CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75264

CORRESPONDENCE

SPEAR PHARMACEUTICALS

April 29, 1998

Director, Office of Generic Drugs
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

ORIG AMENDMENT

MAJOR AMENDMENT

Reference: **ANDA 75-264**
Tretinoin Cream, USP 0.025%

Dear Mr. Sporn:

We are hereby submitting this major amendment to our pending ANDA 75-264 for Tretinoin Cream, USP 0.025%. This amendment is prompted due to our receipt of a deficiency letter on April 13, 1998 from FDA's initial review of our pending ANDAs 75-264 (0.025%) and 75-265 (0.05%).

Please also reference our submitted major amendment to a deficiency letter received by us on March 12, 1998 with respect to ANDA 75-213 (0.1%).

We have addressed all issues raised in these deficiency letters, provided requested additional data, and have modified our specifications and stability protocols as requested. Our specifications and stability protocols have been revised to provide consistent evaluation for all strengths of this product subsequent to FDA approvals.

We have provided archival and review copies of each amendment to your office and a certified Field Copy of each amendment has been sent to our District Office in Orlando.

Please address communications related to this ANDA AMENDMENT by contacting:

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

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1998
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Kim L. Spear, MD
President, Spear Pharmaceuticals, Inc.

4/29/98
Date

002

SPEAR PHARMACEUTICALS

December 2, 1997

Director, Office of Generic Drugs
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

Original ANDA Submission
for Tretinoin Cream, USP 0.025% w/w
Spear Pharmaceuticals
Ref: ANDA 75-213 (0.1% w/w)

Dear Mr. Sporn:

Pursuant to the provisions of Section 505 (j)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 CFR Part 314, Subpart C-Abbreviated Applications, Spear Pharmaceuticals herein submits an Abbreviated New Drug Application for a generic drug product, Tretinoin Cream, USP 0.025%.

The purpose of this submission is to obtain FDA approval for Spear Pharmaceuticals, Inc., to manufacture the topical acne product Tretinoin Cream, USP 0.025% that will be marketed in the USA. This product is the generic equivalent of Retin-A® Cream 0.025%, the reference listed drug which is manufactured and marketed by Ortho Pharmaceutical Corporation (which was originally the R.W. Johnson Company and is a subsidiary of the Johnson and Johnson Company) under the approved application NDA 19-049.

This application also contains data from a bioequivalence study in humans showing statistically validated bioequivalence between Spear Pharmaceuticals' 0.025% Tretinoin and the reference listed drug Retin-A® Cream 0.025%.

Our contractor ?
the Drug Product.

We are simultaneously submitting an original application for the 0.05% strength and have recently submitted an original application for the 0.1% strength (Ref: ANDA 75-213). The 0.1% strength application also included a complete *in vivo* bioequivalence study of that formulation and was accepted to file on October 1, 1997. The three product strengths are all manufactured at the acility.

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U.S. Patent 3,906,108 was granted September 16, 1975, to Johnson and Johnson (assignee), of which Ortho Pharmaceutical is a subsidiary. The subject patent specifically addresses cream formulations of Tretinoin that were the subject new drug products previously approved by the FDA. The subject U.S. Patent 3,906,108 is no longer protected under the provisions of the Drug Price Competition and Patent Term Restoration Act.

Spear Pharmaceuticals' generic drug, Tretinoin cream USP 0.025%, is essentially identical to Ortho Pharmaceutical's Retin-A® (Tretinoin, USP) Cream 0.025% concerning the active ingredient and inactive ingredients both qualitatively and quantitatively. The generic product labels and labeling are identical to the labels and labeling currently approved for the marketing of Retin-A® (Tretinoin, USP) Cream 0.025% except for the NDC number, trade name, distributor (*Dist. by Geneva Pharmaceuticals, Inc. Broomfield CO, 80020*), and other labeling information specific to the pioneer drug which is detailed in Section V of this application in a side-by-side analysis.

This ANDA consists of two volumes, each containing the required Table of Contents. Besides the Archival copy and the Review Copy (Two Parts: (1) Review-Pharmacokinetic copy, and (2) Review-Chemistry copy), an additional copy is provided as the "field copy" which contains all the technical sections of the archival copy and has been sent to the Orlando District Office. All required copies contain four (4) sets of draft labeling. The Archival copy bears original signatures on specific required statements and Form FDA 356h. Please note that according to our discussion with Dr. Ramakant Mhatre on September 4, 1997, we are not including case report forms. These are on file and available upon request.

Portions of this submission are considered confidential. Specifically, these are analytical methods validation, processing instructions, and facilities description.

Please address communications related to this ANDA by contacting:

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

Kim L. Spear, MD
President,
Spear Pharmaceuticals, Inc.

12/2/97
Date

SPEAR PHARMACEUTICALS

CONTROLLED CORRESPONDENCE

November 13, 1998

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: ANDAs 75-213, 75-264, and 75-265
Tretinoin Cream, USP 0.1%, 0.025%, and 0.05%

Dear Mr. Buccine:

As per our telecom of 11/2/98, Spear Pharmaceuticals, Inc., hereby withdrawals the contract laboratory, J, (section 10 of our original submissions) from our above referenced applications. This laboratory has never been used to test any of our clinical batches associated with these ANDAs for any components, release testing, or stability testing in the past and is not used for any testing presently. The only use of as applied to our current applications referenced above, was during our research and development stage to test the innovator product, Retin-A®, for excipients and active content. We used this information, in part, along with similar results obtained from other laboratories to determine the quantitative amounts of o be used in formulating our generic equivalent products.

In our telecom of 11/3/98 you asked that we send you, the results, sampling plan, and specifications for in-process bulk batch uniformity testing for clinical batches. In

NOV 16 1998

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addition, you requested that we provide a new specification for in-process bulk batch uniformity testing to be performed on future commercial batches. Based on data we obtain, we may then request a reduction in testing for batch uniformity in the future after we have gained more experience with the product and the process. These items are attached to this submission.

ATTACHMENTS

1) Clinical Batch Uniformity Results for Assay for Lot 613910-ANDA 75-213 (0.1%).

2) Clinical Batch Sampling Plan for Uniformity Testing of Lot 613910-ANDA 75-213 (0.1%).

3) Revised Manufacturing Instructions (Addendum) to include in-process batch uniformity testing on bulk for future commercial batches of 0.1%.

4) Clinical Batch Uniformity Results for Assay for Lot 613910-ANDA 75-264 (0.025%).

5) Clinical Batch Sampling Plan for Uniformity Testing of Lot 613910-ANDA 75-264 (0.025%).

6) Revised Manufacturing Instructions (Addendum) to include in-process batch uniformity testing on bulk for future commercial batches of 0.025%.

7) Clinical Batch Uniformity Results for Assay for Lot 613910-ANDA 75-265 (0.05%).

8) Clinical Batch Sampling Plan for Uniformity Testing of Lot 613910-ANDA 75-265 (0.05%).

9) Revised Manufacturing Instructions (Addendum) to include in-process batch uniformity testing on bulk for future commercial batches of 0.05%.

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

Thank You,

for Kim Spear 11/13/98
Kim L. Spear, MD Date
13100 Ponderosa Way
Fort Myers, FL 33907
Tel. (941) 936-5098 or (941) 936- 4665
Fax: (941) 936-3591

11/13/98
Robert V. Sarrio Date
3643 NW 111th Terrace
Sunrise, FL 33351
Tel./Fax (954) 572-6533

See attached
in 75213 A2

SPEAR PHARMACEUTICALS

FACSIMILE AMENDMENT

October 14, 1998

FA

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: ANDAs 75-264 and 75-265
Tretinoin Cream, USP 0.025 and 0.05%

Dear Mr. Buccine:

This correspondence represents our response to the agency's list of facsimile deficiencies regarding the above referenced ANDAs issued on October 9, 1998 that we received October 12, 1998. We are submitting this correspondence as a FACSIMILE AMENDMENT to our files as instructed in the deficiency letter.

CHEMISTRY REVIEW COMMENTS AND RESPONSES FOR ANDAs 75-264 AND ANDA 75-265

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

10/14/98

B. (1.)

" Your clinical bioequivalency study and waiver request are under review. Comments, if any, will be forthcoming."

We understand and acknowledge this statement.

B. (2.)

" Firms referenced in your application should be in compliance with cGMP at the time of approval."

We understand and acknowledge this statement.

FACSIMILE AMENDMENT
ANDAs 75-264 AND 75-265

LABELING REVIEW COMMENTS AND RESPONSES FOR ANDA 75-264 ONLY.

The deficiencies noted state that our 0.025% strength expression is difficult to read on the cartons and the tubes.

As per a telecom between Robert V. Sarrio, of Spear Pharmaceuticals, and John Grace, of FDA, on 10/13/1998, we are submitting exhibits of the actual finished printed tubes and cartons for each size of this product strength via FedEx (Exhibit E). Upon your review of this material we believe you will find that the expression of the strength in this finished printing is darker and easier to read than the proofs previously submitted. We believe this answers your concerns that the expression of strength was difficult to read and the final printing demonstrates this.

ATTACHMENTS:

Exhibit A - Comparative Test Results between Retin-A® and Spear's Generic Equivalent from ANDA 75-264.

Exhibit B - Comparative Test Results between Retin-A® and Spear's Generic Equivalent from ANDA 75-265.

Exhibit C - Routine In-Process Batch Uniformity Tests, Procedures, and Specifications from ANDA 75-264.

Exhibit D - Routine In-Process Batch Uniformity Tests, Procedures, and Specifications from ANDA 75-265.

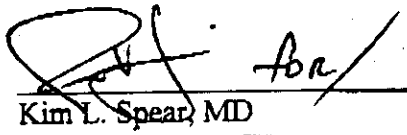
Exhibit E - Finished Printed Labeling for ANDA 75-264 (FedEx only). Forwarded to Joe Buccine via FedEx (with fax hardcopy) to forward to John Grace for his review as per discussion of 10/13/98 with Bob Sarrio. (FedEx – Only)

FACSIMILE AMENDMENT
ANDAs 75-264 AND 75-265

Please accept this latest information to our files.

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

Thank You,



10/14/98

Kim L. Spear, MD Date
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Fort Myers, FL 33907
Tel. (941) 936-5098 or (941) 936- 4665
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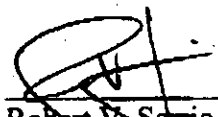

10/14/98

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

Exhibit A

Original ANDA for Spear Pharmaceuticals
Tretinoin Cream USP 0.025%

Comparative Physiochemical Properties Of Ortho Pharmaceuticals' Retin-A® (Tretinoin) Cream 0.025% (Reference Listed Drug) with Spear Pharmaceuticals' Tretinoin Cream USP 0.025% (Generic Equivalent)

PHYSICOCHEMICAL PROPERTY	REFERENCE LISTED DRUG Retin-A (Tretinoin) Cream 0.025% Lot 27B456	GENERIC EQUIVALENT Tretinoin Cream USP 0.025% Lot 702700[1]
Description	Normal	Normal
pH (10% solution)		
Specific gravity @ 25°C		
Apparent Viscosity (cps)[2]		
Tretinoin Content (% w/w)		
Isotretinoin Content (% w/w)		
Other Related Substances (% Area)		
Spreadability (mm)		

1. These results are based on the average taken from the beginning, middle, and end of the packaging run for 45g tubes.
2. The acceptable range for finished packaged product viscosity is

The comparative physicochemical data presented above were generated by Section X, *Outside Firms Including Contract Laboratories* for details related to registration numbers and address). The Spear product compares favorably to the Ortho Pharmaceutical's product. This comparative analysis also demonstrates that the reference listed drug, Retin-A®, appears to contain an approximate overage of as does the Spear product formulation. Spear's overage justification is based upon these comparative results as well as historical stability data on the Spear formulation for the 0.05% strength (ANDA withdrawn). Raw data are available upon request.

It should be noted that some of these physicochemical properties are not addressed in the official USP 23 Monograph for this product. The measurement of apparent viscosity is known to vary significantly with respect to other test methodologies

Exhibit B

Original ANDA for Spear Pharmaceuticals
Tretinoin Cream USP 0.05%

Comparative Physiochemical Properties Of Ortho Pharmaceutical's Retin-A® (Tretinoin) Cream 0.05% (Reference Listed Drug) with Spear Pharmaceuticals' Tretinoin Cream USP 0.05% (Generic Equivalent)

PHYSICOCHEMICAL PROPERTY	REFERENCE LISTED DRUG Retin-A (Tretinoin) Cream 0.05% Lot 26N661	GENERIC EQUIVALENT Tretinoin Cream USP 0.05% Lot 702710[1]
Description	Normal	Normal
pH (10% solution)		
Specific gravity @ 25°C		
Apparent Viscosity (cps)[2]		
Tretinoin Content (% w/w)		
Isotretinoin Content (% w/w)		
Other Related Substances (% Area)		
Spreadability (mm)		

1. These results are based on the average taken from the beginning, middle, and end of the packaging run for 45g tubes.
2. The acceptable range for finished packaged product viscosity is These test results are essentially identical within the limits of experimental error.

The comparative physicochemical data presented above were generated by Novartis Pharma see Section X, *Outside Firms Including Contract Laboratories* for details related to registration numbers and address). The Spear product compares favorably to the Ortho Pharmaceutical's product. This comparative analysis also demonstrates that the reference listed drug, Retin-A®, appears to contain an approximate overage of as does the Spear product formulation. Spear's overage justification is based upon these comparative results as well as historical stability data on the Spear formulation for the 0.05% strength (ANDA which has been withdrawn). Raw data are available upon request.

It should be noted that some of these physicochemical properties are not addressed in the official USP 23 Monograph for this product. The measurement of apparent viscosity is known to vary significantly with respect to other test methodologies.

Page(s) 2

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Information and are not

releasable.

Contracts QA release specifications

SPEAR PHARMACEUTICALS

MINOR AMENDMENT

September 28, 1998

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/Ac

Reference: ANDAs 75-213, 75-265, 75-264
Tretinoin Cream, USP 0.1%, 0.05%, 0.025%

Dear Mr. Buccine:

As dicussed, we are submitting this minor amendment to add Consumer Health, located in J ka, as an alternate testing site for our products. We are submitting this request as an amendment because we wish to transfer ongoing stability studies from our contract manufacturer, site prior to obtaining approval of our pending ANDAs listed above.

We would like to add the at this time. The necessary information follows:

Company Name:
Address:

Phone:
Fax:
Contact Name:
Title:
FDA Registration Number:
Last cGMP Inspection: April 20-24, 1998
Kansas City District Office
Steven B. Barber, CSO
Barbara L. Rogolsky, Analyst
This inspection resulted in a satisfactory cGMP compliance status. NAI

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MINOR AMENDMENT

September 28, 1998
Reference: ANDAs 75-213, 75-265, 75-264

Please address communications related to this document by contacting either of the persons listed below:

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

for Kim Spear 9/28/98
Kim L. Spear, MD/Date
President, Spear Pharmaceuticals, Inc.

9/28/98
Robert V. Sarrio/Date
President
RVS Technical International, Inc.

SPEAR PHARMACEUTICALS

CONTROLLED CORRESPONDENCE

September 14, 1998

NDA ORIG AMENDMENT

N/AA

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

Reference: ANDAs 75-213, 75-265, 75-264
Tretinoin Cream, USP 0.1%, 0.05%, 0.025%

Dear Mr. Buccine:

I am forwarding the attached information to be included in our recent major amendments of 5/13/98 to our above referenced applications. Since the time of these submissions, our active pharmaceutical ingredient (API) manufacturer/supplier and our contract manufacturer have forwarded us new information and therefore we need to make the following minor clarifications and modifications.

RESIDUAL SOLVENTS

Please accept this latest information to our files.

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