

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 75213**

**CORRESPONDENCE**

# SPEAR PHARMACEUTICALS

Office of Generic Drugs  
ATTN: 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

NEW CORRESP

November 24, 1997

## CONTROLLED CORRESPONDENCE

**RE: Original ANDA Submission for Tretinoin Cream, USP 0.1% Spear  
Pharmaceuticals ANDA 75-213**

Dear Mr. Buccine:

FDA received our ANDA 75-213, which is currently under review, on October 1, 1997. Please note that we are submitting the attached Master Formulation Card (MFC) from our contract manufacturer in place of the one originally submitted in Section 11 (starting with page 11-6). The MFC that we were initially provided and was originally submitted; erroneously reflected the process for the two lower strengths (i.e., 0.05 and 0.025% w/w). has revised this MFC to reflect the same process used to make our clinical batch for this 0.1% w/w strength. It is this process that Spear Pharmaceuticals, Inc., intends to validate and subsequently use to make the finished marketed product. Please update this filing as necessary.

If you have any questions please do not hesitate to call us at (954) 370-6111.

Sincerely,



Robert V. Sarrio  
Senior Consultant  
for Spear Pharmaceuticals, Inc.

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**NOV 25 1997**

**GENERIC DRUGS**

cc: Kim Spear, MD  
Susan Fromm  
Ron Hartmann RPh (Geneva)





**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 withdraws the contract laboratory, \_\_\_\_\_ (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<sup>®</sup>, 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 \_\_\_\_\_ to 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 process~~

NOV 16 1998

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**CONTROLLED CORRESPONDENCE**  
**ANDAS 75-213, 75-264, AND ANDA 75-265**

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%.

**CONTROLLED CORRESPONDENCE**  
**ANDAS 75-213, 75-264, AND ANDA 75-265**

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

Thank You,

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

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

See attached  
in 75213 A:



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/A/C

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

Dear Mr. Buccine:

As discussed, we are submitting this minor amendment to add
located in , 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,
to the site prior to obtaining approval of our pending ANDAs
listed above.

We would like to add the 1 site 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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GENERIC DRUGS

**MINOR AMENDMENT**

**September 28, 1998**

**Reference: ANDAs 75-213, 75-265, 75-264**

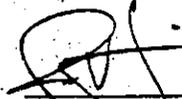
Please address communications related to this document by contacting either of the persons listed below:

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

Robert V. Sarrio  
3643 NW 111<sup>th</sup> 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**

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

N/AA

**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.



**FACSIMILE AMENDMENT**

October 14, 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

NEW CORRESP

NC

**Reference: ANDA 75-213**  
**Tretinoin Cream, USP 0.1%**

Dear Mr. Buccine:

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

CHEMISTRY REVIEW COMMENTS AND RESPONSES FOR ANDA 75-213

Page (s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

10/14/98

**FACSIMILE AMENDMENT  
ANDA 75-213**

We understand and acknowledge this statement.

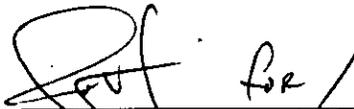
**ATTACHMENTS:**

- Exhibit A - Comparative Test Results between Retin-A<sup>®</sup> and Spear's Generic Equivalent from ANDA 75-213.
- Exhibit B - Routine In-Process Batch Uniformity Tests, Procedures, and Specifications from ANDA 75-213.

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,

 for 10/14/98  
Date  
Kim L. Spear, MD  
13100 Ponderosa Way  
Fort Myers, FL 33907  
Tel. (941) 936-5098 or (941) 936- 4665  
Fax: (941) 936-3591

 10/14/98  
Date  
Robert V. Sarrio  
3643 NW 111<sup>th</sup> Terrace  
Sunrise, FL 33351  
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## CONTROLLED CORRESPONDENCE

August 5, 1998

*This is an amendment*

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:

As suggested, we are submitting this proposal along with a request to add a new testing facility to our applications for your team's critical review and comment regarding our plans to change the site of manufacturing and testing of the above referenced drug products from

As you are aware, our referenced ANDAs for Tretinoin Cream USP products are pending approval. The biobatches for these products were produced at the [redacted]. Each batch was produced using a [redacted] g batch size. We plan to obtain approval of these products at the [redacted] then immediately transfer the manufacturing to our [redacted] plant sometime near the beginning of 1999.

In anticipation of the shut-down at [redacted] we would like to transfer analytical test methods and ongoing stability studies testing to the [redacted] site as soon as possible. Such testing would include the ongoing stability studies for all three biobatches (i.e., one batch for each strength), future stability testing for validation batches made at [redacted], and all future batches made at the [redacted].

C:\WINDOWS\Desktop\Clients\SPR\Site Transfer\Site Change Proposal-SPR v3.doc

**CONTROLLED CORRESPONDENCE**

We would like to add the [redacted] site at this time. The necessary information follows:

Company Name:

Address:

Phone:

Fax:

Contact Name:

Title:

FDA Registration Number:

Last cGMP Inspection: [redacted] satisfactory

It is our intention to manufacture at least three validation batches of each product strength at the [redacted] site in anticipation of FDA granted approvals in the third quarter of 1998. Concomitantly, we would like to scale-up and manufacture the same products at the new [redacted] site. Proceeding in this manner would provide freshly prepared batches from both sites and allow us to perform comparative *in vitro* rate of release, stability, and physico-chemical studies using products of similar age. These data along with comparative process validation results would be used to support a Changes Being Affected (CBE) site change supplement subsequent to approval of our applications.

In the SUPAC-SS Guidance under Section I. PURPOSE OF GUIDANCE, it states that: "Sponsors should contact the appropriate CDER review division to obtain information about tests and application documentation for changes not addressed in this guidance, or for multiple level 2 or 3 changes submitted over a short period."

We wish to proceed as follows with a CBE site change supplement subsequent to approval of our applications and would like your comments prior to our execution of the following plan:

MANUFACTURING SITE (LEVEL 3 CHANGE):

Page (s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

the use of the target LDC name.

#### STABILITY:

We would matrix our stability studies for batches produced at the Lincoln site as follows:

First commercial batch of each strength placed on three month accelerated stability , and first three batches of 0.1% and 0.025% strengths to be placed on long-term stability . The first batch of the 0.05% strength will also be placed on long-term stability.

#### DOCUMENTATION:

All necessary data required by the SUPAC-SS guideline (e.g., release testing data, accelerated stability data, comparative *in vitro* rate of release data, location of new site, updated executed batch records, and specifications) will be submitted in the CBE supplement and the annual reports as required.

We firmly believe that comparative process validation, *in vitro* rate of release studies, physico-chemical, and stability test results between products of similar age manufactured at the proposed and current sites should adequately demonstrate that both sites manufacture equivalent products. We intend to perform such testing to support our contention prior to submitting the planned CBE supplement.

In a telecom between Dr. Kim Spear and Dr. Vinod Shah (co-author of the SUPAC-SS) on 7/29/98, Dr Shah provided us some direction. Specifically, Dr. Shah stated that as long as we have appropriate validations to show that different conditions will produce the same product under the application's physiochemical data ranges and if the *in vitro* dissolution data show sameness then our site change would not present a regulatory problem. Therefore, we hope you will find this proposal reasonable.

### CONTROLLED CORRESPONDENCE

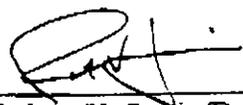
Your commentary is very important to us and much appreciated in this matter. Please do not hesitate to contact us if you have any questions or concerns regarding this matter.

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

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\_\_\_\_\_  
Kim L. Spear, MD/Date  
President, Spear Pharmaceuticals, Inc.  
8/5/98

Robert V. Sarrio  
3643 NW 111<sup>th</sup> Terrace  
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\_\_\_\_\_  
Robert V. Sarrio/Date  
President  
RVS Technical International, Inc.

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**

*UAC*

**MAJOR AMENDMENT**

Reference: **ANDA 75-213**  
Tretinoin Cream, USP 0.1%

Dear Mr. Sporn:

We are hereby submitting this major amendment to our pending ANDA 75-213 for Tretinoin Cream, USP 0.1%. This amendment is prompted due to our receipt of a deficiency letter on March 12, 1998 from FDA's initial review of our pending ANDA 75-213.

Please also reference our submitted major amendments to a deficiency letter received by us on April 13, 1998 with respect to ANDAs 75-264 (0.025%) and 75-265 (0.05%).

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 this amendment to your office and a certified Field Copy of this 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

**RECEIVED**

MAY 15 1998

**GENERIC DRUGS**

*4/29/98*

Date

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

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