CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-529

Approval Letter

ANDA 75-529

FEB 22 2000

Spear Pharmaceuticals, Inc.
Attention: Kim L. Spear, M.D.
13100 Ponderosa Way
Ft. Myers, FL 33907

Dear Sir:

This is in reference to your abbreviated new drug application dated December 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Tretinoin Gel USP, 0.025%.

Reference is also made to your amendments dated February 20, April 5, June 16, December 8, and December 10, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Tretinoin Gel USP, 0.025% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Retin-A® Gel, 0.025% of Johnson and Johnson Consumer Companies Inc.).

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of

Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

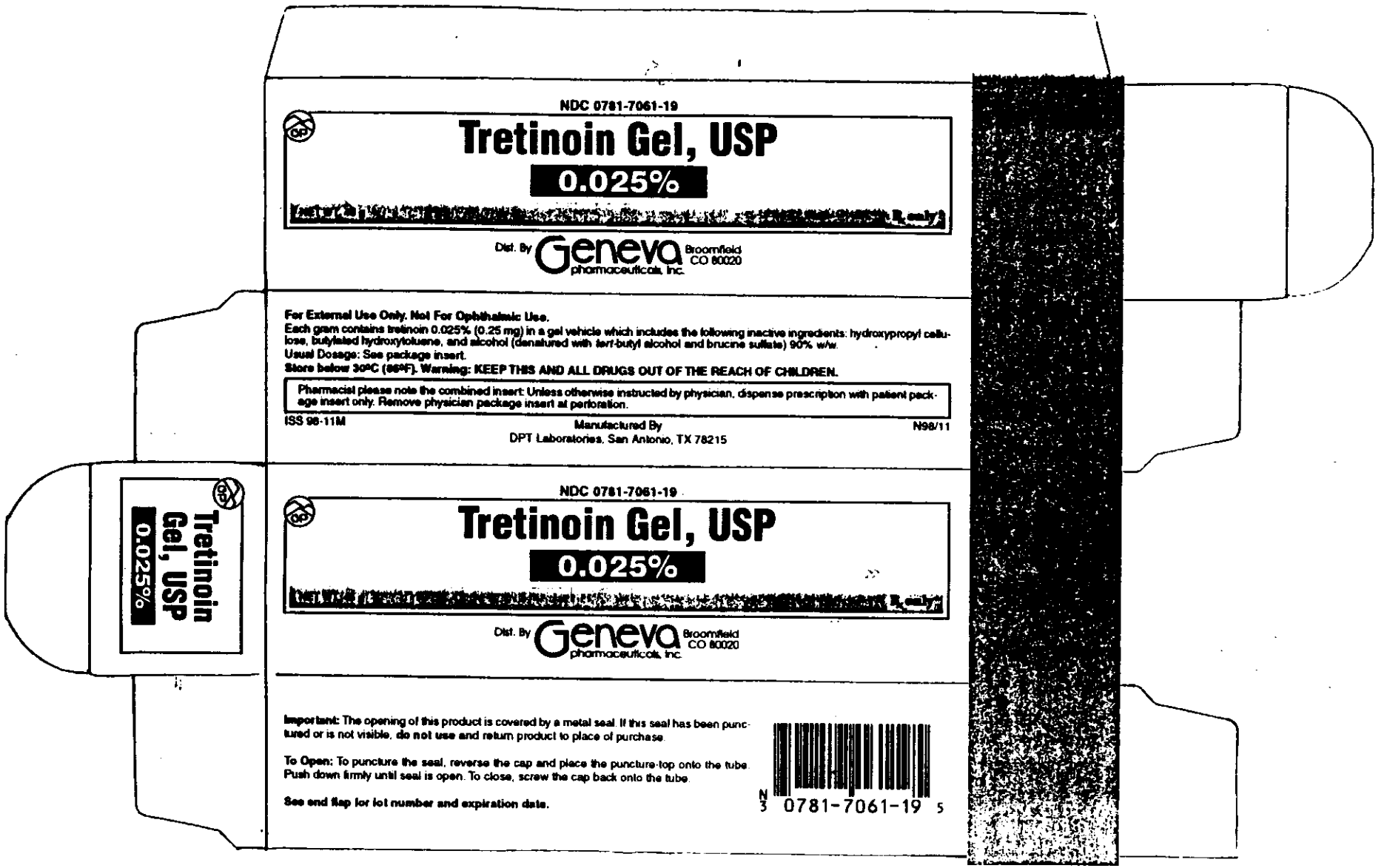
/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-529

FINAL PRINTED LABELING



NDC 0781-7061-19

Tretinoin Gel, USP

0.025%

Rx only

Dist. By Geneva pharmaceuticals, Inc. Broomfield CO 80020

For External Use Only. Not For Ophthalmic Use.
Each gram contains tretinoin 0.025% (0.25 mg) in a gel vehicle which includes the following inactive ingredients: hydroxypropyl cellulose, butylated hydroxytoluene, and alcohol (denatured with *tert*-butyl alcohol and brucine sulfate) 90% w/w.
Usual Dosage: See package insert.
Store below 30°C (86°F). Warning: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Pharmacist please note the combined insert: Unless otherwise instructed by physician, dispense prescription with patient package insert only. Remove physician package insert at perforation.

ISS 98-11M

Manufactured By
DPT Laboratories, San Antonio, TX 78215

N98/11

NDC 0781-7061-19

Tretinoin Gel, USP

0.025%

Rx only

Dist. By Geneva pharmaceuticals, Inc. Broomfield CO 80020

Important: The opening of this product is covered by a metal seal. If this seal has been punctured or is not visible, **do not use** and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

See end flap for lot number and expiration date.

N 3 0781-7061-19 5

Tretinoin Gel, USP 0.025%

NDC 0781-7061-19

Tretinoin Gel, USP

0.025%

[redacted]

Dist. By Geneva pharmaceuticals, inc. Broomfield CO 80020

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For External Use Only. Not For Ophthalmic Use.

Usual Dosage: See package insert.

Store below 30°C (86°F).

Important: Do not use if seal has been punctured or is not visible.

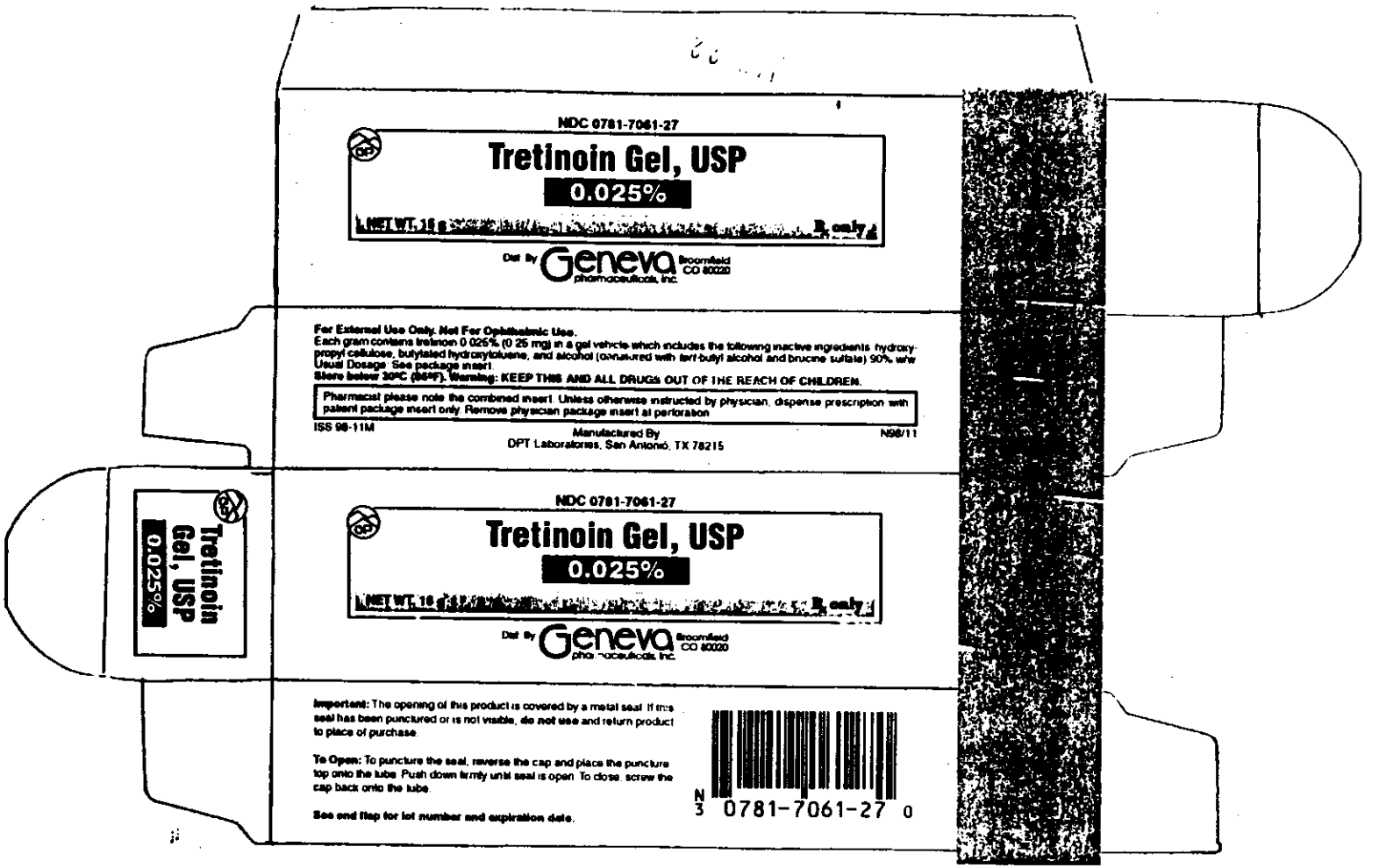
To Open: Use cap to puncture seal.

Warning: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

See crimp end for lot number and expiration date.

ISS 98-11M N98/11

Manufactured By
DPT Laboratories, San Antonio, TX 78215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See end flap for lot number and expiration date.
N 3 0781-7061-27 0
Tretinoin Gel, USP 0.025%

NDC 0781-7061-27

Tretinoin Gel, USP

0.025%

[redacted]

Dist. By Geneva pharmaceuticals, inc. Broomfield CO 80020

Each gram contains tretinoin 0.025% (0.25 mg) in a gel vehicle which includes the following inactive ingredients: hydroxypropyl cellulose, butylated hydroxytoluene, and alcohol (denatured with tert-butyl alcohol and brucine sulfate) 90% w/w.
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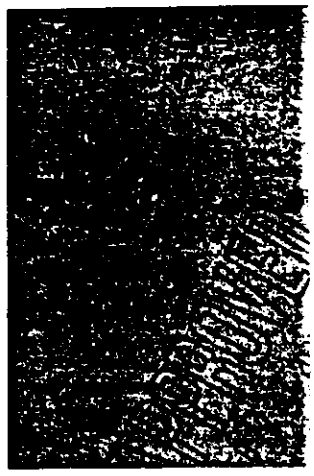
ISS 98-11M N98/11

Manufactured By
DPT Laboratories, San Antonio, TX 78215



CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-529

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-529

3. NAME AND ADDRESS OF APPLICANT

Spear Pharmaceuticals, Inc.
13100 Ponderosa Way
Fort Myers, FL 33907

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge that US Patent 3,729,568 and US Patent 4,247,547 have been expired and no longer entitled to market exclusivity.

5. SUPPLEMENT(s)

Original 12/2/98

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Tretinoin

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/20/99
Amendment 6/16/99
Amendment 12/8/99
Amendment 12/10/99

10. PHARMACOLOGICAL CATEGORY

Treatment of Acne Vulgaris

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

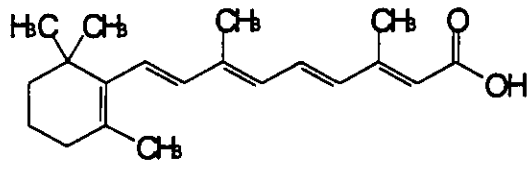
Topical Gel

14. POTENCY

0.025% w/w

15. CHEMICAL NAME AND STRUCTURE

Generic name: Tretinoin
Chemical name: Retinoic acid
Chemical formula: $C_{20}H_{28}O_2$
Molecular weight: 300.44
CAS number: 302-79-4
Chemical structure:



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 12/28/99

Supervisor: Paul Schwartz, Ph.D. 1/4/00

cc:

Endo

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

1/4/00

Chemistry Review #2

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-529

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-529 APPLICANT: Spear Pharmaceuticals

DRUG PRODUCT: Tretinoin Gel, 0.025%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-529

CORRESPONDENCE

SPEAR PHARMACEUTICALS

FACSIMILE AMENDMENT

December 10, 1999

NDA ORIG AMENDMENT
N/FA

Dr. Paul Schwartz
cc: Joseph Buccine
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: (301) 594-0180

Reference: ANDA 75-529
Tretinoin Gel, USP 0.025%

Dear Dr. Schwartz:

In reference to our ANDA 75-529 for Tretinoin Gel USP, 0.025% and our conversation of 12/10/99 regarding updated long-term stability data for related substances, microbiological testing specifications, and expiry extension we are amending our application as follows:

Based upon current available long-term stability data out to 24 months for our 0.025% gel we must revise our tentative specification for *Single* and *Total Related Substances,* (SRS and TRS, respectively) in the finished product. Our latest stability data indicate that this specification should be not more than .
This is amended from our previous amended tentative specifications for SRS and TRS in the finished product of

Updated stability data for ***chemistry*** supporting this amendment are presented in **Attachment 1**. Furthermore, examination of the additional data that follows reveals that our product closely resembles that of the innovator in this respect.

As per our discussions of 11/12/99 and 12/10/99 and following your suggestion, we assayed our product in a side-by-side manner to the corresponding Retin-A® gels that were also aged. **Attachment 2** contains data and representative comparative chromatograms from Spear Gels and Retin-A® Gel. You will find that our chromatographic profiles or stability are essentially the same as those of the innovator.

C:\WINDOWS\Desktop\Business\Clients\Spr\Amendments\Amendment-12-10-99 -75-529-Related Substances.doc

13100 PONDEROSA WAY ■ FORT MYERS, FLORIDA 33907 ■ 941-936-5098 ■ FAX 941-936-5176

testing variability, our product is essentially the same as the innovator's.

We are also submitting updated stability data for ***microbiological*** testing of our product as well as clarifying our specifications for this testing. **Attachment 3** contains our currently available micro data (to 18 months) and our amended (clarified) specifications (replaces original ANDA page 804). Note we have also clarified the **USP Minimum Fill** test in our revised specification.

Finally, we are also submitting a replacement page for original ANDA page 1034 as **Attachment 4**.

This amendment contains a total of 11 pages.

Please accept this latest information to our file.

If you have any questions please feel free to contact us at either of the numbers below.

Thank You,

for Kim L. Spear 12/10/99
Kim L. Spear, MD Date
13100 Ponderosa Way
Fort Myers, FL 33907
Tel. (941) 936-5098 or (941) 936- 4665
Fax: (941) 433-7546

12/10/99
Robert V. Sarrio Date
6329 Whispering Lane
Titusville, FL 32780
Tel. (321) 267-2820
Fax (321) 267-7968

SPEAR PHARMACEUTICALS

FACSIMILE AMENDMENT

December 8, 1999

ORIG AMENDMENT
NFA

Dr. Paul Schwartz
cc: Joseph Buccine
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: (301) 594-0180

Reference: ANDA 75-529
Tretinoin Gel, USP 0.025%

Dear Dr. Schwartz:

In reference to our ANDA 75-529 for Tretinoin Gel USP, 0.025% and our conversations of 11/12/99 regarding updated long-term stability data for related substances, we would like to amend our application as follows:

Based upon current available long-term stability data out to 24 months for our 0.025% and 0.01% gels we must revise our tentative specification for *Single* and *Total Related Substances,* (SRS and TRS, respectively*)* in the finished product. Our latest stability data indicate that this specification should be not more than
% TRS. This is amended from our previous amended tentative specifications for SRS and TRS in the finished product of respectively. The 24-month stability time point for our el products exhibited related substances. Since we also detected these substances at our 9 and 18-month stations, we now have enough data to predict a reasonable trend out to 48 months.

We chose to predict the amount of TRS to the 48 month station since our assay data on stability basically do not show any significant loss of potency from time zero to 24 months. Also, this control is easier to evaluate during normal routine production if we set SRS limits equal to TRS since the individual peaks are very near to each other and minute shifts in relative retention times does not allow us to easily distinguish the individuals from station to station.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 09 1999
OGD

C:\WINDOWS\Desktop\Business\Clients\Spr\Amendments\Amendment-12-06-99 -75-529 Related Substances.doc

13100 PONDEROSA WAY ■ FORT MYERS, FLORIDA 33907 ■ 941-936-5098 ■ FAX 941-936-5176

FACSIMILE AMENDMENT

Updated stability data supporting this amendment as well as calculations of prediction are presented in **Attachment 1**. As a result of evaluating ALL our data we must conclude that SRS and TRS specifications should be set at
respectively, as stated above. Furthermore, examination of the additional data that follows reveals that our product closely resembles that of the innovator in this respect.

Comparative Stability Assays: Spear Tretinoin Gels USP and Retin-A® Gels 0.025% and 0.01%

As per our discussions of 11/12/99 and following your suggestion, we assayed our products in a side-by-side manner to the corresponding Retin-A® gels that were also aged. **Attachment 2** contains data and representative comparative chromatograms from Spear Gels and Retin-A® Gels for comparison. You will find that our chromatographic profiles on stability are essentially the same as those of the innovator.

We also reference ANDA 75-589, which is for our 0.01% gel. Our two product strengths (i.e., 0.025 and 0.01%) are intended to have the same specifications except for the potency values.

This amendment contains a total of 12 pages.

Please accept this latest information to our file.

If you have any questions please feel free to contact us at either of the numbers below.

Thank You,

for Kim Spear 12/8/99

Kim L. Spear, MD Date
13100 Ponderosa Way
Fort Myers, FL 33907
Tel. (941) 936-5098 or (941) 936- 4665
Fax: (941) 433-7546

12/8/99

Robert A. Sarrio Date
6329 Whispering Lane
Titusville, FL 32780
Tel. (321) 267-2820
Fax (321) 267-7968

SPEAR PHARMACEUTICALS

FACSIMILE AMENDMENT

June 16, 1999

NEW CORRESP
NC to
Fax

Mr. Joseph Buccine
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: (301) 827-4337

Reference: ANDA 75-529
Tretinoin Gel, USP 0.025%

Dear Mr. Buccine:

This correspondence represents our response to the agency's list of facsimile deficiencies regarding the above referenced ANDA issued on May 24, 1999. We are submitting this correspondence as a FACSIMILE AMENDMENT to our files as instructed in the deficiency letter.

CHEMISTRY REVIEW COMMENTS AND RESPONSES FOR ANDA 75-529

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

6/16/99

FACSIMILE AMENDMENT
ANDA 75-529

Please accept this latest information to our file.

If you have any questions please contact us at either of the numbers below.

Thank You,

for Kim Spear 6/16/99

Kim L. Spear, MD Date
13100 Ponderosa Way
Fort Myers, FL 33907
Tel. (941) 936-5098 or (941) 936- 4665
Fax: (941) 936-3591

6/16/99

Robert V. Sarrio Date
3643 NW 111th Terrace
Sunrise, FL 33351
Tel./Fax (954) 572-6533
321-267-2820

SPEAR PHARMACEUTICALS

CONTROLLED CORRESPONDENCE

February 20, 1999

Mr. Joseph Buccine
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: (301) 594-0180

NDA ORIG AMENDMENT

N/A

Reference: ANDA 75-529
Tretinoin Gel, USP 0.025%

Dear Mr. Buccine:

In reference to our recently submitted ANDA 75-529 for tretinoin gel USP, 0.025% we would like to amend this application as follows:

Based upon current available stability data for our 0.025% and 0.01% gel (the 0.01% gel has been submitted), we must revise our tentative specification for *Total Related Substances* in the finished product. Our data indicate that this specification should be not more than *Total Related Substances*. This is amended from our initial tentative specification for *Total Related Substances* in the finished product of This single revision from applies to the following pages of the original ANDA application 75-529: pp. 611, 760, 804, 865, 914, 972, 984, 1004, 1014, 1025, 1032, 1036, 1048, 1068, 1078, 1088, and 1105.

Amended pages follow as Attachment 1.

We are also removing all references to performing accelerated stability studies on the first production batch of this product. This statement applies to pages 1031 and 1033.

Amended pages follow as Attachment 2.

RECEIVED

FEB 25 1999

GENERIC DRUGS

13100 PONDEROSA WAY ■ FORT MYERS, FLORIDA 33907 ■ 941-936-5098 ■ FAX 941-936-5176

Please accept this latest information to our file.

If you have any questions please feel free to contact us at either of the numbers below.

Thank You,

for Kim Spear 2/20/99

Kim L. Spear, MD Date
13100 Ponderosa Way
Fort Myers, FL 33907
Tel. (941) 936-5098 or (941) 936- 4665
Fax: (941) 936-3591

2/20/99

Robert V. Sarrio Date
3643 NW 111th Terrace
Sunrise, FL 33351
Tel./Fax (954) 572-6533