing and in-line sampling equipment (reportedly the firm has not notified the FDA of this equipment preparation operation).

* Lack of procedures for documenting the passivation of sampling equipment.

* Lack of validating residual Tretinoin on stainless steel surfaces.

* Failure to calibrate the Shiamadzu spectrophotometer as per firm's and manufacturer of the instrument's instructions.

NOL-DO reinspection on 1/22-23/96 reveals that the firm has corrected the previous FDA-483 items as stated above (see FAX dated 1/26/96 from Patricia K. Schafer, Supervisory Investigator).

The corrected actions were described in NDA amendment dated 1/2/96.

(d) Advanced Polymer Systems, 3696 C Haven Avenue, Redwood City, CA 94063 (for the quality control of Tretinoin Microsponge 1.05% and Tretinoin USP bulk drug). EER requested via CIRTS on 6/30/95 (EER ID 8400). Inspection of these facilities was completed on 12/5/95. **Memo dated 1/29/96 from the Office of Compliance found these facilities unacceptable.** Violation of the Application Integrity Policy (AIP) found by the San Francisco District Office of APS facilities was cited as the reason for the unacceptable recommendation. Chemist Review # 3 will address the AIP and the District findings.

(e)

(for microbial limit tests on Tretinoin Microsponge). EER requested via CIRTS on 6/30/95 (EER ID 8400). Inspection of these facilities was completed on 7/6/95. **Memo dated 1/29/96 from the Office of Compliance found these facilities acceptable.**

(f) Ortho Pharmaceutical Corporation, 1000 US Highway Route 202, Raritan, NJ 08869-0602 (preparation of Nuretin Gel 0.115%; DMF
Inspection of these facilities was completed on 9/20/95. **Memo dated 1/29/96 from the Office of Compliance found these facilities acceptable.**

(g) Ortho Pharmaceutical Corporation, Road # 2, Km 45.6, Bo Campo Alegre, Manati, Puerto Rico 00674 (for the preparation of Nuretin Gel 0.115%; DMF . Inspection of these facilities was completed on 1/29/96. **Memo dated 1/29/96 from the Office of Compliance found these facilities acceptable.**

2. Environmental Assessment: Acceptable EA was reported; see Chemist review #1 dated 9/11/95. Pending HFD-102 for concurrence.

   A satisfactory abbreviated EA was prepared as per 25.31a(b)(3); see EA review dated 9/7/95, and forwarded to HFD-102 for FONSI signature on 1/29/96.

3. Methods Validation: Pending Acceptable EERs from the Office of the Office of Compliance; see item 1 above.

CONCLUSIONS & RECOMMENDATIONS:

The New Drug Application is not approvable from manufacturing and controls standpoint under section 505 (b) (1) of the Act for failure to comply with GMPs [see item 1 (d) above].

EGP 2/4/96

Ernest G. Pappas

Review Chemist

cc: Org. NDA 20-475

HFD-540/Division File
HFD-540/EGPappas
HFD-540/Huene
HFD-540/Alam
HFD-160/Cooney
HFD-540/Ajayi
HFD-540/Srinivasan
HFD-540/Fornaro
HFD-540/De Camp WST 2/96
HFD-830/Sheinin

MAY 6 1996

MAY 6 1996

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-475

REVIEW # 3 **DATE REVIEWED:** 5/2/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC	28-AUG-95	30-AUG-95	
BC	17-OCT-95	18-OCT-95	
SNC	15-DEC-95	18-DEC-95	
EIR (fax)	undated	2-FEB-96	2-FEB-96
W/H (fax)	4-OCT-95	2-FEB-96	2-FEB-96
W/H (fax)	4-OCT-95	2-FEB-96	2-FEB-96
telecon	3-NOV-95	2-FEB-96	2-FEB-96
meeting memo	7-NOV-95	2-FEB-96	2-FEB-96
EIR exhibits	undated	2-FEB-96	2-FEB-96
OC memo (Lynch)	1-DEC-95	3-FEB-96	3-FEB-96
NC	20-FEB-96	22-FEB-96	

NAME & ADDRESS OF APPLICANT:

Advanced Polymer Systems, Inc. (APS)
3696 Haven Avenue, Redwood City, CA 94063
Sergio Nacht, Ph.D., Senior V.P., Science and Technology,
415-366-2626

DRUG PRODUCT NAME

Proprietary: **NURETIN GEL 0.1%** (for marketing by Ortho Dermatological)

Established: Tretinoin microsponge gel (Tretinoin gel is a USP monograph item)

Code Name/#: Tretinoin microsponge gel is also designated as TMG

Chem.Type/Ther.Class: 5-S

PHARMACOL. CATEGORY: For acne treatment

DOSAGE FORM: Gel; Nuretin is supplied in 2, 20 and 45 gm. tubes.

STRENGTHS: 0.1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Tretinoin, USP; (all-E) 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid; all-*trans* Retinoic acid (TRA); $C_{20}H_{28}O_2$; Mol. wt. 300.4; CAS# 302-79-4

SUPPORTING DOCUMENTS:

Chemist's review #1 (Maturu, 9/11/95)
Chemist's Review #2 (Pappas, 2/4/96)

RELATED DOCUMENTS:

IND
DMF
DMF
DMF
DMF

DMF
DMFs

REMARKS:

A product-specific GMP inspection of the applicant's Redwood City, CA, facilities took place 7/31/95 to 8/8/95. This covered both the current NDA

The EIR for the inspection was forwarded to HFD-324 on 10/4/95, including a recommendation to withhold approval for both applications, as well as a recommendation that the Application Integrity Policy be applied. Review of the EIR was completed by HFD-324, and forwarded to HFD-540 on 12/1/95. However, there is no record that this document was ever received by the Division. The EIR from SAN-DO, the referral memo to HFD-324, plus two additional documents describing discussions between SAN-DO and APS at a meeting on October 27 and by telephone on October 30 were provided by fax on 2/2/96. The supporting exhibits for the EIR were mailed by overnight delivery to this reviewer's home address, where they were received at 2:05 PM on Saturday, February 3. The submission of December 15 stated that APS has "corrected and solved the problems" identified at the August inspection. Since none of these problems required an amendment to the NDA as a solution, this submission is correctly classified as correspondence.

An additional product-specific GMP inspection for both products was performed at the Lafayette, LA, facility where the microsponge encapsulation is carried out. This EIR also recommended withholding approval (see Chemist's Review #2). The operations carried out at the Redwood City, CA, facility are quality control analyses for the microsponge encapsulation. This is an intermediate product in the drug manufacture. The encapsulated tretinoin microsponges are

shipped to other sites (Ortho, Raritan, NJ, and Ortho, Manati, PR) for manufacture, packaging and labeling of the finished drug product. The finished product release and stability testing are performed at the Redwood City, CA, facility.

The reintegration of analytical chromatograms is a practice of questionable acceptability. While such a procedure is possible with contemporary integration software, the need for it typically suggests that the operating parameters were incorrectly established, or that the detection electronics are malfunctioning (see 2.G., comment #14). In either event, a follow-up investigation should be done. Since there is no documented supervisory concurrence or follow-up (2.G., comment #11), and since the lot of bulk tretinoin used in the biobatch failed testing twice before passing (2.G., comment #15), a reasonable conclusion is that the identity, strength, quality and purity of the biobatch has not been demonstrated.

The validity of the clinical trials may, therefore, be in question. In the meeting of October 27, the District deferred this question to CDER.

This review also identified the fact that the applicant has been given reference authorization to an incorrect DMF. DMF is a DMF for the The correct reference for the manufacture of is DMF The DMF holder has been advised by telephone (2/6/96).

CONCLUSIONS & RECOMMENDATIONS:

This review concurs with the recommendation from SAN-DO to withhold approval. A not approvable letter should be issued to the applicant, citing 21 CFR 314.125(b)(13). Reinspection of the applicant's Redwood City, CA, facility should be requested following a response to this letter.

This issue is separate from the recommendation below concerning the application of the Application Integrity Policy. The GMP justification for the issuance of a not approvable letter remains valid, regardless of any decision concerning the AIP.

The inspection findings at the Redwood City, CA, facility are clearly materially related to the approvability of the application. As noted in the comments following Item G in the Review Notes, the analytical testing performed by APS reflects substandard laboratory practices. The accuracy of any numerical data reported by APS is clearly questionable. If the NDA had included accurate statements concerning these procedures, it is likely that the initial reviewer's decision would have been different. There seems to be no technically sound reason to disagree with the recommendation of the District or the Office of Compliance that the Application Integrity Policy be applied to APS.

There are no technically sound reasons derived from this application to disagree with the recommendation of the District or the Office of Compliance that the Application Integrity Policy be applied to APS.

Wilson H. DeCamp, Ph.D.

5-6-96
Eric B. Sheinin, Ph.D.

cc: Orig. NDA 20-475
following copies are distributed without appendices:
HFD-540/Division File (NDA 20-475
HFD-007/Maturu
HFD-540/Huene
HFD-540/Alam
HFD-540/Ajayi
HFD-160/Cooney
HFD-540/DeCamp
HFD-540/Kozma-Fornaro
HFD-324/Hartman
HFR-PA150/Bobrowicz
filename: N 20-475
NOT SATISFACTORY

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
HFD-540

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-475

JAN 2 1997

REVIEW # 4 **DATE REVIEWED:** 12/20/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	2-6-95	2-6-95	2-16-95
AMENDMENT	6-29-95	7-3-95	
AMENDMENT	7-17-95	7-18-95	
AMENDMENT	1-2-96	1-4-96	
NEW CORRES.	5-21-96	5-21-96	5-23-96
AMENDMENT (AZ)	8-7-96	8-8-96	8-16-96
AMENDMENT (BC)	12-6-96	12-9-96	12-11-96
faxes			12/18&19/96

NAME & ADDRESS OF APPLICANT:

Advanced Polymer Systems Inc (APS)
3696 Haven Avenue, Redwood City, CA 94063
Sergio Nacht, Ph.D., Senior V.P., Science and Technology,
415-366-2626

DRUG PRODUCT NAME

Proprietary: **NURETIN GEL 0.1%** (For marketing by Ortho Dermatological)

Established: Tretinoin microsponge gel (Tretinoin gel is a USP monograph item)

Code Name/#:

Chem.Type/Ther.Class: 5-S

PHARMACOL. CATEGORY: For acne treatment

DOSAGE FORM: Gel; whether Nuretin product should be classified as a gel or suspension was discussed between FDA/USP personnel on 10/13/92; Nuretin is supplied in 2, 20 and 45 gm. tubes.

STRENGTHS: 0.1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Tretinoin USP; (all-E) 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid; all-*trans* Retinoic acid (TRA); $C_{20}H_{28}O_2$; Mol. wt. 300.4; CAS# 302-79-4.

RELATED DOCUMENTS:

IND

DMF
DMF
DMF
DMF
DMF
DMFs

REMARKS:

The applicant responded on 5/21/96 and 8/7/96 to FDA's Not Approvable letter dated 5/6/96 with additional information. This information addressed the CMC issues which were found not approvable;

Reference is made to chemist review #1 dated 9/11/95 for all information regarding chemistry, manufacturing and controls (CMC) for the subject New Drug Application. Chemist review #1 found the NDA approvable from a CMC standpoint. Reference is also made to chem. reviews #2 and #3 dated 2/4/96 and 5/2/96, respectively, which summarizes the findings of the Establishment Inspections, Environmental Assessment and potential the violation of the Application Integrity Policy by APS. Chemist reviews #2 and #3 recommended the NDA not approvable from a manufacturing and controls standpoint for failure to comply with GMPs and Application Integrity Policy (Note: This applied to only the Redwood, CA facilities).

The following information summarizes the status for:

Establishment Inspections: Acceptable for all facilities except Advanced Polymer System, Redwood City, CA. facilities; waiting status on the Redwood facilities from the Office of Compliance and FUR of facilities approved on 1/29/96 (see EER dated 10/10/96).

Note: The Redwood City, CA facility will not be used in the approval of this NDA because the applicant has removed it as an alternate testing site from the NDA (see applicant's cover letter dated 8/7/96). The reason for this is because of FDA's concerns regarding failed assay results for bulk tretinoin (Lot 774) found during a pre-approval inspection, whereby a "483" was given to the applicant as the result of the Redwood City, CA site inspection.

Environmental Assessment: According to Chemist review #1, an acceptable EA was reported as per 25.31a(b)(3). An EA and FONSI was drafted on 9/7/96 by the Chemist and sent to Nancy Sager (HFD-357) for concurrence. In this regard, deficiencies were observed in the original EA review (see Memo dated 2/1/96 from Nancy Sager. Note: These deficiencies were conveyed to the applicant with our NA letter of 5/6/96. They were corrected with the Applicant amendment on 8/7/96 .

However, the applicant failed to submit a self certification that is in accordance with the instruction in the Industry Guide for foreign facilities (IV, pg.12). **Note: Our NA letter of 5/6/96 did not request this information.** ✓

In this regard, the applicant was requested by telecon on 12/18/96 to submit the self certification statement of compliance with local and national environmental laws (Section VI; pg. 31 of EA guidelines). A hard copy of this certification statement os forthcoming from the applicant. ✓

Therefore, the EA, as amended, is found acceptable. An new EA and FONSI was drafted on 12/19/96 and forwarded to HFD-357 for concurrence. The FONSI was approved by Nancy Sager (HFD-357) on 12/20/96 (see fax).

Methods Validation: Pending; to be requested.

Labeling:

The trademark Retin-A Micro was approved by the Labeling and Nomenclature Committee. However, the Committee recommended the established name for the product be labeled as (tretinoin topical gel), with the term "Microsphere" outside the parenthesis instead of inside of the parenthesis . The Division (HFD-540) recommends the term be removed from the established name, as recommended by the Labeling and Nomenclature Committee.

In this regard, the applicant was requested per telecon on 11/27/96 to revise the product name accordingly. Therefore, the applicant revised the labeling as Retin-A Micro (tretinoin gel) Microsphere, 0.1%. ✓

The original labeling for the package insert was reviewed and found acceptable from a technical standpoint with the exception of the product name. Therefore, the applicant should revised the labeling to reflect the L & N Committee's recommendation (above).

A specimen of the tube and carton labels were submitted on 12/6/96 per FDA's request. These labels contained the name change as recommended by the L & N Committee. The labeling is approvable from a technical standpoint. A hard copy of the official submission is forthcoming.

FPL should be requested.

CONCLUSIONS & RECOMMENDATIONS:

The New Drug Application (NDA) is approved from manufacturing and controls standpoint. The NDA is approved for CMCs, based on acceptable establishment inspections for all facilities except Advanced Polymer System, Redwood City, CA. facilities. The Redwood City site has been removed as a testing facility from the NDA by the applicant. This facility will be requested with a supplement at later date .

NOTE: The approvability of this NDA covers the period up to 12/29/96. Should the approval letter for the NDA not issue before 12/29/96, A FUR for the EERs approved on 1/29/96 will be required. In this regard, the FUR was requested on 10/29/96, in case the approval for this NDA was indeed not issued before the 12/29/96 date.

Environmental assessment was reviewed and found acceptable; FONSI was drafted. Nancy Sager (HFD-357) found the EA and FONSI acceptable

The labeling is approvable from a technical standpoint; FPL should be requested.

Methods Validation is pending.

Ernest G. Pappas 12/20/96
Ernest G. Pappas
Review Chemist

cc: Org. NDA 20-475

HFD-540/Division File
HFD-540/EGPappas
HFD-540/Alam
HFD-540/Ajayi
HFD-540/Cintron
HFD-830/Sheinin
HFD-540/Huene
HFD-160/Cooney
HFD-540/Srinivasan
HFD-540/De Camp WD 1/7/97

9w 1/8/96

Consult #695 (HFD-540)

RETIN-A MICRO tretinoin microsphere gel, 0.1%

RETIN-A is already approved as a proprietary name and was not evaluated. MICRO is a trademark for a certain type of Roche gel and is acceptable for use in conjunction with the product proprietary name.

The Committee feels the most appropriate established name for this product is (tretinoin topical gel) with the term "microsphere" appearing outside the parenthesis as descriptive terminology. The term "microsphere" is not yet an officially accepted compendial term and should appear outside of the established name for now and, if accepted by the USP, be moved into the parenthesis later.

D Boring 11/4/96, Chair
CDER Labeling and Nomenclature Committee

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Mr Dan Boring, Chair, (HFD-530)

From: Division of Dermatologic and Dental Drug Products (HFD-540)
Attention Ernie Pappas Phone: 827-2066

WS 9/24/96

SEP 2 4 1996

Date: 9/24/96

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: RETIN-A MICRO NDA# 20-475

Company Name: Advanced Polymer System

Established name, including dosage form: tretinoin microsphere gel, 0.1%

Other trademarks by the same firm for companion products: N.A.

Indications for Use (may be a summary if proposed statement is lengthly): Treatment of acne vulgaris

Initial comments from the submitter (concerns, observations, etc.):

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Sept.95

DIV

Consultative Review to HFD-540
DIVISION OF MEDICAL IMAGING, SURGICAL,
and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #1
10 April 1995

A. 1. NDA 20-475
APPLICANT: Advanced Polymer Systems, Inc.
3696 Haven Avenue
Redwood City, CA 94063

2. PRODUCT NAMES: Nuretin® Gel 0.1%
Tretinoin Microsponge® Gel 0.1%
Tretinoin Microsphere Gel 0.1%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Topical gel for application to affected facial areas.

4. METHODS OF STERILIZATION:
The product is a topical and as such is not a sterile preparation, but, conforms to microbial limit specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of acne vulgaris.

B. 1. DATE OF INITIAL SUBMISSION: 6 February 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:

Table 1. Documents referenced in this NDA.

Document	Subject Document Holder
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	
IND	
IND	
IND	
NDA 16-921	
NDA's 17-340, 17-522, 17-579, 17-955, 19-049	
NDA 19-963	

4. ASSIGNED FOR REVIEW: 22 February 1995

C. REMARKS: The application is for a new topical gel used in the treatment of acne. As a product intended for topical application it is not produced as a

sterile product, but should conform to microbiological specifications. These specifications are reviewed here.

D. CONCLUSIONS: The submission is recommended for approval on the basis of microbial integrity and preservative effectiveness.

10 April 1995

Paul Stinavage, Ph.D.

PTC 4/10/95

cc: Original NDA 20-475
HFD-160/Stinavage/Consult File
HFD-540/Div File/J. Holmes
Drafted by: P. Stinavage
R/D initialed by P. Cooney

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF AMENDMENT
14 November 1996

A. 1. NDA 20-475
APPLICANT: Advanced Polymer Systems, Inc.
3696 Haven Avenue
Redwood City, CA 94063

2. PRODUCT NAMES: Nuretin® Gel 0.1%
Tretinoin Microsponge® Gel 0.1%
Tretinoin Microsphere Gel 0.1%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Topical gel for application to affected facial areas.

4. METHODS OF STERILIZATION:
The product is a topical and as such is not a sterile preparation, but, conforms to microbial limit specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of acne vulgaris.

B. 1. DATE OF INITIAL SUBMISSION: 6 February 1995

2. DATE OF AMENDMENT: 9 August 1996

3. RELATED DOCUMENTS: Table 1. Documents referenced in this NDA

Document	Subject Document Holder
DMF	
DMF	
DMF	
DMF	
DMF	
DMF	

DMF

DMF

DMF

DMF

DMF

DMF

IND

IND

IND

NDA 16-921

NDA's 17-340, 17-522, 17-579, 17-955, 19-049

NDA 19-963

---

4. ASSIGNED FOR REVIEW: 13 November 1996

C. REMARKS: The applicant has responded to comments contained in Microbiologist's Review #1 dated 10 April 1995 in this submission.

D. CONCLUSIONS: The application is recommended for approval on the basis of microbial integrity and preservative effectiveness. The microbiologist's comments contained in "Microbiologist's Draft of Letter to the Applicant" should be communicated to the applicant.

14 November 1996

Paul Stinavage, Ph.D.

cc: Original NDA 20-475
HFD-805/Stinavage/Consult File
HFD-540/Div File/O. Cintron

Drafted by: P. Stinavage, 14 November 1996
R/D initialed by P. Cooney D. Hussong for PH Cooney 11/19/96

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Nuretin gel 0.1%
Tretinoin microsponge gel

Indicated for acne treatment

NDA 20-475

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-540

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-475

Nuretin gel 0.1%

Tretinoin microsponge gel

Indicated for acne treatment

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, Advance Polymer Systems has prepared an abbreviated environmental assessment (21 CFR 25.31a(b)(3) which evaluates the potential environmental impacts of the manufacture and use of Nuretin gel (Tretinoin microsponge gel), 0.1%. The drug is indicated for acne treatment. The point source(s) of manufacture of the drug substance is at [Roche-Switzerland and BASF-Germany], and the finished product is at [Ortho Dermatological, Raritan NJ and Manati, Puerto Rico]. The firm has provided documentation from the foreign governments of compliance with their environmental regulations.

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.

12/19/96 Ernest G. Pappas
DATE

PREPARED BY
Ernest G. Pappas
Chemist
HFD-540/HFD-830

12/19/96 Wilson H. DeCamp, Ph.D
DATE

DIVISION CONCURRENCE
Wilson H. DeCamp, Ph.D
Chemistry Team Leader
HFD-540/HFD-830

12/20/96 Nancy B. Sager
DATE

CONCURRED
Nancy B. Sager
Environmental Team Leader
Office of the Center Director
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet (drug substance)

CC: Original NDA 20-475/HFD-540
HFD-540/Pappas
HFD-540/DeCamp
HFD-540/Cintron
HFD-104/FONSI File [NDA 20-475]
HFD-104/Docket File
HFD-019/FOI Copy

ENVIRONMENTAL ASSESSMENT

1.0 DATE: **July 16, 1996**

2.0 NAME OF APPLICANT: **Advanced Polymer Systems, Inc.**

3.0 ADDRESS OF APPLICANT: **3696 Haven Avenue**
Redwood City, CA 94063

4.0 DESCRIPTION OF PROPOSED ACTION:

(a) Requested Approval

Advanced Polymer Systems, Inc. has filed a New Drug Application (NDA No. 20-475) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%), packaged in aluminum tubes. An Abbreviated Environmental Assessment (AEA) has been submitted pursuant to 21 CFR Part 25.31a(b)(3) since the product is intended for topical application.

(b) Need for Action

The new drug product, Tretinoin MICROSPONGE® Gel 0.1% (TMG), will be utilized in the treatment of acne by topical application to the affected areas once a day.

(c) Production Locations

The bulk drug, Tretinoin USP raw material is manufactured by either one of the manufacturers identified in Appendix VI. The manufacturers have Drug Master Files (DMF) on file with the Agency. Copies of letter permitting Advanced Polymer Systems, Inc. to cross-reference the respective DMFs are also attached in Appendix VI.

The active ingredient will be entrapped within a synthetic polymer system (Tretinoin in Acrylates Copolymer) by:

Advanced Polymer Systems, Inc.
301 Laser Lane
Lafayette, LA 70507

The final drug product, Tretinoin MICROSPONGE® Gel, 0.1% will be manufactured, processed, packaged, labeled, and controlled by:

1. Ortho Pharmaceutical Corporation
1000 U.S. Hwy Route 202
P.O. Box 300
Raritan, NJ 08869-0602

and

2. Ortho Pharmaceutical
Div. of OMJ Pharmaceuticals, Inc.
Road #2, Km. 45.6
Bo. Campo Alegre
Manati, Puerto Rico 00674

The Advanced Polymer Systems manufacturing facility at Northpark High Technology Industrial Center falls within the North Park Industrial Park which is located off of Pont Des Mouton between US Interstate Highway 49 and Louisiana State Highway 182. The Zoning Classification for the entire industrial park, including the Advanced Polymer Systems, Inc. facility, is Light Industry, designated as I-1. The permitted uses for Zoning Classification I-1 include the manufacture of drugs and cosmetics as well as a variety of other manufacturing processes. The facility is bounded by a security fence on all four sides. Advanced Polymer Systems, Inc. owns the lots on either side of the facility. There are approximately 50 residences 0.7 kilometer north northwest, 10 residences 0.5 kilometer to the west along State Highway 182, and approximately 80 residences from 1 to 2 kilometers to the south of the facility. There is a trailer park about 2 kilometers to the east.

Ortho's Raritan NJ site is located on 234 acres. The facility is bordered to the North, East and West by low/medium density residential development and office buildings. To the South lies a pharmaceutical manufacturer with emphasis on the production of diagnostic test kits. The Ortho Pharmaceutical, Manati, PR facility occupies 59 acres. To the North of the facility lies Highway #2, a pharmaceutical company, and several smaller businesses. The remaining area surrounding the facility is undeveloped land which is sparsely populated.

(d) Locations of Use

The product will be dispensed by pharmacies, and will be utilized as a prescription product by outpatients (e.g. in the home).

(e) Disposal Sites

A. Manufacturer of Tretinoin in Acrylates Copolymer Entrapment

Advanced Polymer Systems, Inc.
301 Laser Lane
Lafayette, Louisiana 70507

All of the returned, expired or rejected materials produced at Advanced Polymer Systems' Lafayette facility will be disposed off by incineration and/or fuels blending by a facility which is licensed by the EPA or an appropriate state authority to destroy hazardous materials. One or more of the disposal companies identified in the table below are currently being used. (Note: The EPA ID # and the permit # is the same for the following facilities). Washwater from the manufacturing process is disposed off through permitted discharge to the local Publicly Owned Treatment Works in Lafayette, Louisiana.

Disposal Facility	License/Permit No.	Expiration Date	Issuing Agency
	ARD 069748192	June 26, 1998	Department of Pollution Control and Ecology State of Arkansas
	ARD 981057870 (Part A RCRA) Part B Pending	None required for Part A	Department of Pollution Control and Ecology State of Arkansas
	TXD 046844700	September 15, 1997	Texas Natural Resources Conservation Commision
	ALD 981020894	November 5, 2002	Alabama Department of Environmental Management
	LAD 010395127	March 21, 2001	Louisiana Department of Environmental Quality
	LAD 079464 095 (Part A RCRA) Part B Pending	None required for Part A	Louisiana Department of Environmental Quality

B. Manufacturer of the Drug Product, Tretinoin MICROSPONGE® Gel, 0.1%

Ortho Pharmaceutical
Division of OMJ Pharmaceuticals, Inc.
Road #2, Km. 45.6
Bo. Campo Alegre
Manati, Puerto Rico 00674
and
Ortho Pharmaceutical Corporation
1000 U.S. Hwy Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Returned, expired or rejected drug product generated by Ortho Pharmaceutical Raritan, New Jersey and Manati, Puerto Rico will be disposed off by high temperature incineration at a facility which is licensed by the EPA or an appropriate state authority to destroy hazardous materials. The facilities currently being used are described in the table below.

PRODUCT SITE	DISPOSAL FACILITY	LICENSE/ PERMIT NO.	EXPIRATION DATE	ISSUING AGENCY
Manati, P.R.	Commercial Incineration, P.O. Box 9086 Carolina, P.R. 00988	PFE-LC-16-0393-0305-III-0	1/97	P.R. Envir. Quality Board
Raritan N.J.	American Ref-Fuel Co. 600 Avenue C at Stewart Ave. Hempstead, Westbury, N.Y. 11590	1-2820-01727/00001-0	8/96	N.Y. Dept. of Envir. Conservation

Washwater from the manufacturing process will be disposed through permitted discharge to the wastewater treatment facilities at Ortho Pharmaceutical, Manati, Puerto Rico, and at the local Publicly Owned Treatment Works in Barceloneta, Puerto Rico and Bridgewater, New Jersey.

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

The drug substance in the product--Tretinoin MICROSPONGE® Gel 0.1% -- is *all-trans* retinoic acid (Figure 5-1). It is a naturally occurring substance (Napoli et al., 1991), prepared synthetically from Vitamin A aldehyde (Windholz et al., 1983).

a. NOMENCLATURE

(i) Established Name(s)

Tretinoin
Retinoic Acid

(ii) Brand/Proprietary Name

None

(iii) Chemical Names

(1) Chemical Abstracts Index Name

all-trans - Retinoic Acid

(2) Systematic Chemical Name

(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

b. Chemical Abstracts Service (CAS) registration number

302-79-4

c. Molecular Formula

$C_{20} H_{28} O_2$

d. Molecular Weight

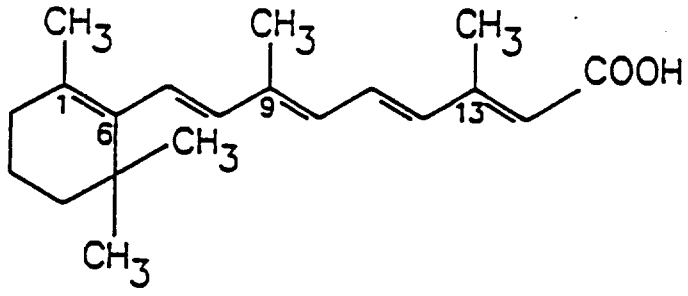
300.42

e. **Structural (graphic) Formula**

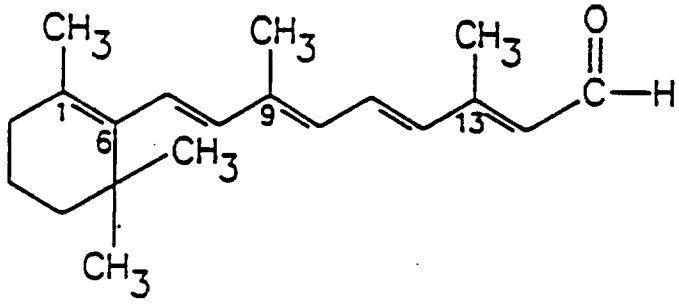
(See Figure 5-1)

f. **PHYSICAL DESCRIPTION**

The drug substance is a yellow to light orange crystalline solid. Its chemical and physical properties are listed in Table 5-1.



RETINOIC ACID (ALL TRANS)



VITAMIN A ALDEHYDE

FIGURE 5–1
STRUCTURES OF RETINOIC ACID
AND VITAMIN A ALDEHYDE

TABLE 5-1

Chemical and Physical Properties of Retinoic Acid

Molecular formula[a]	$C_{20}H_{28}O_2$
Molecular weight[a]	300.42
Melting point[a] *(all-trans)*	180-182°C
Solubility in water[b]	0.063 mg/L
Density[c]	ND
Vapor Pressure[d]	ND
Log octanol-water partition coefficient[e]	5.76
Log soil adsorption coefficient[f]	4.30
Acidic dissociation[g]	$4.5 \pm .05$
pK_a	
Electromagnetic absorption maximum(>290 nm)[a]	351 nm
(all-trans)	

---

[a]Merck Index, Tenth Edition (Windholz et. al., 1983).

[b]Measured spectrophotometrically at 21-23°C in physiological saline (150 mM NaCl, 1mM phosphate, pH 7.3) for *all-trans* retinoic acid (Szuts and Harosi, 1991).

[c]Not determined because density is a colligative property rather than a molecular property. Thus, density of retinoic acid (as a separate solid phase) is not relevant to the behavior of the dissolved molecules. If environmental releases of retinoic acid occur, they will always be in the dissolved state--either in water or in the lipophilic additives of the drug product. This justification for not measuring density is substantiated by 21 CFR 25.1(b) (3).

[d]Not determined for retinoic acid because its expected strong adsorption to sludge and sediment precludes transport via volatilization. This justification for not measuring the vapor pressure is substantiated by 21 CFR 25.1(b) (3).

[e]Calculated from the solubility using the equation *log 1/S (mole/L* = 1.339 *log* K_{ow} - 0.978 (Lyman et. al., 1982).

[f]Calculated from the solubility using the equation log K_{oc} = 3.64 - 0.55 *log* S (mg/L) (Lyman et. al., 1982).

[g]Range of pK_a values for carboxylic acids (Lyman et. al., 1982).

g. ADDITIVES

The naturally occurring isomers of retinoic acid and Vitamin A aldehyde are *all-trans*. There are no additives in the raw material.

h. IMPURITIES

all-trans retinoic acid is known to photo-isomerize in light and to oxidize in the presence of air. The composition of the Tretinoin in Acrylates Copolymer and the drug product is provided in Appendices IV and V.

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

a. Substances Expected to be Emitted

Advanced Polymer Systems, Inc., is requesting a claim for an abbreviated environmental analysis as per 21 CFR Part 25.31a(b)(3). This action satisfies the FDA conditions for an abbreviated assessment as Tretinoin MICROSPONGE® Gel will be administered to patients as a topical application. The active ingredient, tretinoin, is obtained by the from the manufacturers as identified in Appendix VI. The active ingredient is then entrapped within a synthetic polymer MICROSPONGE® System by Advanced Polymer Systems, Inc., Lafayette, LA. The loaded microsponge is subsequently incorporated into a gel at Ortho Pharmaceutical, Raritan, NJ and Manati, PR. The potential emissions of the drug substance are from washwater released into the water via wastewater treatment and to a lesser extent from airborne particulates. This environmental assessment will address the introduction and fate of the drug substance, tretinoin, in the environment.

The entrapment process occurs as a 385.49 kg batch operation. The manufacturing process consists of a 170 gal. stainless steel jacketed mix tank and a 2000 L stainless steel jacketed plow blender. The materials to be entrapped are dissolved in the mix tank. The mixture is then transferred into the blender for mixing with the polymer. The wet polymer powder is then dried with heat and vacuum to remove the solvent (acetone). The manufacturing process is not expected to result in the release of Tretinoin as an air-borne contaminant through the generation of dusts, aerosols, vapors or gases. The solvent used will be condensed and collected for disposal in an off-site licensed facility, with small releases occurring within the permitted limits. For a description of the air pollution control devices see section 6.1.1.

The equipment cleaning is expected to release Tretinoin as a constituent in the site's wastewater stream. Therefore the releases to the environment as a water-

borne contaminant will be discussed in detail below (section 6.1.2).

The gel manufacturing process occurs as a 2200 kg batch operation. The manufacturing process consists of a 2400 liter stainless steel kettle into which the entrapped active ingredient (Tretinoin in Acrylates Copolymer) is combined with excipients under slight vacuum to produce the final product. The process has been designed in part to limit air releases during the addition of the entrapped active, which is a light, dry powder. As such the manufacturing process is not expected to result in the release of air-borne contaminants through the generation of dusts, aerosols, vapors, or gases. However, a description of the associated air pollution control devices will be discussed below (sections 6.2.1 and 6.3.1).

Equipment cleaning is expected to release Tretinoin as a constituent in the manufacturing site's wastewater stream. Therefore, the releases to the environment as a water-borne contaminant will be discussed in detail below (sections 6.2.2 and 6.3.2).

b. Controls Exercised

6.1 Advanced Polymer Systems, Lafayette, LA

6.1.1 Air

The entrapment manufacturing process takes place in a mix tank and blender. The mix tank is vented through a carbon bed to absorb volatile organic compounds. The solvent is pumped into the mix tank from 55 gal drums. The dry components are added to the mix tank through a hatch on top of the mix tank. The liquid component is pumped into the mix tank from a 55 gal drum. A nitrogen sweep is provided to the mix tank. The mix tank agitator shaft has a double mechanical seal to prevent vapors from escaping. The rinse solvent is weighed into a covered plastic pail and then pumped into the mix tank after the solution is transferred to the blender.

The blender is vented through a dust collector and the vapor stream passes through a condenser, knock-out tank and steam jet. The blender is normally operated under vacuum. The dust collector is fitted with 14 GORE-TEX membrane filter bags. These bags are rated at removing 99.9% of all particles above 0.5 microns. The system is permitted by the Louisiana Department of Environmental Quality under Permit No. 1520-00044-01. The filter bags containing the active ingredient are disposed off through a licensed off-site disposal facility.

Based upon the 5th year production forecast for tretinoin entrapment, the manufacture of the entrapment at the Advanced Polymer Systems facility may result in airborne releases of 1.1×10^{-3} lbs/year. This is based upon a conservative estimate of 1 lb particulates released per batch to the aforementioned pollution control equipment. This is not expected to affect APS' ability to comply with its' air pollution permit.

6.1.2 Water

Water-borne releases are likely to occur from cleaning process equipment. Following product removal at the end of a batch run, the blender and room are cleaned and rinsed following a standard cleaning procedure. This cleaning operation is expected to release less than 3.85 kg of Tretinoin in Acrylates Copolymer which contains 1% Tretinoin into the facility's wastewater stream. The active release is less than 0.038 kg per batch. This wash-down residual will combine with the facility's 26,500 liters per day (LPD) wastewater stream. This stream passes through a filter press where 99% of the particulate matter is removed. The stream then passes through a primary and secondary carbon filtration system to reduce the Total Toxic Organics (TTO) level to less than the permitted levels of 2.13 parts per million (ppm). Since the Tretinoin will be entraped in the polymer particles, the active will be in the filter cake from the filter press. That filter cake is disposed off in an off-site licensed disposal facility. The potential 1% of the Tretinoin that may escape with the particulate matter will yield a wastewater concentration of 15 parts per billion (ppb) of active per batch at the receiving publicly owned treatment works.

Advanced Polymer Systems discharges its wastewater directly to the Lafayette Utilities Systems Wastewater Treatment Northeast Plant located in Lafayette, LA. The wastewater treatment plant provides secondary treatment via an oxidation ditch with secondary lime stabilization for approximately 3,330,000 LPD of wastewater. Assuming the active ingredient passes through the plant without undergoing biological degradation, the amount of active which would reach the environment would be 0.1 ppb per batch. Based on the 5th year production schedule (11 batches per year), the total yearly release to the environment is anticipated to be less than 5 gm.

Effluent limitations are set forth in Advanced Polymer Systems wastewater discharge permit. Under conditions of the Advanced Polymer Systems discharge permit, the manufacture of the Tretinoin entrapment is not expected to result in a non-compliance or to adversely affect the operation or efficiency of the wastewater treatment plant. The mix tank is cleaned with fresh solvent and that material is disposed off in a licensed off-site disposal facility.

6.2 Ortho Pharmaceutical, Raritan, NJ

6.2.1 Air

The gel manufacturing process will take place within a closed system (Fryma Module) located within the Cream manufacturing section of the plant. Designed as a 2200 kg batch operation, the active ingredient is loaded into the closed kettle through a transfer hose under slight vacuum. The manufacturing process continues under slight vacuum until complete.

The Fryma Module, by operating under a slight vacuum, considerably reduces the opportunity for air releases of the active ingredient. The Fryma Module is served by a re-circulating air system and a local exhaust ventilation system. The local exhaust system is capable, if needed, of removing particulate emissions by 99%. This system consists of a dust collector with 72 non-woven polypropylene tubes with a maximum rated capacity of 10,036 cubic feet per minute (cfm). The system is permitted by the New Jersey Department of Environmental Protection (DEP) under Permit No. 098298. Air filters containing the active ingredient will be disposed off through high temperature incineration at a commercially licensed incinerator. Because the Fryma Module operates in a manner which does not ordinarily generate air-borne emissions of the active ingredient, the local exhaust system is not an integral control device in this process. A conservative estimate of less than 1 lb of particulates will be generated per batch (2 batches/year at 5th year production schedule for APS TMG). This system is expected to limit particulate emssions from this manufacturing process to 0.02 lbs/year containing 1% tretinoin, or 2×10^{-4} lbs/year tretinoin. Collected particulates and filter media are disposed through high temperature incineration at a commercial solid waste incinerator.

Total RENOVA® and RETIN-A® production at Raritan is expected to be 115 batches/year. Total airborne releases for tretinoin from these products are estimated to be 5.7×10^{-4} lbs/year, but may increase to 7.7×10^{-4} lbs/year when APS TMG manufacturing is considered. This amount is not expected to affect Ortho's ability to comply with air pollution regulations or permit conditions applicable to this site and process.

6.2.2 Water

Water-borne releases are likely to occur from cleaning process equipment. Following product removal at the end of the batch run, the process vessels are cleaned and rinsed following a standard cleaning procedure. A cleaning agent is agitated within the stainless steel kettle, is rinsed with hot water, with a final purified water rinse being applied. This cleaning operation is expected to release

less than 0.03 kg of Tretinoin (per 2200 kg batch) into the facility's wastewater stream. This wash-down residual would then combine with the facility's 378,500 LPD wastewater stream, thereby yielding a wastewater concentration of 0.08 parts per million (ppm) of active at the receiving publicly owned treatment works.

Ortho discharges its wastewater directly to the Somerset Raritan Valley Sewerage Authority (SRVSA) located in Bridgewater, NJ. The SRVSA wastewater treatment plant provides secondary treatment for approximately 49,205,000 LPD of wastewater. Effluent from the SRVSA is discharged into the Raritan River. Assuming the active ingredient passes through the treatment plant without undergoing biological degradation, the amount of active which would reach the environment would be 0.61 parts per billion (ppb) per batch.

Effluent limitations applicable to the SRVSA are set by the New Jersey Department of Environmental Protection (DEP) through the New Jersey Pollutant Discharge and Elimination System. Although Ortho is not subject to these State discharge limits, it is subject to discharge limits imposed by the SRVSA as noted in Ortho's wastewater discharge permit. Under the conditions of Ortho's wastewater discharge permit, the manufacture of Tretinoin MICROSPONGE® Gel is not expected to result in non-compliance or to adversely affect the operation or efficiency of the wastewater treatment plant. The 5th year production of APS TMG, RENOVA®, and RETIN-A® at the Ortho Raritan plant is estimated to result in tretinoin releases to water of 745 gm/year.

6.3 Ortho Pharmaceutical, Manati, Puerto Rico

The manufacturing process at Manati will be identical to the process at the Raritan site (Section 6.2, above). As such releases to the environment may occur principally as water-borne emissions a discussion on the introduction of Tretinoin into the local environment follows.

6.3.1 Air

The gel manufacturing process will be identical to the process employed at Ortho's Raritan facility. The Fryma Module allows the active ingredient (Tretinoin in Acrylates Copolymer®) to be loaded into the closed kettle under vacuum, thereby minimizing the generation of airborne releases. General ventilation will remove any airborne particulates by passing air first through a dust collector rated at 90% removal efficiency, which is then further filtered by passing through High Efficiency Particulate Air (HEPA) filters which are rated at a 99% removal efficiency. The twice-filtered air is exhausted to atmosphere.

It is estimated that less than 1 lb of particulates will be generated per batch (14 batches/year at 5th year production schedule). This system is expected to limit particulate emissions from this manufacturing process to 0.014 lb/year containing 1.048% tretinoin, or 1.4×10^{-4} lbs/year. Filters containing the entrapped active substance will be destroyed by incineration by a commercial solid waste incinerator.

RENOVA® and RETIN-A® production at Manati is expected to be 200 batches/yr (based on 5th year production schedule). Combined airborne releases are expected to be 0.2 lbs/year containing 0.05% tretinoin, or 1×10^{-4} lbs/year tretinoin. When combined with the 1.4×10^{-4} lbs/year estimated release for APS TMG, total airborne releases are estimated to be 2.4×10^{-4} lbs/year. This amount is not expected to affect Ortho's ability to comply with air pollution regulations or permit conditions applicable to this site and process.

6.3.2 Water

Ortho Pharmaceutical's Manati facility operates a 473,125 LPD wastewater treatment plant. Records at the plant show that the treatment plant is operating at 57% of capacity, or about 268,735 LPD. The treatment plant is a sequential batch reactor design that employs activated sludge as the means to provide biological treatment. Treated effluent is discharged to the Barceloneta Regional Wastewater Treatment Plant under a pretreatment discharge permit issued by the Puerto Rico Aqueduct and Sewerage Authority (PRASA). Additional treatment (primary and secondary) of Ortho's effluent is provided by the Barceloneta facility.

The concentration of Tretinoin in the facility's effluent is calculated to be 0.11 ppm per batch. This is based upon an expected loss of 27 kg of product from process equipment washing containing 0.1% (0.03 kg) of the active. The Barceloneta facility has a treatment capacity of 31,415,500 LPD. Therefore, assuming no biodegradation occurs at either the Ortho or Barceloneta treatment plants, the maximum environmental concentration of Tretinoin released to water is expected to be 0.95 ppb. This proposed action is not expected to adversely affect Ortho's wastewater treatment plant operation, or to result in non-compliance with the operating permit. Total APS TMG, RENOVA®, and RETIN-A® production in Manati during the 5th year is expected to result in water emissions of tretinoin of 1700 gm/year.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Attached are statements from Advanced Polymer Systems, Lafayette, Louisiana (manufacturer of Tretinoin in Acrylates Copolymer entrapment) and Ortho-McNeil (manufacturer of Drug Product, Tretinoin MICROSPONGE® Gel, 0.1%) certifying that the respective facilities currently comply and will continue to comply with the applicable emission requirements (Appendix II).

Material Safety Data Sheet for all-trans retinoic acid (tretinoin) from the two manufacturers, BASF Aktiengesellschaft and Hoffman-LaRoche, Inc. are attached in Appendix I.

A list of emission permits is provided for each facility alongwith the permit number, authorizing agency and expiration dates in Appendix II. Per the November 1995 guidelines, copies of permits and licences are not included in this AEA but are available upon request.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Based upon the 5th year production forecast for APS TMG, the approval and manufacture of APS TMG at Ortho's Raritan and Manati facilities may result in airborne and water-borne releases of 3.4×10^{-4} lbs/year and 480 gm/year, respectively. Advanced Polymer Systems estimates releases of 1.1×10^{-3} lbs/year to air and 5 gm/year to water. The total amount of tretinoin released to the environment by this action is expected to be 1.4×10^{-3} lbs/year to air and 485 gm/year to water. Site specific release information is provided in Section 6.1 through 6.3

e. Expected Introducton Concentrations

Current Tretinoin emissions generated by the production of RETIN-A® at Ortho, Raritan and Ortho, Manati are expected to total 3.3×10^{-4} lbs/year into the air and 741 gm/year into the water. In addition, another tretinoin containing product application was approved by the Agency (RENOVA®, NDA 19-963) in December 1995. With this approval, an additional amount of 3.5×10^{-4} lbs/year for air-borne release is expected, while water releases may increase by 1,220 gm/year. In total, the production of Tretinoin in Acrylates Copolymer®, APS TMG, RENOVA® and RETIN-A® may result in environmental releases of tretinoin of 2.1×10^{-3} lbs/year to air and 2,450 gm/year to water.

The increase in production subsequent to approval is not expected to affect compliance with current emission requirements.

(i) Expected Introduction Concentration from Use

The new drug product will be administered by patients as a topical medication. It is expected that less than 2% of the active will be absorbed systemically, while the remaining drug product will be flushed from the body by washing. To meet patient demands, the 5th year production estimate for the new drug product will require 44.44 kg of Tretinoin. Assuming that disposal will occur through wastewater collection systems, an estimate of the Maximum Expected Emitted Concentration (MEEC) yields a Tretinoin environmental concentration of 0.87 parts per trillion (see Appendix III for MEEC derivation). When combining RENOVA® and RETIN-A® patient demands with this proposed action, the cumulative MEEC yields a tretinoin concentration of 4.7 parts per trillion. Material discarded by the consumer will be incinerated or landfilled at sanitary/municipal solid waste facilities. Incineration is expected to destroy the active substance. As APS TMG, RENOVA® AND RETIN-A® are practically insoluble in water, the migration potential from sanitary landfills is low.

(ii) Expected Introduction Concentration from Disposal

Returned goods will be received and managed by Ortho Pharmaceutical Corporation's Distribution Center in Bridgewater, New Jersey. Disposal of product will be through high temperature incineration at a commercially licensed incinerator. It is the policy of Ortho to destroy all returned products in this fashion. The high temperatures of incineration (>1500° F) is expected to destroy the active ingredient, with the resultant ash posing no environmental hazard. This practice insures that returned goods are managed in an environmentally sound manner.

7.0 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Documentation is ordinarily not required as per 21 CFR 25.31a(b)(3)(ii) for topically administered drug products.

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Documentation is ordinarily not required as per 21 CFR 25.31a(b)(3)(ii) for topically administered drug products.

9.0 USE OF RESOURCES AND ENERGY

Documentation is ordinarily not required as per 21 CFR 25.31a(b)(3)(ii) for topically administered drug products.

10.0 MITIGATION MEASURES

Documentation is ordinarily not required as per 21 CFR 25.31a(b)(3)(ii) for topically administered drug products.

11.0 ALTERNATIVES TO THE PROPOSED ACTION

Documentation is ordinarily not required as per 21 CFR 25.31a(b)(3)(ii) for topically administered drug products.

12.0 LIST OF PREPARERS

12.1 Bradford B. Gardner
Manager, Environmental Engineering
Ortho Pharmaceutical Corporation

Ten and a half years of professional environmental experience. Seven and a half within the pharmaceutical industry, and two and a half in hazardous waste management, and half a year with the New Jersey Department of Environmental Protection.

Bachelor of Science Degree in Environmental Science
Master of Science Degree in Environmental Health
Registered Environmental Manager, No. 5991.

12.2 Donald E. Cummins
Plant Manager
Advanced Polymer Systems (APS)

12 years of chemical industry experience, the past three years involved with environmental and safety efforts with APS.
Bachelor of Science Degree in Chemical Engineering.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm responsible for preparation of the Environmental Assessment.

The undersigned official certifies that the EA summary document (pages 1-23) and Appendices I-II(pages 24-39) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR 1506.6.

Bradford B. Gardner
Manager, Environmental Engineering
Ortho Pharmaceutical Corporation

July 24, 1996
Date

14. REFERENCES

Lyman, W.J., Rheel, W.F., and Rosenblat, D.H., eds. 1982. Handbook of Chemical Property Estimation Methods. New York: McGraw-Hill Book Company.

Napoli, J.L., Posch, K.P., Fiorella, P.D., and Boerman, M.H.E.M. 1991. Physiological occurrence, biosynthesis and metabolism of retinoic acid: evidence for roles of cellular retinol-binding protein (CRBP) and cellular retinoic acid-binding protein (CRABP) in the pathway of retinoic acid homeostatis. Biomedical & Pharmacotherapeutics 45: 131-143.

Szuts, E.Z., and Harosi, F.I. 1991. Solubility of retinoids in water. Archives of Biochemistry and Biophysics 287: 297-304.

Windholz, J., ed. 1983. The Merck Index, Tenth Edition. Rahway, N.J.: Merck & Co., Inc.

Pharmaceutical Manufacturers Association, Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. July, 1991.

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research, November 1995.

15. APPENDICES

a. NON-CONFIDENTIAL

Appendices I - II

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

Original Date: 01/04/1994
Revision Date: 05/25/1994

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)
Molecular Wt.: 300.4
Chemical Family: Vitamin

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:	~ 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			
Autoignition:	~ 265		C	DIN 51794

SECTION 4 - FIRE AND EXPLOSION DATA (cont)

Extinguishing Media:
Use foam, CO2 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 studies have shown that vitamin A is teratogenic in several species.

SECTION 5 - HEALTH EFFECTS (cont)

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:
See below.

Conditions/Hazards to Avoid:
Avoid dust cloud formation.

Hazardous Decomposition/Polymerization:
Polymerization: Does not occur.

Corrosive Properties:
Not Corrosive.

Oxidizer Properties:
Not an oxidizer

Incompatability: Acids, Oxygen.

SECTION 7 - PERSONAL PROTECTION

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

Eyes:
Chemical Goggles

Respiration:
If dusts are generated, wear an approved dust respirator.

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 in cool dry place. Keep containers tightly closed when not in use. Store in light impervious containers.

SECTION 10 - REGULATORY INFORMATION

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

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
DOT Poison Constituent:

BASF Commodity Codes: 453 **UN/NA Code:** N/A **E/R Guide**

Bill of Lading Description:

SECTION 11 - TRANSPORTATION INFORMATION (cont)

FOOD, DRUGS OR MEDICINE, NOIBN

	CLASS:	P. G.	SHIPPING NAME:
IATA:	NONE	NA	NONE
IMO:	NONE	NA	NONE
TDG:	NONE	NA	NONE

WHILE BASF CORPORATION BELIEVES THE DATA SET FORTH HEREIN ARE ACCURATE AS THE DATE HEREOF, BASF CORPORATION MAKES NO WARRANTY WITH RESPECT THERETO AND EXPRESSINGLY DISCLAIMS ALL LIABILITY FOR RELIANCE THEREON. SUCH DATA ARE OFFERED SOLELY FOR CONSIDERATION, INVESTIGATION, AND VERIFICATION.

END OF DATA SHEET

Roche Vitamins and Fine Chemicals
Member of the Roche Group
40 Kingsland Street
Nutley, NJ 07110-1199

Emergency: (800)-827-6243
Chemtrec: (800)-424-9300
Information: (800)-526-0189

MATERIAL SAFETY DATA SHEET

SECTION 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Material Name .....: Retinoic Acid
Inventory Code .....: 63886
RO # .....: 01-5488
CAS Number .....: 302-79-4
Synonyms .....: retinoic acid
3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid, all trans
all trans-retinoic acid
13-trans-retinoic acid
vitamin A acid
Tretinoin
TSCA Status .....: On TSCA Inventory.
Chemical Family ....: Retinoid
Formulations Used In: VESANOID(R)

SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient Name	CAS Number	Concentration %
Retinoic Acid	302-79-4	>=99

SECTION 3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW
Physical State .....: Powder.
Color .....: Yellow to slight orange
Odor .....: Characteristic odor

Violent decomposition may occur when heated or in a fire based on information on related materials.
Possible dust explosion hazard based on information on related materials.
May cause birth defects based on animal data.

POTENTIAL HEALTH EFFECTS
Relevant Routes of
Exposure .....: Inhalation, Skin Contact, Ingestion.
Target Organs .....: Dermal System, Immune System, Central Nervous System, Gastrointestinal System, Hepatic System.

SECTION 3. HAZARDS IDENTIFICATION (Continued. . .)

Acute Effects
General .....: May cause drying and/or irritation of the mucous membrane. May cause central nervous system effects such as headache, dizziness, drowsiness, fatigue, and lack of muscular coordination. May cause headaches. May cause musculoskeletal effects such as muscle weakness or pain and skeletal abnormalities. May cause gastrointestinal effects such as nausea, vomiting, diarrhea, constipation, cramps, and loss of appetite. May cause hepatic (liver) system effects. Signs and symptoms may include elevation of liver enzyme levels and jaundice (yellowing of the skin and eyes).
Skin .....: May cause skin irritation.

Chronic Effects ....: No adverse effects known.

Carcinogenicity ....: Not listed by NTP, IARC, or OSHA.

Reproductive
Toxicity .....: May cause birth defects based on animal data. Since this material may affect the developing fetus, females planning to have a child and pregnant women should exercise caution regarding exposure. It is also advisable for nursing mothers to exercise caution regarding exposure.

Conditions
Aggravated .....: Liver conditions and/or impaired liver function.

SECTION 4. FIRST AID MEASURES

Inhalation .....: Remove to fresh air. If discomfort occurs or persists, get medical attention.
Skin Contact .....: Remove contaminated clothing and shoes. Wash skin with soap and plenty of water. If irritation occurs or persists, get medical attention. Wash clothing and shoes before reuse.
Eye Contact .....: Immediately flush eyes with plenty of water. If irritation occurs or persists, get medical attention.
Ingestion .....: If large quantities of this material are swallowed, get medical attention immediately. Do not induce vomiting unless directed by medical personnel. Never give anything by mouth to an unconscious person.

SECTION 5. FIRE FIGHTING MEASURES

Flash Point .....: Not Applicable
Extinguishing Media : Water, Carbon Dioxide, Dry Chemical, Foam.

SECTION 5. FIRE FIGHTING MEASURES (Continued. . .)

Unusual Fire and Explosion Hazards ..: Violent decomposition may occur when heated or in a fire based on information on related materials. Possible dust explosion hazard based on information on related materials.

Fire Fighting Instructions .....: Wear NIOSH/MSHA approved positive pressure, self contained breathing apparatus and full protective turn out gear. Use caution in approaching fire. Use water to keep fire exposed containers cool.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Spill Clean Up Procedures .....: Review Section 3-Hazards Identification, and Section 8-Exposure Controls/Personal Protection before proceeding with the clean up. Shut off the source of the spill or leak if it is safe to do so. Follow appropriate grounding procedures. Scoop or shovel spilled material into a suitable labeled container with a tight fitting lid. Wash spill area thoroughly with soapy water. Collect wash with a noncombustible absorbent material and transfer to labeled container for treatment and disposal. Secure the container lid with an airtight seal such as tape and move the container to a safe holding area.

Treatment and Disposal .....: Decontaminate equipment. Dispose of protective clothing with the spilled material. Dispose of in accordance with recommendations in Section 13 Disposal Considerations.

Reporting Requirements .....: The United States Environmental Protection Agency (USEPA) has not established a Reportable Quantity (RQ) for releases of this material. In New Jersey, report all releases which are likely to endanger the public health, harm the environment or cause a complaint to the NJDEPE Hotline (1-609-292-5560) and to local officials. State and local regulations vary and may impose additional reporting requirements.

SECTION 7. HANDLING AND STORAGE

Storage Temperature (min/max) .....: 8-15 C

Special Sensitivity : Heat. Light. Humidity. Do not heat above 90 degrees C.

SECTION 7. HANDLING AND STORAGE (Continued. . .)

Handling & Storage
Precautions .....: Do not generate dust or expose to ignition sources.
Ground and bond all transfer equipment.
Milling/mixing/drying should be done at the lowest possible temperature under vacuum or inert conditions.
Use with adequate ventilation.
Avoid contact with eyes, skin and clothing.
Avoid breathing dust.
When handling, use proper personal protective equipment specified in section 8.
Wash thoroughly after handling.
Keep container tightly closed when not in use.
Store under inert atmosphere in light resistant containers.

SECTION 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

ENGINEERING CONTROLS
Ventilation .....: Local ventilation is recommended when using this material.

PERSONAL PROTECTION
Respirator Type(s) .: Half Face, Negative Pressure Air Purifying, Toxic Dust/Mist/Fume High Efficiency Filter.
Conditions for Use .: Respiratory protection is recommended as a precaution to minimize exposure. OSHA considers effective engineering controls to be the primary means to control worker exposure. Respiratory protection should not substitute for feasible engineering controls. Whenever respiratory protection is used, a complete respirator program should be developed in accordance with OSHA Subpart I (29CFR1910.134) requirements.
Glove Materials ....: Any plastic or rubber glove.
Conditions for Use .: Gloves are required if there is a potential for skin contact.
Skin Protection ....: Use protective clothing (lab coats, disposable coveralls, etc.) in both production and laboratory areas.
Eye Protection .....: Safety Glasses Required, Safety Goggles Recommended.

OTHER CONTROL MEASURES
Additional
Protective Measures : Prevent the accumulation of dust in the work area by thorough periodic cleaning of the area.

EXPOSURE LIMITS
Retinoic Acid
Roche IOEL: 1.00 ug/m3 Time Weighted Average.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Physical State .....: Powder.
Color .....: Yellow to slight orange
Odor .....: Characteristic odor
Molecular Weight ...: 300.44
Chemical Formula ...: C20H2802
Pure/Mixture .....: Pure.
Melting Point .....: 180-182 C
H2O Solubility .....: Insoluble.
Solubility - Other .: Slightly soluble in alcohol and chloroform.

SECTION 10. STABILITY AND REACTIVITY

Stability .....: Normally stable but may become unstable at elevated temperatures or reacts with water, releasing some energy but not violently.
Conditions to Avoid : Dust Accumulation
Airborne Dust
Sources of Ignition
Elevated Temperatures
Sunlight
Sources of heat
Humidity
Incompatibility -
Materials to Avoid .: Oxidizing agents.
Decomposition
Products .....: Carbon monoxide and carbon dioxide
Polymerization .....: No
Conditions of
Polymerization .....: Will not occur.

SECTION 11. TOXICOLOGICAL INFORMATION

Retinoic Acid
Acute Oral, Single Dose, Rat: 2000 mg/kg
Summary: Acute oral LD50 (rat) is 2000 mg/kg body weight at 10 days which clasifies this material as moderately toxic orally under the study conditions utilized.

Reproductive Rat
Summary: In a segment 1 and segment 3 study, no effects on gonadal function, fertility, conception rate, gestation, parturition or neonatal viability were observed in rats treated at doses up to 2 mg/kg/day. At a dose of 5 mg/kg/day, offspring survival was somewhat decreased, under the study conditions utilized.

Teratogenicity Oral,
Summary: This material was found to be teratogenic in rats, rabbits, and mice at doses of 6, 6, and 2 mg/kg/day respectively, under the study conditions utilized.

SECTION 11. TOXICOLOGICAL INFORMATION (Continued. . .)

Teratogenicity Oral, Monkey
Summary: Evidence of questionable teratogenic effects was observed in monkeys at oral doses of 10 mg/kg, administered daily during the gestation days 10 through 20 and then adminstered twice during gestation days 21 through 24, under the study conditions utilized.

Mutagenicity Salmonella Typhimurium
Summary: No evidence of mutagenicity was observed in the Ames assay, with or without metabolic activation, under the study conditions utilized.

SECTION 12. ECOLOGICAL INFORMATION

No ecological data available on this material.

SECTION 13. DISPOSAL CONSIDERATIONS

Disposal
Recommendations ....: This material is suitable for incineration. These recommendations are based on the product as shipped. Use, processing, alteration or contamination may affect these disposal recommendations. State, local or site restrictions affecting the available proper disposal options may vary.
RCRA Waste # .....: Not regulated under RCRA
Empty Containers ...: Empty containers must be triple rinsed prior to disposal, recycling, or reuse.

SECTION 14. TRANSPORTATION INFORMATION

Enforcement Agency .: US Dept. of Transportation
Country/Community ..: USA
Proper Ship. Name ..: Non-regulated

Enforcement Agency .: International Air Transport Association
Transportation Mode : Air.
Country/Community ..: International
Proper Ship. Name ..: Non-regulated

SECTION 15. REGULATORY INFORMATION

Law/Regulation .....: Hazardous Chemical Reporting: Community Right-To-Know 40CFR370
Common Name .....: SARA Title III Section 312 - Hazardous Chemical Inventory
Enforcement Agency .: Environmental Protection Agency (EPA)
Governing Authority : USA
Criteria Met .....: Acute, Fire

SECTION 15. REGULATORY INFORMATION (Continued. . .)

Law/Regulation .....: Safe Drinking Water and Toxic Enforcement Act of 1986
Proposition 65
Common Name .....: Prop 65
Enforcement Agency .: California Environmental Protection Agency
Governing Authority : California, USA
Criteria Met .....: Known to the state to cause reproductive toxicity

SECTION 16. OTHER INFORMATION

Additional
Information .....: NFPA RATING: These ratings are based on NFPA Code 704 and are intended for use by emergency personnel to determine the immediate hazards of a material.
....Health 1
....Fire 2
....Reactivity 1

APPROVAL INFORMATION
Preparer .....: Janet L. Kolodziey
Approver .....: Corporate Environmental & Safety Affairs
Approval Date .....: 06/12/95
Previous Approval
Date .....: 06/10/94
Reason For Issue ...: Add Roche Internal Occupational Exposure Limit (IOEL)

The information presented on this MSDS is, to the best of our knowledge, accurate and reliable. It is provided in good faith without warranty or acceptance of any liability on the part of Hoffmann-LaRoche, Inc. It is the responsibility of the user to evaluate the relevance and completeness of this information for their application and to determine the safety, suitability and status under applicable regulations relating to this product or byproducts arising out of their process.

APPENDIX II

EMISSION PERMIT TABLE

PERMITS FOR ADVANCED POLYMER SYSTEMS, LAFAYETTE, LOUISIANA			
EMISSION	**AUTHORIZING AGENCY**	**PERMIT #**	**EXPIRATION DATE**
Air Pollution	Department of Environmental Quality State of Louisiana	1520-00044-01	None
Wastewater Discharge	Wastewater Treatment Division Lafayette Utilities System Lafayette, Louisiana	700	December 31, 1997

Advanced Polymer Systems

May 9, 1996

To Whom It May Concern:

This is to certify that the Advanced Polymer Systems, Inc. manufacturing facility in Lafayette, Louisiana is in compliance with all federal, state and local emissions requirements as specified in its operating permits for wastewater, storm water and air discharges. Advanced Polymer Systems, Inc. will continue to comply with emissions requirements, present and future, for emissions according to all applicable federal, state and local regulations.

Sincerely,

Don Cummins

Plant Manager

02 00037 .a

301 Laser Lane, Lafayette, Louisiana 70507
Tel: 318/232-6838 Telex: 510 601 4939 APS LA UQ FAX: 318/235-8118

APPENDIX II (Cont'd)

EMISSION PERMIT TABLE

PERMITS FOR ORTHO PHARMACEUTICAL, RARITAN, NEW JERSEY			
EMISSION	AUTHORIZING AGENCY	PERMIT #	EXPIRATION DATE
Air Pollution	New Jersey State Department of Environmental Protection	098298	July 06, 1999
Wastewater Discharge	Somerset Raritan Valley Sewarage Authority Bridgewater, New Jersey	7A	October 31, 2000

ORTHO McNEIL PHARMACEUTICAL

RARITAN, NEW JERSEY 08869

CERTIFICATE OF COMPLIANCE: EMISSIONS STATEMENT

TRETINOIN MICROSPONGE® GEL

Ortho McNeil Pharmaceutical, Raritan, New Jersey, certifies that it is 1) in compliance with all local and national environmental laws; 2) in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval and subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws, applicable to the production of Tretinoin MICROSPONGE® Gel.

Signature: G F Cunstatt

Title: Vice-President, Operations

Date: 5/8/96

APPENDIX II (Cont'd)

EMISSION PERMIT TABLE

PERMITS FOR ORTHO PHARMACEUTICAL, MANATI, PUERTO RICO			
EMISSION	AUTHORIZING AGENCY	PERMIT #	EXPIRATION DATE
Air Pollution	Environmental Quality Board Commonwealth of Puerto Rico Arecibo Regional Office	PFE-01-47-0793-1090- I-II-0	January 17, 2001
Wastewater Discharge	Water & Sewage System Authority Commonwealth of Puerto Rico	GDA-88-210-002	June 1, 1997

ORTHO PHARMACEUTICAL, a division of

Johnson & Johnson Pharm Co., Inc. (P.R.)

MANATI, PUERTO RICO 00701

CERTIFICATE OF COMPLIANCE: EMISSIONS STATEMENT

TRETINOIN MICROSPONGE® GEL

Ortho Pharmaceutical, a division of Johnson & Johnson Pharm Co., Inc. (P.R.), Manati, Puerto Rico, certifies that it is 1) in compliance with all local and national environmental laws; 2) in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval and subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws, applicable to the production of Tretinoin MICROSPONGE® Gel.

Signature: O T Comstock

Title: Vice-President, Operations

Date: 5/8/96

15. APPENDICES

b. CONFIDENTIAL

Appendices III - VI

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB - 5 1996

NDA 20-475

Advanced Polymer Systems, Inc.
Attention: Sergio Nacht, Ph.D.
3696 Haven Avenue
Redwood City, California 94063

Dear Dr. Nacht:

We acknowledge receipt on January 4, 1996, of a January 2, 1996, amendment to your new drug application for Nuretin (tretinoin microsponge gel) Gel, 0.1%.

We consider this a major amendment received by the Agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is May 6, 1996.

If you have any questions, please contact:

Mary Jean Kozma-Fornaro, RN, MSA
Project Manager
(301) 827-2020

Sincerely yours,

4/5/96

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

RECORD OF A TELEPHONE CONVERSATION

DATE: August 2, 1995

FROM: Subhash Saxena, Ph.D.
Vice President, Pharmaceutical Sciences and Regulatory Affairs
Advanced Polymer Systems
(415) 366-2626

TO: Joanne Holmes
Project Manager
Division of Topical Drug Products
(301) 594-6627

SUBJECT: Question from the Reviewing Medical Officer

NDA NUMBER: NDA 20-475

DRUG: Nuretin (tretinoin MICROSPONGE gel), 0.1%

SPONSOR: Advanced Polymer Systems

Ms. Holmes had called Dr. Sergio Nacht to relay a question from the Reviewing Medical Officer. Dr. Saxena returned the call. The question is:

> When the data on mean reduction in lesion counts and the baseline counts provided in the fax of June 27,1995, are used to calculate the mean percent reduction in counts, the results do not tally with the tabulations of percent reduction in counts provided in the NDA. This is true for both total non-inflammatory counts and total inflammatory counts in both studies B0222E and B0223E. The data also appear to be inaccurate in CP1.

Dr. Saxena stated that the data would be reviewed prior to requesting further clarification from the Medical Officer.

cc:
Orig NDA 20-475
HFD-540
HFD-007/CHEM/Maturu
HFD-160/MICRO/Stinavage
HFD-540/PHARM/Alam
HFD-713/BIOSTAT/Harkins
HFD-426/BIOPHARM/Ajayi
HFD-540/MO/Huene
HFD-540/PROJ MGT SUPV/Cook
HFD-540/PROJ MGR/Holmes 8/2/95

NDA 20-475

Advanced Polymer Systems, Inc.
Attention: Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology
3696 Haven Avenue
Redwood City, CA 94063

FEB 16 1995

Dear Dr. Nacht:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug or Product: Nuretin (tretinoin MICROSPHERE gel), 0.1%

Therapeutic Classification: S

Date of Application: February 6, 1995

Date of Receipt: February 6, 1995

Our Reference Number: NDA 20-475

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 7, 1995 in accordance with 21 CFR 314.101(b).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning the NDA, please contact:

Joanne M. Holmes, M.B.A.
Project Manager
(301) 594-4877

Sincerely yours,

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
ORIG. NDA 20-475
HFC-130/JAllen
HFD-82
HFD-540
HFD-540/SMO/Chambers
HFD-540/SChem/DeCamp
HFD-540/SPharm/Jacobs
HFD-520/SMicro/Sheldon
HFD-426/SBiopharm/Pelsor
HFD-713/SBiostat/Harkins
HFD-540/SPMS/Cook
[redacted] 2/15/95

ACKNOWLEDGEMENT

540
Fornaro

MEETING MINUTES

Meeting Date: July 11, 1996 Time: 2:20 PM Location: N225

Sponsor: Advanced Polymer Systems

NDA: 20-475 Nuretin

Meeting Type: Discuss Not Approvable Letter

Meeting Chair: Dr. Jonathan Wilkin

Meeting Recorder: Mary Jean Kozma Fornaro, Project Manager

FDA Attendees:

Jonathan K. Wilkin, M.D., Division Director, DODDDP, HFD-540
Eric Sheinin, Ph.D., Director, DNDC 3, HFD-830
Wilson DeCamp, Ph.D., Team Leader, Chemistry, HFD-540
Brian Hasselbalch, CSO, Office of Compliance, HFD-325
Bruce Hartman, Office of Compliance, HFD-324
Olga Cintron, Project Manager, HFD-540
Mary Jean Kozma Fornaro, Project Manager, HFD-540

Sponsor Attendees:

John J. Meakem, Chairman, President and CEO
Sergio Nacht, Ph.D., Senior Vice President, Science and Technology
Subhash Saxena, Ph.D., Vice President, Pharmaceutical Sciences and Regulatory Affairs
Ronald F. Tetzlaff, Ph.D., Regulatory Consultant, Kemper-Masterson, Inc.

Meeting Objectives:

1. To determine if Agency agrees that APS has sufficient data to support conformance to specifications for raw material lot 774.

2. To verify that there are no other unresolved issues of concern to the FDA that have bearing on the approval of NDA 20-475.

3. Status of tradename request submitted on February 20, 1996.

Discussion points and agreement::

1. The agency accepts the response and additional data submitted on Biobatch lot 774.

2. GMP issues remain a concern. A "for cause" request site reinspection will be forwarded to the Office of Compliance when a complete official response to the not approvable action letter is submitted. Sponsor agreed to provide a complete listing of interactions between Advanced Polymer Systems and the District Office relating to the 483 issuance, and a complete listing of all corrective actions and the dates implemented.

3. A complete official response submission must address all the issues listed in the not approvable letter. The Environmental Assessment section needs specific information plus an FOIable version per Guidance to Industry issued November, 1995.

4. The agency agreed to work with the sponsor in a cooperative manner on labeling issues, during the review process of the official complete response to the not approvable letter.

5. The new tradename request submitted on February 20, 1996 has not been submitted to the Nomenclature Committee. Sponsor agreed to submit a letter of understanding/agreement from Ortho, which allows use of the new tradename request to Advanced Polymer Systems, with the complete official response to the not approvable letter.

Signature, minutes preparer: 7/25/96
Concurrence, Chair: 8/2/96

cc:

Original NDA 20-475
HFD-540/DIV FILE
HFD-540/Wilkin
HFD-540/DeCamp 7/25/96
HFD-830/Sheinin
HFD-324/Hartman
HFD-325/Hasselbalch
HFD-540/Fornaro

MEETING MINUTES

® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

AUG 7 1996

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
Amendment No. 017 - Amendment to a Pending Application
Chemistry, Manufacturing & Controls, Safety Update Report, Trade Name Change Request

Dear Dr. Wilkin:

This submission is being made in response to your letter of May 6, 1996 (Dr. Wilkin to Dr. Nacht) as well as the request for additional information made during our meeting of July 11, 1996. APS is confident that this response satisfactorily addresses all the issues for the Agency to grant approval of this NDA.

The submission is divided in two volumes. Volume I contains the following:

- Final responses to May 6, 1996 letter.
- Request for trade name change from Nuretin™ to Retin-A Micro™ and letter from authorizing APS to use the Retin-A trade name.
- Per Dr. Wilson DeCamp's request, a historical summary of the correspondence between APS and the FDA, San Francisco District Office.
- Request for removal of APS Redwood City, CA facility from the NDA. This site serves as an R&D/Corporate headquarter facility. No manufacturing is done at this facility and the original intent of keeping this facility in the NDA was for it to act as a backup to the Lafayette Quality Control Laboratory which supports our sole manufacturing site.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

- The above request notwithstanding, a letter of commitment that the APS, Redwood City, CA facility is in compliance with CGMPs as an analytical laboratory and may be re-inspected.

Volume II consists of the complete amended Environmental Assessment per Dr. DeCamp's request. The original report has been re-formatted to meet the requirements specified in "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements", CDER (November 1995). It also contains the information that was requested in the action letter of May 6, 1996.

Based on our discussion during the July 11, 1996 meeting, it is our understanding that once you have received this submission, we will obtain from Ms. Mary Jean Kozma-Fornaro the labeling changes so that we can finalize any labeling issues in parallel with the review of this submission.

We would like to thank all the members of the Agency for their valuable support and guidance on this NDA and hope that soon an approval can be granted.

Thank you.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

Advanced
Polymer
Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

February 5, 1997

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA No. 20-475
RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%
Revised Labeling: Letter of Acceptance

Dear Dr. Wilkin:

We are in receipt of the revised labeling (Physician's Insert and Patient Instructions) dated February 5, 1997 sent via facsimile by Ms. Olga Cintron, Project Manager. This labeling is acceptable to us without further revisions.

Our understanding is that this completes the satisfactory review of this NDA and we hope to receive approval of the NDA at this stage. Any efforts to expedite the issuance of the approval letter will be highly appreciated.

Should you have any questions, please call me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
R&D/Regulatory Affairs

SS/sp

Enc.

cc: Ms. Olga Cintron (FDA)
Ms. Mary Jean Kozma-Fornaro (FDA)
Regulatory Files
Project File - P.006

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

October 26, 1994

Ms. Amanda B. Pedersen
Chief Mediator and Ombudsman
Food and Drug Administration
Office of the Commissioner
5600 Fishers Lane
Room 14-105 (HF-7)
Rockville, MD 20857

RE: **Request for Small Business Exception To New Drug Application (NDA) under the Prescription Drug User Fee Act of 1992**
User Fee I.D. Number: 2559
NDA No. N020475

Dear Ms. Pedersen:

On September 28, 1994 Advanced Polymer Systems, Inc. (APS) was granted a one year deferral of payment of the application fee for its new drug application NDA , User Fee I.D. No. 2572 for Prozone (Melanin) Sunscreen.

APS is now preparing an NDA that it plans on filing in December 1994 or soon thereafter. This NDA (No. N020475, User Fee I.D. Number 2559) is for Tretinoin MICROSPONGE® Gel 0.1% for the treatment of acne. The application will contain clinical data.

The status of APS has not changed since September 28, 1994 when it was granted the deferral for its first NDA. APS still

a. has fewer than 500 employees including employees of other affiliated companies;

b. does not have a prescription drug product introduced or delivered for introduction into interstate commerce, and does not expect to introduce a prescription drug product within the next twelve months; and

c. expects to be prepared to submit an application to the Agency within 90 days of this request.

The Sponsor of this NDA is:

Advanced Polymer Systems, Inc.
3696 Haven Avenue
Redwood City, CA 94063

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

The authorized representative of Advanced Polymer Systems who may be contacted regarding the request is:

Mr. Michael O'Connell
Senior Vice President
Chief Financial and Administrative Officer
Advanced Polymer Systems, Inc.
3696 Haven Avenue
Redwood City, CA 94063

Telephone: (415) 366-2626
Fax: (415) 365-6490

Thank you in advance for considering this request.

Sincerely,

Michael O'Connell
Senior Vice President
Chief Financial and Administrative Officer

MOC/SS:sp

cc: R. Johannes
J. Meakem
S. Nacht, Ph.D.
G. Sangster
S. Saxena, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Commissioner
5600 Fishers Lane
Room 14-105, HF-7

Food and Drug Administration
Rockville MD 20857

C. Rod. J. Golden | F-I

November 17, 1994

Mr. Michael O'Connell
Senior Vice President
Chief Financial and Administrative Officer
Advanced Polymer Systems, Inc.
3696 Haven Avenue
Redwood City, CA 94063

Re: Prescription Drug User Fee Act of 1992
Small Business Exception Request
Our File: SBE-95-005

Dear Mr. O'Connell:

On November 4,1994, the Food and Drug Administration received your small business exception request pertaining to the fiscal year 1995 application fee for NDA 20-475, Tretinoin MICROSPONGE® Gel 0.1%. It has been assigned file number SBE-95-005. Please refer to this file number in any future correspondence you submit concerning this request.

It is our intention to provide you with a response to this small business exception request within 90 days of the date of receipt. Due to the complexity of some requests and depending upon the number of requests pending, however, this is not always possible.

If you have any questions regarding this matter, please contact me at 301-443-1306.

Sincerely yours,

Suzanne O'Shea
Office of the Chief Mediator
and Ombudsman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Commissioner
5600 Fishers Lane
Room 14-105, HF-7
Rockville, MD 20857
301-443-1306

Food and Drug Administration
Rockville MD 20857

December 14, 1994

Mr. Michael O'Connell
Senior Vice President
Chief Financial and Administrative Officer
Advanced Polymer Systems, Inc.
3696 Haven Avenue
Redwood City, CA 94063

Re: Prescription Drug User Fee Act of 1992
Small Business Exception Request
Our File: SBE-95-005

Dear Mr. O'Connell:

This letter responds to your letter on behalf of Advanced Polymer Systems, Inc. (APS), dated October 26, 1994, requesting the Food and Drug Administration (FDA) to reduce and defer payment of the application fee assessable upon submission of the marketing application for Tretinoin Microsponge® Gel 0.1% (NDA 20-475) as prescribed by the small business exception to the Prescription Drug User Fee Act of 1992, 21 U.S.C. § 379h(b)(2). Pursuant to the small business exception, FDA hereby grants APS a deferral of payment of the application fee for NDA 20-475 for one year from the date of submission of the marketing application. FDA will determine whether to reduce the application fee approximately one year after APS submits the marketing application for Tretinoin Microsponge®.

By letter dated September 28, 1994, FDA granted APS, pursuant to the small business exception to the User Fee Act, a one year deferral of payment of the application fee for the marketing application for APS plans to submit the marketing application for Tretinoin Microsponge® (NDA 20-475) in December 1994 or soon thereafter.

The small business exception to the User Fee Act entitles qualified small businesses to a 50 percent reduction and a one year deferral of the application fee charged for a new drug application under 21 U.S.C. § 379h(a)(1). To qualify for reduction and deferral of payment of an application fee under the small business exception, a business must have fewer than 500 employees, and have no prescription drug products within the meaning of the User Fee Act, introduced, or delivered for introduction, into interstate commerce.

RECEIVED
DEC 21 1994

Ordinarily, a sponsor must pay one half of an application fee when it submits a marketing application for review, and the second half of the application fee when FDA issues an action letter pertaining to the marketing application, 21 U.S.C. § 379h(a)(1)(B). However, a sponsor who qualifies for the small business exception is entitled to defer payment of any portion of the application fee for one year after submission of the marketing application. At the end of the one year deferral period, a sponsor who still qualifies for the small business exception is entitled to a 50 percent reduction in the amount of the application fee. If FDA has issued an action letter by the end of the one year deferral period, a qualifying sponsor will be assessed half of a full application fee (i.e., the total reduced application fee). If FDA has not yet issued an action letter at the end of the deferral period, a qualifying sponsor will be assessed one quarter of the full application fee (i.e., the first half of the reduced application fee). Another quarter of the full application fee (i.e., the second half of the reduced application fee) will be assessed upon FDA's issuance of an action letter. A sponsor who does not continue to qualify for the small business exception will be assessed the full application fee.

FDA's decision to grant a one year deferral to APS is based on two findings. First, APS currently has no prescription drug product introduced or delivered for introduction into interstate commerce according to FDA records. Second, APS employs fewer than 500 individuals, as demonstrated by the Small Business Administration's (SBA) size evaluation made in connection with APS' request for the small business exception for documented in a letter to FDA's Chief Mediator and Ombudsman, dated September 22, 1994, and as confirmed by APS in its letter requesting the small business exception for Tretinoin Microsponge®, dated October 26, 1994, which states that APS' status has not changed since SBA previously found it to be small. Therefore, FDA grants APS a one year deferral of payment of the application fee for the marketing application covering Tretinoin Microsponge® provided the marketing application is submitted not significantly later than 90 days after the date of this letter. (See Draft Interim Guidance Document for Waivers of and Reductions In User Fee, Attachment G to User Fee Correspondence 2, dated July 16, 1993.) If APS is unable to submit the marketing application within that time period, contact Ms. Suzanne O'Shea, of this office, at 301-443-1306, regarding the process for determining APS' size at the time the marketing application will be submitted.

In order for FDA to reduce the fee assessed to APS, FDA must confirm that APS continues to qualify for the small business exception at the time the application fee is due. Accordingly, approximately nine months after the submission date of the marketing application, FDA will request that SBA conduct another size determination of APS. At that time, FDA also will review its records to confirm that APS continues to have no prescription drug product introduced or delivered for introduction into interstate commerce. Following these determinations, FDA will notify APS of

the fee that is due. If APS does not continue to qualify for the small business exception at the end of the one year deferral period, FDA will assess APS the full application fee if an action letter has issued on the marketing application, and half of a full application fee if no action letter has issued on the marketing application.

Please note that as announced in User Fee Correspondence 3, dated August 5, 1993, FDA plans to disclose information about its actions granting or denying waivers and reductions, consistent with the laws and regulations governing the disclosure of confidential commercial or financial information. For application fees, the agency will disclose the names of all entities requesting a waiver or reduction, the products covered by the applications for which waivers or reductions were requested, the statutory provisions under which the waivers or reductions were sought, and FDA's resolution of the requests. FDA will not disclose information pertaining to application fee waivers or reductions until after the applications are approved.

Please include a copy of this letter in the marketing application for Tretinoin Microsponge® (NDA 20-475). If you have any questions, please call Ms. Suzanne O'Shea, of this office, at 301-443-1306.

Sincerely yours,

Amanda B. Pedersen

Amanda B. Pedersen
Chief Mediator and Ombudsman

ORIGINAL

® Advanced Polymer Systems

JUN 23 1995

SU-21

Jonathan K. Wilkin, M.D.
Director, Division of Topical Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Proj. #P.006

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial No. 009
Four-Month Safety Update Report (Item 8)

Dear Dr. Wilkin:

Submitted with this letter, in accordance with 21CFR 314.50 (d) (5) (vi) (b), is the initial (4-month) Safety Update Report for our Nuretin™ 0.1% Gel (Tretinoin Microsphere Gel 0.1%) NDA 20-475.

We are submitting, as usual, one archival copy and two copies, in tan binders, for the appropriate reviewers.

Should there be any questions, please feel free to call me or Dr. Subhash Saxena at (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/sp

Enc.

cc: S. Saxena, Ph.D.
Project File
Regulatory File

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 26 1995

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

DEC 15 1995

Ms. Patricia C. Ziobro 510 337-6898
Acting District Director
Food and Drug Administration
San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94502

Project No. P.006

RE: New Drug Application (NDA) No. 20-475
Tretinoin Microsponge® Gel, 0.1%
APS Redwood City, CA Facility Preapproval Inspection

Dear Ms. Ziobro:

We wish to certify that we have corrected and solved the problems related to NDA 20-475 reported to Advanced Polymer Systems, Inc. (APS) on the Form FDA 483, "Inspectional Observations," issued during the preapproval inspection of our facility in Redwood City, CA on July 31 through August 8, 1995 and in your letter of August 31, 1995 to Mr. John J. Meakem, President, Chairman and CEO.

As mentioned during our meeting on October 27, 1995 at your office, our corrective measures have included implementation of the plans as stated in our response to the items on Form 483 "Inspectional Observations". In addition, we hired an outside independent consultant to conduct a complete review of all the raw data pertaining to the NDA for accuracy, completeness and compliance with established standards. After his review, he has concluded that the data and conclusions presented in the NDA are supported by the audited raw data.

We have also hired a full-time permanent chemist to conduct complete review of data generated in our laboratories in a timely fashion. We feel confident that with these measures in place, we are capable of conducting the analytical tests referred to in the subject NDA in compliance with cGMPs/GLPs.

Please note that this certification addresses only the issues pertaining to NDA 20-475. We will be responding to the issues on our other NDA separately at a later date.

Therefore, at this time we are ready to be re-inspected at your earliest convenience, should you deem it necessary.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

DEC 15 1995

Should you have any questions regarding this letter, please call me @(415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

cc: Gregory Bobrowicz - FDA 510 337 6771
Jack Meakem
Sergio Nacht
Project Files
Regulatory Files

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: New Drug Application (NDA) No. N020-475
User Fee I.D. No. 2559
Original New Drug Application for Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)

Dear Dr. Wilkin:

This submission provides a full New Drug Application (NDA) as prescribed in Title 21, Code of Federal Regulations, 314, to market the Advanced Polymer Systems, Inc. drug product, Nuretin™ Gel 0.1% (Tretinoin MICROSPONGE® Gel, 0.1%) as a prescription drug.

The sponsor of NDA N020-475 is Advanced Polymer Systems, Inc., located at 3696 Haven Avenue, Redwood City, CA 94063.

This submission contains Form FDA 356h and attachment, one archival (original) and one review copy of the full application.

Advanced Polymer Systems, Inc. operates the following facilities:

Corporate Headquarters and Research & Development:

3696 Haven Avenue
Redwood City, CA 94063
(Phone: 415-366-2626)

Manufacturing of the Polymeric Systems:

(Registered with the FDA as a Bulk Pharmaceutical Chemical Manufacturing facility, Drug Establishment Registration No. 2315837)

301 Laser Lane
Lafayette, LA 70507
(Phone: 318-232-6838)

The drug substance, Tretinoin, is obtained from the supplier and entrapped in one of our polymeric systems at this facility.

Manufacturing of the Drug Product:

Tretinoin MICROSPONGE® Gel 0.1%, the drug product, subject of this NDA, will be produced at one of the following contract manufacturer's facilities:

Ortho Pharmaceutical Corporation (OPC)
1000 U.S. Hwy Route 202
P.O. Box 300
Raritan, NJ 08869-0602

or:

Ortho Pharmaceutical
Division of OMJ Pharmaceuticals, Inc.
Carr. #2, Km. 45.6
Bo. Campo Alegre
Manati, Puerto Rico 00674

The supplies for all the pivotal clinical studies as well as the stability batches were produced at one or both of these facilities.

All the above mentioned facilities operate under cGMP's and will be ready for inspection at your convenience.

The FDA District offices of San Francisco, New Orleans, Newark and Manati will receive Review Copies of Volume 1 containing Item 1, "Index to the Application", Item 2, "Summary", Item 13, "Patent Information", and Item 14, "Patent Certification" and those volumes containing Item 3, "Chemistry, Manufacturing and Controls", all certified to be true copies of the original documents.

Please note that throughout this NDA, the drug product is referred to as Tretinoin MICROSPONGE® Gel (TMG). Since the term MICROSPONGE® is a registered trademark and may not be used as a part of a generic name, the proposed labeling (package insert) refers to the generic name as Tretinoin Microsphere Gel.

Advanced Polymer Systems, Inc. has requested and has been granted small business status for purposes of the Small Business Exception to the Prescription Drug User Fee Act of 1992 (21 U.S.C. 379h (b) (2). Copies of the correspondence relating to APS' request to FDA for this exception and the Small Business Administration's (SBA) granting of this exception are enclosed.

We are also enclosing a copy of the FDA letter granting the reduction and deferral of the user fee. The User Fee Cover Sheet (Form FDA 3397) duly completed is attached.

As agreed with the Agency at the pre-NDA meeting held on November 3, 1992, Advanced Polymer Systems, Inc. submitted a justification for a waiver on carcinogenicity studies for this drug product on November 15, 1994. As per a conversation with Dr. S. Alam held on February 2, 1995, (record of contact enclosed), should the Agency decide that further studies in support of the new drug product are needed, Advanced Polymer Systems, Inc. will conduct them as part of the Phase IV of this NDA.

The authorized persons whom the Agency may contact regarding this application are:

Sergio Nacht, Ph.D.
Sr. Vice President
Science & Technology
and/or
Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

at:

Advanced Polymer Systems, Inc.
3696 Haven Avenue
Redwood City, California 94063
Telephone: (415) 366-2626
Fax : (415) 368-4470

Should you have any questions regarding this application, please call Dr. Saxena or me.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

SN:SS/sp

cc: J. Meakem
S. Saxena, Ph.D.
Regulatory File

Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

MAR -8 1995

DUPLICATE

BS

Jonathan K. Wilkin, M.D.
Director, Division of Topical Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

P.006

RE: New Drug Application (NDA) No. 20-475
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
CANDA Submission for Pivotal Safety Efficacy Studies: B0222E and B0223E, Protocol CP8

Dear Dr. Wilkin:

Please find enclosed electronic files and hard copy documentation for the CANDA submission of the above specified studies.

This submission was prepared in consultation with Ms. Elizabeth Turney of the FDA Biostatistics group.

Included in this submission are two sets of the electronic files (11 diskettes per set) and three sets of the hard copies (7 volumes per set). The hard copies are true representations of the electronic files. The sets include an archival and a review copy, and a separate desk copy.

Should you have questions on this submission, please contact me at (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.

SN:rmt
Enclosures

cc: S. Saxena, Ph.D.
Regulatory Files

Sent diskette to Ms. Holmes.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

MAR 30 1995

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: New Drug Application (NDA) No. N020-475
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin
MICROSPONGE® Gel, 0.1%)
GENERAL INFORMATION FOR NDA FILE

Dear Dr. Wilkin:

Enclosed is a letter sent to Ms. Joanne Holmes, Project Manager, FDA, via FAX on 3/22/95 in response to her request for information regarding this NDA. At her request, we are making this submission to this NDA file.

Should you have any questions regarding this submission please call me at (415) 366-2626.

Sincerely,

Sergio Nacht/ss

Sergio Nacht, Ph.D.

SN:rmt
Enclosure

cc: S. Saxena, Ph.D.
Regulatory File

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

FAX

March 22, 1995

Ms. Joanne Holmes
Project Manager
Division of Topical Drugs
Room No. 17B-45
Food and Drug Administration

RE: Nuretin™ NDA No. 20-475

Dear Joanne:

This is in response to the questions that you left in my voice mail early this morning.

1. Efficacy Summary

   There are summaries of the efficacy data in two different places in the NDA as follows:

   Vol.1.1 - Item 2, Chapter 8-26, starting on Page 02-00193; in particular, the efficacy summary of the pivotal studies is on Pages 02-00209 to 00220.

   In addition, there is a larger summary included in the ISE located in Vol. 1.51, Pages 08-06449 to 08-06505.

2. Integrated Summary of Safety

   It is included in Vol. 1.52, starting on Page 08-06515.

   In particular, the worldwide marketing history is included in Vol. 1.52 starting on Page 08-06668. A summary of these data is also included on Vol. 1.1, Item 2, Chapter 8-53, Page 02-00220.

   The cutoff date for all adverse reactions reports was May 31, 1994. In the forthcoming 4-month safety update for the NDA, we intend to bring the cutoff date of the adverse event up to March, 1995.

3. Literature References

   They are all in English except for reference T70 which is in French, but an official translation in English has been included.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

4. GLP Compliance for Animal Studies

The statement for GLP compliance is included in Vol. 1.11, Item 5, Page 05-00025.

It states that all animal studies have been conducted under GLP conditions, except for the range finding studies which were not. In addition, each individual study includes its own specific statement.

I believe this answers all the questions but, if not, please let me know.

On another subject, I will be in Washington and visiting the FDA on Friday, March 31, and I would like very much to be able to see you to say "hello". I will call you within the next couple of days to arrange a convenient time for you.

Best regards.

Sincerely,

Sergio Nacht, Ph.D.

SN:rmc

Polymer Systems

April 7, 1995

ORIGINAL

NC

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel 0.1%)
NDA No. 20-475
User Fee I.D. No. 2559

Dear Dr. Wilkin:

We have been informed by the Division of Topical Drugs, FDA, Rockville, Maryland that the above-referenced NDA has been accepted for filing. One of the next steps may involve a pre-approval inspection (PAI) of our facilities or those of our contract manufacturers by the relevant District Office. At present, we are at the stage of preparing our complete validation package. We understand that completion of process validation is not a prerequisite to a PAI, however, we feel that it is a critical component of the inspection. In order to avoid your having to make duplicate visits and to ensure the inspection is complete and efficient, we request that the PAI be delayed to a date when the validation package has been completed. We plan to have this completed within the next few months. APS will contact your office immediately upon completion. I hope you agree that this will be the best utilization of the resources of both FDA and APS.

If there are any questions, please do not hesitate to call me at (415) 366-2626.

Sincerely,

Sergio Nacht/sax

Sergio Nacht, Ph.D.
Sr. Vice President
Science and Technology

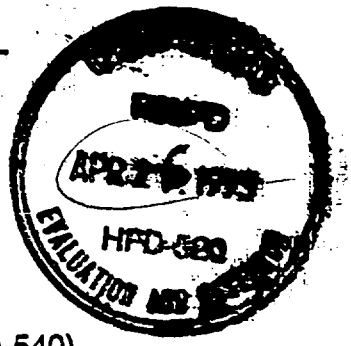
SN/sp

sax367

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

ORIGINAL



NC

April 13, 1995

Proj: #P.006

Ms. Joanne Holmes
Project Manager
Division of Topical Drug Products (HFD-540)
Room No. 17B-45
Center For Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: **Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)**
NDA No. 20-475
Correspondence

Dear Ms. Holmes:

Attached is a copy of the Adverse Events Listings by Center and time of occurrence relative to enrollment date for the pivotal efficacy studies (B0222E and B0223E) as requested by the Statistics Reviewer. You had conveyed this request to me on March 29, 1995 during our telephone conversation. Kindly forward this information to the appropriate individual in the department.

In addition, you had indicated that Dr. Maturu wanted to have some more information on the Environmental Assessment, especially pertaining to Fate and Environmental Effects. It is our understanding that documentation on these items is not ordinarily required for topically administered drug substances as per 21 CFR 25. 31 a (b) (3) (ii), and as indicated in our NDA. Unfortunately, I have not been able to connect with Dr. Maturu. Could you please seek a clarification with him on our behalf. Specifically,

(a) What particularly would he like to see added to the Environment Assessment; given that we are dealing with a topical product?

(b) Is the issue with a particular manufacturing site?

Thank you so much for your assistance. We are still working on Dr. Ajayi's request and hope to have it ready in the near future. If you have any questions, please feel free to call me.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

Thanks once again.

Sincerely,

S. Saxena

by

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

cc: S. Nacht, Ph.D.

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

ORIGINAL

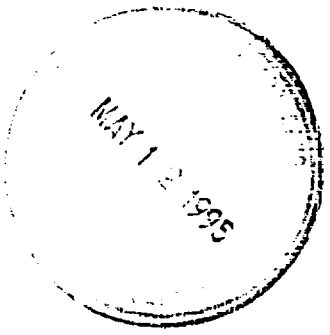
B-001

MAY 11 1995

BM

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

P006



RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial 003
Human Pharmacokinetics and Bioavailability

Dear Dr. Wilkin:

This submission is in response to a request by Dr. Funmi Ajayi, Biopharmaceutics Reviewer, for electronic files containing in vivo and in vitro percutaneous absorption data submitted in the Human Pharmacokinetics and Bioavailability section of the original submission of this NDA.

Per Dr. Ajayi's specific request, included in this submission are data from the two in vivo percutaneous absorption studies, B0225S, Protocol CP9 and B0281S, Protocol CP20 and the in vitro studies, carried out to show the equivalence of three Tretinoin MICROSPONGE® Gel 0.1% (TMG 0.1%) formulations. The data are provided in electronic files (diskettes) as well as hard copy.

A **"Reviewer's Guide"** is included to assist in the review process.

This submission includes an archival and a reviewer's copy of the two volume set.

Should you have any questions regarding this submission, you may call Dr. Subhash Saxena or me @ (415-366-2626).

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
an.011

cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

DUPLICATE

Sergio Nacht, Ph.D
Senior Vice President
Science & Technology

MAY 24 1995

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

P006

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial #004
Electronic Files of Draft Labeling For Clinical Reviewer

Dear Dr. Wilkin:

This submission is in response to a request by Dr.Phyllis Huene, Clinical Reviewer for electronic files containing draft labeling for our drug product, Nuretin™ 0.1%, submitted in NDA 20-475. The data are provided in electronic files (diskettes) as well as hard copy.

Included in this submission are electronic files (2 diskettes) containing the Physician's Insert, Patient Instructions, and the various Tube and Carton labels. Also included is a hard copy of NDA 20-475, Item 4.c. Labeling, for reference.

An archival and two reviewer's copies of the electronic files and Item 4.c. are provided.

I would appreciate, very much , if you would provide Dr. Huene with a reviewer's copy.

Should you have any questions regarding this submission, you may call Dr. Subhash Saxena or me @ (415-366-2626).

Sincerely,

Sergio Nacht

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
sn.013

cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

CENTER FOR
MAY 25 1995
HFD-520
EVALUATION AND RESEARCH

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626

Advanced Polymer Systems

June 8, 1995

Sergio Nacht, Ph.D
Senior Vice President
Science & Technology

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

P006

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial No. 005
Table of Contents for Volume 1.13 of NDA (Item 5)

Dear Dr. Wilkin:

This amendment No. 005 is in response to a request by Dr. Syed Alam for amending the Table of Contents (TOC) for Volume 1.13 of the original NDA 20-475. As requested, the TOC has been amended to include the specific NDA page numbers. These changes affect Page Nos. 05-00329 through 05-00333 of Volume 1.13.

An archival and two reviewer's copies of the amended TOC are provided.

I would appreciate, very much , if you would provide Dr. Alam with a reviewer's copy. At his request, the information has already been faxed to him.

Should you have any questions regarding this submission, you may call Dr. Subhash Saxena or me at (415-366-2626).

Sincerely,

Sergio Nacht/BG

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
sn.016
cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

Sergio Nacht, P
Senior Vice Presic
Science & Techno

BP

June 15, 1995

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

P006

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial No. 006
Batch Summary for Nonclinical Studies (Item 5)

Dear Dr. Wilkin:

This amendment No. 006 is in response to a request by Dr. Syed Alam for a table summarizing Tretinoin Microsphere Gel (TMG) Lot Numbers, Formulations and APS Study Numbers. As requested, the table is attached. These do not affect any existing information in the NDA.

An archival and two reviewer's copies of the table are provided.

I would appreciate, very much , if you would provide Dr. Alam with a reviewer's copy. At his request, the information has already been faxed to him.

Should you have any questions regarding this submission, you may call Dr. Subhash Saxena or me at (415)-366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
sn.018

cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 16 1995
HFD-520

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

June 21, 1995

Jonathan K. Wilkin, M.D.
Director
Food & Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial No 007
Lot Number Identification for Three Nonclinical Studies (Item 5)

Dear Dr. Wilkin:

This amendment No. 007 is being submitted in response to a clarification requested by Dr. Syed Alam.

Dr. Alam stated that in one of our studies, APS Study No. B0143S (NDA Vol. 1.14, Page 05 01091), the sample is identified as "T-Retinoic Acid Gel, Lot No. 10208" in the report submitted by the testing laboratory, He pointed our that this lot number is that of T-Retinoic Acid Gel Vehicle based on the tables provided to him in NDA Amendment No. 006.

We have confirmed that the lot number as listed. i.e., Lot 10208 is in fact that of T-Retinoic Acid Gel (TMG IA) Vehicle. The Testing laboratory has incorrectly identified it as T-Retinoic Gel. All samples including the vehicle sent to for that study were identified as "T-Retinoic Acid Gel." The identity of the vehicle was purposely not disclosed to them. In reviewing this, we also uncovered that the same situation applies to two other studies, APS Study Nos. B0142S and B0147S. Accordingly, please amend the following pages in the NDA. The "Sample" should read "T-Retinoic Gel Vehicle" instead of "T-Retinoic Acid Gel."

NDA Vol. 1.14, Pages 05 01091 through 05 01109 (Study No. B0143S)
NDA Vol. 1.19, Pages 05 02433 through 05 02450 (Study No B0147S)
NDA Vol. 1.19, Pages 05 02620 through 05 02638 (Study No B0142S)

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

JUN 22 1995

DUPLICATE

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

[redacted]

BA-A
4
B2

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Document Control Room No. 12B-30
5600 Fishers Lane
Rockville, MD 20857

P006

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial No. 008
Clinical Data Tables with Mean Values (Item 8)

Dear Dr. Wilkin:

This amendment No. 008 is in response to a request by Dr. Phylis Huene. She requested calculation of mean changes from baseline for the various lesion counts, rather than the percentage mean changes as reported in the original NDA. As requested, the tables are attached. These do not affect any existing information in the NDA nor do the they change any conclusions drawn from the results.

An archival and two reviewer's copies of this amendment are provided. A diskette containing data files and SAS data sets from which the tables were made, is also provided with each copy.

I would appreciate, very much , if you would provide Dr. Huene with a reviewer's copy. We have already faxed this information to her.

Should you have any questions regarding this submission, you may call Dr. Subhash Saxena or me at (415)-366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
sn1019

cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 23 1995
HFD-520

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

JUN 23 1995

Proj. #P.006

Jonathan K. Wilkin, M.D.
Director, Division of Topical Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION - Serial No. 009
Four-Month Safety Update Report (Item 8)

Dear Dr. Wilkin:

Submitted with this letter, in accordance with 21CFR 314.50 (d) (5) (vi) (b), is the initial (4-month) Safety Update Report for our Nuretin™ 0.1% Gel (Tretinoin Microsphere Gel 0.1%) NDA 20-475.

We are submitting, as usual, one archival copy and two copies, in tan binders, for the appropriate reviewers.

Should there be any questions, please feel free to call me or Dr. Subhash Saxena at (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/sp

Enc.

cc: S. Saxena, Ph.D.
Project File
Regulatory File

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 26 1995

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

JUN 2 9 1995

DUPLICATE

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

Proj. #P.006

Jonathan K. Wilkin, M.D.
Director, Division of Topical Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION-Serial No. 010
Chemistry, Manufacturing and Controls (Section 3)
Updated Stability Report.

Dear Dr. Wilkin:

This submission includes an Updated Stability Report for our Nuretin™ 0.1% Gel (Tretinoin Microsphere Gel 0.1%) NDA 20-475.

This updated stability report demonstrates that Nuretin 0.1% Gel is stable for at least 18 months. Accordingly, we are requesting that the proposed expiration dating for Nuretin 0.1% Gel be extended to 18 months.

This submission is comprised of two volumes. A Reviewer's Guide is provided in each volume to assist in the location of the specific items within the Report.

We are submitting one archival copy and two reviewer's copies to the Central Document Room 12B-30.

Should there be any questions, please feel free to call me or Dr. Subhash Saxena at (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/sp
Enc.
cc: S. Saxena, Ph.D.
Project File
Regulatory File

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

Advanced Polymer Systems

JUL 17 1995

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

Proj. #P.006

Jonathan K. Wilkin, M.D.
Director, Division of Topical Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

BC

RE: New Drug Application (NDA) No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
AMENDMENT TO A PENDING APPLICATION-Serial No. 011
Chemistry, Manufacturing and Controls (Section 3)
Certification That A Field Copy of Amendments No. 010, and 011
Have Been Sent To FDA District Offices

Dear Dr. Wilkin:

In accordance with the Code of Federal Regulations, Title 21, Part 314.60 (c), we wish to certify that field copies of Amendment #010, Updated Stability Report, and this Amendment #011 to this NDA have been sent to our four FDA District Offices.

Copies of correspondence which accompanied the above field copies are provided in this submission.

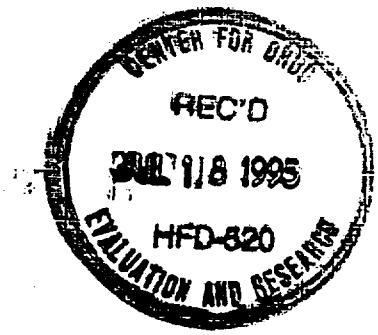
We are submitting one archival copy and two reviewer's copies of this amendment to the Central Document Room 12B-30. A field copy has been sent to each of the four FDA District Offices.

Should there be any questions, please feel free to call me or Dr. Subhash Saxena at (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
Enc.
cc: S. Saxena, Ph.D.
Project File
Regulatory File
SN:030



3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

AUG 2 8 1995

Jonathan K. Wilkin, M.D. P006
Director, Division of Topical Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: New Drug Application (NDA) No. 20-475
User Fee I.D. No. 2559
Tretinoin MICROSPONGE® Gel, 0.1%
AMENDMENT TO A PENDING APPLICATION-SERIAL No. 012
Chemistry, Manufacturing and Controls (Item 3)
Pre-Approval Inspection of Advanced Polymer Systems, Redwood City, California Facility: Observations, Responses, and Corrective Measures to Form 483

Dear Dr. Wilkin:

This submission contains responses and corrective measures for observations listed on the Form 483 issued during the Pre-Approval Inspection of our APS Redwood City facility on 7/31 - 8/4 and 8/8/95. This inspection covered our two pending New Drug Applications: NDA No. 20-475 for our Tretinoin MICROSPONGE® Gel 0.1% drug products.

These responses and corrective measures were submitted to the FDA San Francisco District Office on 8/22/95. They were submitted in two volumes, one volume for each NDA's observations. We are providing in this submission the responses (Volume Two) for NDA 20-475 Tretinoin MICROSPONGE® Gel, 0.1%.

In accordance with the Code of Federal Regulations, Title 21, Part 314.60.(c), we wish to certify that field copies of Amendment #012 to this NDA have been sent to our three FDA District Offices.

We also wish to certify that the field copies submitted to the FDA District Offices are true copies and identical in relevant part to the archival and review copies submitted in support of NDA

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

AUG 2 8 1995

We are submitting one archival copy and two reviewer's copies of this amendment to the Document Control Room 12B-30.

Should there be any questions, please feel free to call me or Dr. Subhash Saxena at (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg

Enc.

cc: S. Saxena, Ph.D.
Project File
Regulatory File

SN:045

® Advanced Polymer Systems

September 6, 1995 ✓ ORIGINAL NC

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Topical Drug Products (HFD-540)
Attn: Document Control Room #12B-30
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 20-475
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)

Dear Sir/Madam:

Authorization is hereby granted to the Food and Drug Administration to refer to **NDA No. 20-475** on behalf of

in support of their filing of Annual Reports for NDAs covering their approved tretinoin-containing drug products.

By virtue of this letter, we also authorize

to incorporate by reference the aforementioned application in their Annual Reports for NDAs covering their approved tretinoin-containing drug products.

The information in NDA 20-475 is judged to be privileged trade secret and confidential commercial information within the meaning of section 4.61 (b) of the Freedom of Information Act and 21 CFR 20.61 and thus should not be publicly disclosed.

We will inform you in the event that this authorization is withdrawn.

Should you have any questions, please contact me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp
Enc.

cc: Lewis Gryziewicz (PRI)
Sergio Nacht, Ph.D.
Regulatory Files

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

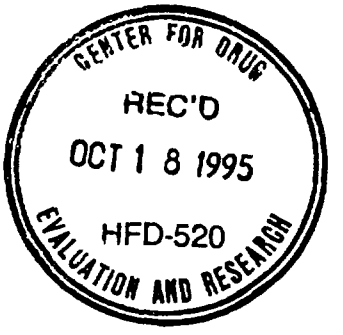
® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

OCT 17 1995

P006

Jonathan K. Wilkin, M.D.
Director, Division of Topical Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 12B-30
5600 Fishers Lane
Rockville, MD 20857



RE: New Drug Application (NDA) No. 20-475
User Fee I.D. No. 2559
Tretinoin MICROSPONGE® Gel, 0.1%
AMENDMENT TO A PENDING APPLICATION-SERIAL No. 013
Chemistry, Manufacturing and Controls (Item 3)
Pre-Approval Inspection of Advanced Polymer Systems, Lafayette, Louisiana Facility: Observations, Responses, and Corrective Measures to Form 483

Dear Dr. Wilkin:

This submission contains responses and corrective measures for observations listed on the Form 483 issued during the Pre-Approval Inspection of our Lafayette, Louisiana Bulk Pharmaceutical Chemical facility between 8/1 and 8/23/95. This inspection covered our two pending New Drug Applications:
and NDA No. 20-475 for our Tretinoin MICROSPONGE® Gel 0.1% drug products.

These responses and corrective measures were submitted to the FDA New Orleans District Office on 10/16/95. They were submitted in two volumes, one volume for each NDA's observations. We are providing in this submission the responses (Volume Two) for NDA 20-475, Tretinoin MICROSPONGE® Gel, 0.1%.

In accordance with the Code of Federal Regulations, Title 21, Part 314.60.(c), we wish to certify that field copies of Amendment #013 to this NDA have been sent to our four FDA District Offices.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

OCT 17 1995

We also wish to certify that the field copies submitted to the FDA District Offices are true copies and identical in relevant part to the archival and review copies submitted in support of NDA No. 20-475.

We are submitting one archival copy and one reviewer's copy of this amendment to the Document Control Room 12B-30.

Should there be any questions, please feel free to call me or Dr. Subhash Saxena at (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg

Enc.

c: S. Saxena, Ph.D.
Project File
Regulatory File

4:052

® Advanced Polymer Systems

ORIGINAL

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

December 15, 1995

Ms. Mary Jean-Kozma Fornaro
Project Manager
Division of Dermatologic and Ophthalmologic
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

SUPPL NEW CORRESP

SNC

RE: New Drug Application (NDA) No. 20-475
Tretinoin MICROSPONGE® Gel, 0.1%
APS Redwood City, CA Facility Preapproval Inspection

Dear Ms. Fornaro:

Attached is a letter we sent to Ms. Patricia Ziobro of the FDA San Francisco District Office today regarding corrective action we have taken to deficiencies found during the Pre-Approval Inspection of our facility in Redwood City, CA on July 31 through August 8, 1995.

I would appreciate if you would distribute a copy (ies) of this correspondence as you deem appropriate.

Should you have any questions regarding this letter, please call me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/bg
SS.005

cc: Sergio Nacht, Ph.D.
Subhash Saxena, Ph.D.
Regulatory File
Project File

CENTER FOR DRUG
REC'D
DEC 1 8 1995
HFD-
EVALUATION AND RESEARCH

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

ORIGINAL

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

JAN 2 1996

Ac

NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room #12B-30
5600 Fishers Lane HFD-540
Rockville, MD 20857

P006

RE: New Drug Application (NDA) No. 20-475
Tretinoin MICROSPONGE® Gel, 0.1%
AMENDMENT TO A PENDING APPLICATION SERIAL No. 014
Chemistry, Manufacturing and Controls (Item 3)
Pre-Approval Inspection of Advanced Polymer Systems, Lafayette, Louisiana Facility: Observations, Responses, and Corrective Measures to Form 483 and FDA New Orleans District Letter

Dear Dr. Wilkin:

This submission contains a copy of our response sent to Mr. James Gamet, Director, FDA New Orleans District Office certifying that we have corrected and solved the problems reported to Advanced Polymer Systems, Inc. (APS) on the Form FDA 483, "Inspectional Observations", regarding NDA 20-475 issued during the preapproval inspection of our facility in Lafayette, LA on August 1-23, 1995 and in the letter from Mr. Gamet of September 13, 1995 to Mr. John J. Meakem, President , Chairman and CEO of APS.

We have previously responded to the observations made on Form 483 (Saxena to Gamet, dated October 16, 1995 and NDA 20-475, Amendment #13, 10/17/95). Attached are additional documents in response to the comments in Mr. Gamet's letter of September 13, 1995 to Mr. John J. Meakem as well as any updates on the responses previously submitted. Each item in the letter and Form 483 along with our response is tabbed individually.

Please note that this certification addresses only the issues pertaining to NDA 20-475. We will be responding to the issues on our other NDA at a later date.

JAN 2 1996

In accordance with the Code of Federal Regulations, Title 21, Part 314.60. (c), we wish to certify that field copies of Amendment #014 to this NDA have been sent to our four FDA District Offices. Copies of correspondence which accompanied the field copies are provided in this submission.

We also wish to certify that the field copies submitted to the FDA District Offices are true copies and identical in relevant part to the archival and review copies submitted in support of NDA No. 20-475.

We are submitting one archival copy and one reviewer's copy of this amendment to the Document Control Room 12B-30.

Should you have any questions regarding this submission, please contact Dr. Subhash Saxena or me @ (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg

cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

sn.077

ORIGINAL

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

January 3, 1996

NEW CORRESPONDENCE

P006

Ms. Mary Jean Kozma-Fornaro
Project Manager
Division of Dermatologic and Ophthalmologic
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: New Drug Application (NDA No. 20-475
Tretinoin MICROSPONGE® Gel, 0.1%
Amendment To A Pending Application Serial No. 014

Dear Mary Jean:

Please find enclosed a DESK COPY of the above NDA Amendment for your use and/or appropriate distribution.

Field copies have been sent to our corresponding FDA district offices. An original archival plus a reviewer's copy of this amendment have also been sent to the Document Control Room, 12B-30.

Should you have any questions regarding this amendment, please contact me @ (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

SN/bg

SN.082

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

FEB 20 1996

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room #12B-30
5600 Fishers Lane HFD-540
Rockville, MD 20857

P006

RE: New Drug Application (NDA) No. 20-475
Tretinoin MICROSPONGE® Gel, 0.1%
AMENDMENT TO A PENDING APPLICATION SERIAL No. 016
General Correspondence

Dear Dr. Wilkin:

In accordance with the Code of Federal Regulations, Title 21, Part 314.60. (c), we wish to certify that field copies of Amendment #016 to this NDA have been sent to our four FDA District Offices. Copies of correspondence which accompanied the field copies are provided in this submission.

We also wish to certify that the field copies submitted to the FDA District Offices are true copies and identical in relevant part to the archival and review copies submitted in support of NDA No. 20-475.

Should you have any questions regarding this submission, please contact Dr. Subhash Saxena or me @ (415) 366-2626.

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

n.088

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

Sergio Nacht, Ph.D.
Senior Vice President
Science & Technology

FEB 2 0 1996

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Ophthalmologic Drug Products
Center for Drug Evaluation & Research
Document Control Room No. 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

Project: P006

RE: NDA No. 20-475
Tretinoin MICROSPONGE® Gel, 0.1%
Amendment To A Pending Application No. 016
GENERAL CORRESPONDENCE

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-475 for Tretinoin MICROSPONGE® Gel 0.1%. Reference is also made to the tradename NURETIN™ which was included in the original application submitted on February 6, 1995.

At this time we request the Agency to consider the trademark, RETIN-A MICRO™, in place of NURETIN™, for Tretinoin MICROSPONGE® Gel, 0.1%, and that this name be submitted to the FDA Nomenclature and Labeling Committee for review and consideration at their next scheduled meeting.

Should you have any questions regarding this issue, please contact Dr. Subhash Saxena or me @ (415-366-2626).

Sincerely,

Sergio Nacht, Ph.D.
Senior Vice President
Science and Technology

SN/bg
sn.086

cc: Subhash Saxena, Ph.D.
Regulatory File
Project File

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APSINC UD FAX: 415/365-6490

® Advanced Polymer Systems

DUPLICATE

NEW CORRESP

NC

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

May 8, 1996

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

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

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
CORRESPONDENCE TO NDA RE: ACTION LETTER OF MAY 6, 1996

Dear Dr. Wilkin:

We are in receipt of your letter dated May 6, 1996 in reference to the above-mentioned drug application indicating that our application, as amended, is not approvable at this point.

Per your letter and in accordance with 21 CFR 314.120(a)(1), this is to inform you that Advanced Polymer Systems intends to amend the application to correct the deficiencies listed and to provide the supplemental information requested.

In addition, we formally request a meeting with the appropriate reviewers for the purpose of clarifying the observations included in the May 6, 1996 letter and obtaining a clear understanding of the appropriate way to provide the information required. To this effect, we will be working with Ms. Mary Jean Kozma-Fornaro, Project Manager, to set up this meeting.

For completion, we are sending a copy of this letter to the Document Control Room 12B-30 as official correspondence to the NDA.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 13 1996
HFD

SS/sp

cc: R. Johannes
S. Nacht, Ph.D.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

ORIGINAL

® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

May 13, 1996

NEW CORRESPONDENCE

Mary Jean Kozma-Fornaro, RN, MSA
Project Manager
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
CORRESPONDENCE TO NDA RE: ACTION LETTER OF MAY 6, 1996

Dear Ms. Kozma-Fornaro:

We are in receipt of a letter from Dr. Jonathan K. Wilkin regarding the above-mentioned NDA for Nuretin™ 0.1% Gel indicating that it is not-approvable at this time.

This is to formally request a meeting with the Division Director, appropriate reviewers and personnel from the Chemistry Department, Compliance Division and whoever you feel will be necessary. The objective of the meeting will be to obtain a clear understanding of the issues raised and to reach a resolution of those issues in order to change the status of the referenced NDA from non-approvable to approvable leading to the approval of the NDA.

As discussed with Ms. Rose Mary Cook on May 7, 1996, and as I mentioned to you earlier today, we will submit a DRAFT response for review by the Agency prior to the meeting. All the information requested for the Environmental Assessment Evaluation, the commitment to conduct a Phase 4 mutagenicity battery of tests on a clarification of which formulation was used for each study, and Safety Update report will be provided in our response.

Our DRAFT response will also include our proposed responses to items 1 and 2 of Dr. Wilkin's letter. In the meeting we would primarily like to get a resolution on these two items dealing with the GMP issues and also the issue of conducting Preservative Effectiveness Testing (PET) initially and at expiry of each lot.

Attendees of the meeting from APS are likely to be:

Mr. Jack Meakem, Chairman, President & CEO
Dr. Sergio Nacht, Sr. V.P., Science & Technology
Dr. Subhash Saxena, V.P. Pharmaceutical Sciences & Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

We would appreciate a meeting as soon as possible. We will try our best to accommodate the proposed dates.

Thank you.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

cc: R. Johannes
S. Nacht, Ph.D.

® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

MAY 21 1996 NEW CORRESPONDENCE

JUN 5 1996

Paid 6/3/96

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
CORRESPONDENCE TO NDA RE: ACTION LETTER OF MAY 6, 1996

Dear Dr. Wilkin:

As discussed with Ms. Mary Jean Kozma-Fornaro, attached is a DRAFT response to the issues raised in your letter of May 6, 1996. Please route them to the appropriate people for review before the requested meeting. Per Ms. Kozma-Fornaro's suggestion, eight copies of the DRAFT document are included. A desk copy is also being sent to her under separate cover.

We believe that we have appropriately responded to the issues and provided all additional information that was requested and are hopeful that this information will be adequate to change the status of the NDA to an approvable status.

If I can provide any additional information, please feel free to call me at (415) 366-2626.

Thank you.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

cc: R. Johannes
S. Nacht, Ph.D.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

ORIGINAL

NEW CORRESP

NC

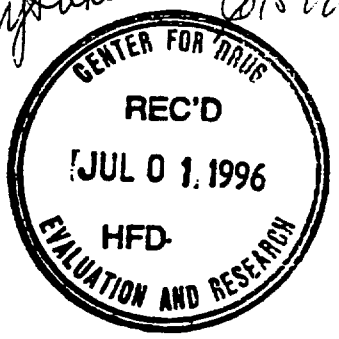
® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

Noted - Packets distributed to meeting attendees Fri 7/5/96

June 28, 1996

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850



RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
Agenda for APS/FDA Meeting, July 11, 1996

Dear Dr. Wilkin:

APS appreciates the opportunity to meet with you and the other FDA representatives on July 11, 1996. The objective of the meeting is for APS to review the relevant information and data that it believes will resolve the outstanding concerns of the Agency about the quality of raw material used in the biobatch. APS is confident that once Agency personnel have had the opportunity to review the supporting data, they will reach the same conclusions and grant approval of our NDA.

Based on various conversations with Agency officials, it is our understanding that the only issue that remains unresolved is that of the quality of raw material Tretinoin lot 774 that was used in the biobatch. We propose to focus the July 11, 1996 meeting on this issue, unless you advise us in advance that there are any other unresolved issues of concern to the FDA that have a bearing on the approval of our NDA.

Since our response dated May 21, 1996 to the FDA non-approvable letter of May 6, 1996, APS has obtained the following new information, [which will be discussed in detail at the meeting]:

1. APS obtained an independent evaluation of this issue from Dr. Ronald F. Tetzlaff of Kemper-Masterson, Inc. Dr. Tetzlaff prepared a comprehensive report dated June 26, 1996 which summarizes his findings. A complete copy of this report is attached for your review. His conclusion is that there is substantial evidence to believe the two out-of-specifications results were an artifact of testing (probably due to laboratory error). His report, which is attached, includes a detailed analysis of each factor that is relevant to this issue. APS is confident that this summary addresses all issues of concern to the FDA. APS would be pleased to

assist FDA reviewers or compliance personnel as necessary to clarify any matters relevant to this report. Please feel free to call me (415-366-2626) or Dr. Tetzlaff (770-641-9100) if there are any questions.

2. APS has new data that have not yet been provided to the Agency that provide confirmation of the validity of the original testing of lot 774. In June 1996 retain samples of Tretinoin lot 774 were tested. These retain samples were taken at the same time as the initial analytical samples in August 1992 (stored at refrigerated temperature). Retain samples from each of three jars individually passed HPLC assay (done in triplicate). These assay results provide convincing new evidence that lot 774 conformed to specifications, and reaffirms that the out-of-specifications values were inconsistent with the overwhelming data that confirm the lot was within specifications.

APS is confident that, based on the new data and information that are summarized in the attached report, together with our May 21, 1996 response, FDA will conclude that the NDA is approvable. We look forward to the July 11, 1996 meeting and appreciate the Agency's efforts to reach a resolution of this issue. A copy of the proposed agenda is attached.

Under separate cover, eight copies of this correspondence are being shipped to Ms. Sandy Childs for distribution to the attendees.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

cc: J. Meakem
S. Nacht, Ph.D.
R. Tetzlaff, Ph.D. - Kemper-Masterson, Inc.

ORIGINAL

ORIG AMENDMENT

BZ

Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

October 24, 1996

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
Amendment To A Pending Application No. 018
Labeling Revisions: Pharmacology/Toxicology

Dear Dr. Wilkin:

PR

This submission includes revised labeling for our drug product, Nuretin™ 0.1% Gel. We have revised the labeling according to the Pharmacology Reviewer's comments sent to us by Ms. Olga Cintron on 9/23/96. All three points in the Pharmacology Reviewer's comments have been addressed. Attached is the revised labeling for the following sections:

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Pregnancy: Teratogenic Effects. Pregnancy Category C
- Preclinical Toxicity Studies (new category requested by Reviewer)

If there are further questions, please let us know. I hope we can receive the labeling comments from the Clinical Reviewer and others as soon as possible.

One archival and one reviewer's copy have been sent to Document Control Room N-115.

Thank you.

Sincerely,

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

SPEC

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp
Enc.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

ORIGINAL

® Advanced Polymer Systems

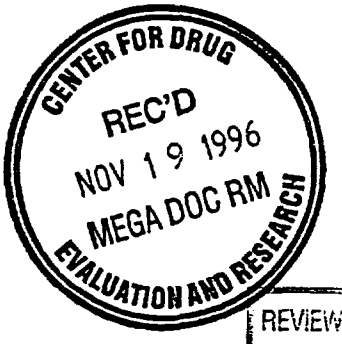
Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

November 18, 1996

BL

NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850



REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)
Amendment to Pending Application No. 019
Labeling Revisions: Clinical

Dear Dr. Wilkin:

This submission is in response to the Medical Officer's comments on labeling. Specifically, we have been requested to revise the CLINICAL PHARMACOLOGY section dealing with Irritation Potential of Nuretin™, 0.1%.

We have made the revisions which, we feel, address the comments by the Medical Officer. We'd like to point out that there were three sets of clinical studies where the irritation potential of Nuretin was assessed:

1. Phase III, 12 week Safety and Efficacy pivotal studies conducted in 347 acne subjects (APS Study Nos. B0222E and B0223E) as presented in the original NDA, Vol. 1.40, pages 08 01869 thru 08 01878 and Vol. 1.43, pages 08 03200 thru 08 03209, respectively. Copies of these pages are attached for your convenience. As can be readily seen from the figures, in each study, all irritation parameters, i.e., erythema, peeling, burning-stinging and itching, were graded as either less than mild or less than slight. In addition, even the mild irritation subsided after peeking at 2 weeks.

2. In a comparative study (APS Study No. B0178S) in women with sensitive skin, but without acne, where Nuretin 0.1% was compared with the commercial tretinoin cream 0.1%, Nuretin was found to be significantly better tolerated and less irritating than the tretinoin cream 0.1%. The data are presented in the original NDA, Vol. 1.38, pages 08 00991 thru 08 00994, 08 01013 thru 08 01015 and 08 01034 thru 08 01035. Copies are attached.

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

3. The last study (APS Study No. B0285S) was a 21-day cumulative irritancy study in men and women with healthy skin. As expected, Nuretin 0.1% was found to be mildly irritating but tretinoin cream 0.1% was substantially more irritating. These findings were presented in the original NDA, Vol. 1.37, pages 08 00782 thru 08 00785. Copies of these pages are attached.

These studies show that Nuretin was consistently found to be only mildly irritating. We believe that the revised labeling as presented in this submission accurately reflect these observations and findings.

At this time, we would like to propose two other labeling changes.

1. In the Physician's Insert, under "Pediatric Use", (NDA Vol. 1.10, page 04 00542) change text to read "Safety and effectiveness in patients below the age of 12 have not been established."

This change is supported by the demographic data (NDA Vol. 1.52, page 08 06542). A copy of this page is attached.

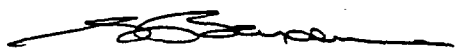
2. In the Patient Instructions Leaflet, under the "How to Use Nuretin (tretinoin microsphere gel) 0.1%" section, (Vol. 1.10, page 04 00545) we wish to remove the sentence "Wait 20 to 30 minutes before applying medication; it is important for your skin to be completely dry in order to minimize possible irritation." This is shown in the attached copy of Page 04 00545.

This change is supported by the patient instructions used in the two Phase III clinical protocols for this product which instruct "Subjects will cleanse their face, without harsh rubbing, with a mild soap provided by the investigator (Neutrogena®) each evening before retiring. After each of these cleansings, dispense a quantity of the assigned material equal to about <u>One (1)</u> inch (500 mg) from the tube, and apply to the <u>full face</u>".

A waiting period was not required before dosage for the pivotal trials and therefore is not needed for the marketed product. NDA 20-475 Vol. 1.41, page 08 02192 and Vol. 1.44, page 08 03516 from the clinical protocols for the pivotal Phase III studies B0222E and B0223E provide the support for this change. Copies of these pages are attached.

If there are further questions or comments, please do not hesitate to contact me at (415) 366-2626.

Sincerely,



Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

November 19, 1996

NEW CORRESPONDENCE

Ms. Olga Cintron
Project Manager
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
Nuretin™ 0.1% Gel (Tretinoin MICROSPONGE® Gel, 0.1%)

Dear Ms. Cintron:

As requested during our telephone conversation earlier today, enclosed is a diskette in Word Perfect 6.1 containing the revised clinical labeling as submitted in our NDA 20-475, Amendment 019 (Vol. 19.1). There are two sections in the Physician's Insert, viz. Irritation Potential and Pediatric Use, and one section in the Patient Instructions, viz. How to Use Nuretin which have been revised.

The diskette contains five (5) files:

	File Name	Description
1.	irritpot. rev	Revised Labeling (Physician's Insert): Irritation Potential Section
2.	peduse.rev	Revised Labeling (Physician's Insert): Pediatric Use Section
3.	patinst.rev	Revised Labeling (Patient Instructions): How to Use Section
4.	physins.org	Original Physician's Insert (Text) as submitted in NDA
5.	patinst.org	Original Patient's Instructions (Text) as submitted in NDA

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

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

Besides the diskette a printout of the files is also attached for your convenience. If we can provide any additional information to expedite the review process, please do not hesitate to call me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

cc: Project File P.006
Regulatory File

® Advanced Polymer Systems

DUPLICATE

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

December 6, 1996

BC

NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%
Amendment to Pending Application No. 020
Labeling Revisions

Dear Dr. Wilkin:

This submission is in response to the Chemistry Reviewer's request for the revised labeling for the tubes and cartons of the above product. The revisions reflect the approved name of the product. Please note that there are three (3) sizes: 20g, 45g and Physician's sample (2g).

Enclosed are four (4) official copies of the labeling of the tube and carton. These include an archival copy and three reviewer's copy. In addition, under separate cover we have sent two (2) DESK copies to Ms. Olga Cintron, Project Manager.

If there are further questions or comments, please do not hesitate to contact me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

ORIGINAL

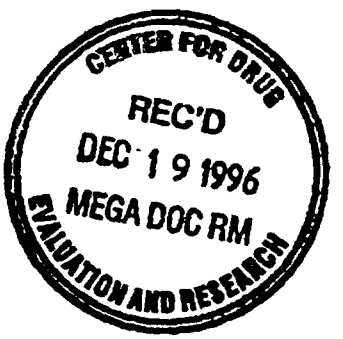
® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

December 18, 1996

BC
NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850



RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%
Amendment to Pending Application No. 021
Chemistry: Vendor Environmental Protection Certificate

Dear Dr. Wilkin:

This submission is in response to the Chemistry Reviewer's request for a certificate of compliance from F. Hoffmann-La Roche that their Switzerland plant operates in accordance with the local and national environmental laws.

Enclosed are three (3) official copies of the certificate. These include an archival copy and two reviewer's copy. In addition, under separate cover we have sent two (2) DESK copies to Ms. Olga Cintron, Project Manager.

If there are further questions or comments, please do not hesitate to contact me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

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

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

ORIGINAL

® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

December 19, 1996

NEW CORRESPONDENCE

Ms. Olga Cintron
Project Manager
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

RE: New Drug Application (NDA) No. 20-475
User Fee I.D. No. 2559
RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%
Amendment To A Pending Application No. 022
Chemistry: Vendor Environmental Protection Certificate

Dear Ms. Cintron:

Enclosed are two desk copies of the above amendment as you requested. Please distribute them as you deem necessary.

An official archival and two reviewer's copies have been sent to the Document Control Room.

Thank you for your assistance.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/bg

Enc.

cc: Project File P.006
Regulatory File

RJ:126

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I ☐ MEMO

CSO INITIALS DATE

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

ORIGINAL

® Advanced Polymer Systems

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

December 19, 1996

BC

NDA ORIG AMENDMENT

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

RE: **New Drug Application (NDA) No. 20-475**
User Fee I.D. No. 2559
RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%
Amendment to Pending Application No. 022
Chemistry: Vendor Environmental Protection Certificate

Dear Dr. Wilkin:

This submission is in response to the Chemistry Reviewer's request for a certificate of compliance from . plant operates in accordance with the local and national environmental laws.

Enclosed are three (3) official copies of the certificate. These include an archival copy and two reviewer's copy. In addition, under separate cover we have sent two (2) DESK copies to Ms. Olga Cintron, Project Manager.

If there are further questions or comments, please do not hesitate to contact me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/sp

Enc.

REC'D
DEC 20 1996
HFD
EVALUATION AND RESEARCH

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

® Advanced Polymer Systems

JAN 13 1997

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences
and Regulatory Affairs

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room N-115
9201 Corporate Blvd.
Rockville, MD 20850

BL
NDA ORIG AMENDMENT

RE: New Drug Application (NDA) No. 20-475
User Fee I.D. No. 2559
RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%
Amendment to Pending Application No. 024
Microbiology: Statement of Commitment To Perform
Preservative Effectiveness Testing (PET)

Dear Dr. Wilkin:

This submission is in response to the Microbiology Reviewer's request for a final statement of commitment by Advanced Polymer Systems, Inc. that Preservative Effectiveness Testing (PET) will be performed initially and at expiry on the first three production lots of the drug product, RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%.

The correspondence of 1/9/97 received from Ms. Olga Cintron regarding that request and our statement of commitment are provided in this submission.

Enclosed are three (3) official copies of this submission. These include an archival copy and two reviewer's copies. In addition, under separate cover we have sent two (2) DESK copies to Ms. Olga Cintron.

If there are further questions or comments, please do not hesitate to contact me at (415) 366-2626.

Sincerely,

Subhash J. Saxena, Ph.D.
Vice President
Pharmaceutical Sciences and Regulatory Affairs

SS/bg- RJ:128
cc: Project File : P006
Regulatory File

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490

Advanced Polymer Systems

Statement of Commitment to Conduct Phase 4 Preservative Effectiveness Testing (PET) For The Drug Product During The Stability Protocol.

Advanced Polymer Systems, Inc. hereby commits to conduct Phase 4 Preservative Effectiveness Testing (PET) for the drug product, RETIN-A® MICRO™ (tretinoin gel) microsphere, 0.1%, on the first three production lots. This testing shall be performed on these lots initially and at expiry. Upon demonstration of appropriate antimicrobial effectiveness, PET testing shall be discontinued beyond the testing of the first three production lots.

Signature: _____

Name: Subhash J. Saxena, Ph.D.

Title: Vice President, Pharmaceutical Sciences and Regulatory Affairs

Date: 1/13/97

3696 Haven Avenue, Redwood City, California 94063
Tel: 415/366-2626 Telex: 361-290 APS INC UD FAX: 415/365-6490