

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-489

Product: (S) 177-89-0

CORRESPONDENCE

**Copley
Pharmaceutical
Inc.**

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

July 27, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville, MD 20855-2773

AMENDMENT
N/AC

Telephone Amendment
Hydrocortisone Valerate Cream USP, 0.2%
ANDA No. 74-489

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Hydrocortisone Valerate Cream USP, 0.2%, ANDA No. 74-489, and to the telephone discussion between J. Buccine, Project Manager, and I. Nudelman of Copley Pharmaceutical, Inc., dated July 27, 1998.

During the telephone discussion, the Agency requested Copley to revise the blend uniformity commitment submitted in the major amendment dated October 31, 1997. Specifically, the Agency requested Copley to commit that the suspension of the blend testing is contingent upon approval of a prior approval supplement. In response to the Agency's request, Copley respectfully re-submits the blend uniformity commitment as follows:

A prior approval supplement will be submitted to the FDA for the deletion of blend uniformity testing for Hydrocortisone Valerate Cream USP, 0.2% after sufficient data is generated. The deletion will only be implemented upon approval of the supplemental application.

We believe the information provided in this telephone amendment properly addresses the Agency's request. This telephone amendment is provided to the Agency via facsimile, as well as Federal Express mail service. Please contact I. Nudelman at (781) 575-7695 or Ms. Regina Yeh (Senior Regulatory Affairs Associate) at (781) 575-7828 should you have any question.

Thank you!

Sincerely,


I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.

RECEIVED

JUL 29 1998

GENERIC DRUGS

**Copley
Pharmaceutical
Inc.**

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

July 9, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

Nc

**Telephone Amendment
Hydrocortisone Valerate Cream USP, 0.2%
ANDA No. 74-489**

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Hydrocortisone Valerate Cream USP, 0.2%, ANDA No. 74-489, and to the telephone conferences between J. Buccine, Project Manager, and P. Schwartz, Ph.D., Team Leader of the Office of Generic Drugs and I. Nudelman of Copley Pharmaceutical, Inc., dated June 26, 1998.

We have revised Tables II (a) to (e) submitted in our previous Facsimile Amendment dated March 16, 1998. The revised tables include the requested revisions as per the above referenced telephone conference.

The following revisions have been made to Tables II (a) to (e) according to the Agency's request::

- (1) Added expiration dates for the reference products, Westcort® Cream, 45 g - Lots 81F109 and 81E016.
- (2) Recalculated the values for the degradation product, using the response factor.
- (3) Added additional data where available. No additional Westcort® Cream data on other lots were available.

RECEIVED

JUL 17 1998

GENERIC DRUGS

In addition, corrections were made to the original reported data as follows:

- (1) Table II (a) - eliminated 3 mo./40°C data for lot 81F109. This was a transcription error in the original submitted data. Lot 81F109 was never placed on 40°C accelerated stability storage.
- (2) Tables II (a) to (e) - added clarification to storage conditions to reflect the real time storage relative to stability pull dates and test dates.
- (3) Tables II (a) to (e) - clarified labeling tubes 1 and 2 and sampling locations (top-middle-bottom portions).

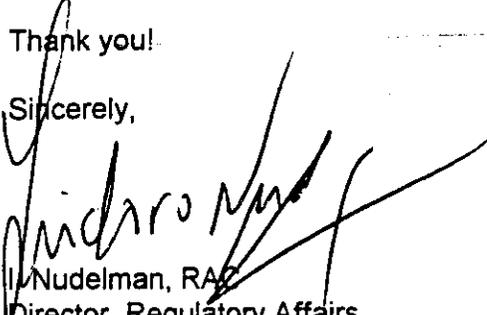
Regarding the recalculation of values for the degradation product, using the response factor, we provide the following comments:

- (1) The standard provided by _____ (manufacturer of drug substance) identified as the _____ was not pure (e.g. two chromatographic peaks were observed. The estimated purity of the principle peak determined to be the _____ was approximately _____. The response factor of 0.79 was derived from the main peak representing the _____ only. Thus, the actual _____ values calculated using the response factor is expected to be lower than the values reported in Tables II (a) to (e). This was the reason that the area percent, not response factor, was used in the original calculations for the _____. The reported data is about 25% higher for _____ when a response factor of 0.79 is used.
- (2) The twenty-four month stability data (real time is 26 months RT) for the ANDA biobatch (lot 679Z02) does not meet the current proposed specifications for _____ using the response factor calculation. The stability studies for the 45 g (STZ/033/93), the 60 g (STZ/034/93) and the 120 g (STZ/035/93) packages of Hydrocortisone Valerate Cream USP, 0.2% exhibit data values for _____ above the proposed specifications listed as follows: [QC87-679 (Dated 4/21/98) provided in Telephone Amendment of April 22, 1998]
 - a) NMT _____ calculated as the mean of the top, middle, and bottom portions.
 - b) No individual value for Hydrocortisone greater than _____
- (3) It is recommended, based on the issue stated in Comment 2 above, that Copley propose an 18 month expiration date (vs. 24 month).
- (4) The analytical test method for Finished Product (QC83-679) must be revised to include the use of a response factor. In the current test method area percent is employed in the calculation. This revision will be made after the approval of this product.

We believe the information provided in this telephone amendment properly addresses the Agency's requests. Please contact I. Nudelman at (781) 575-7695, should you have any question.

Thank you!

Sincerely,



I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.



COPLEY PHARMACEUTICAL, INC.

Telephone Amendment
Hydrocortisone Valerate Cream USP, 0.2%
ANDA No. 74-489

Field Copy Certification

This is to certify that the field copy submitted in accord with 21 CFR § 314.94 (d)(5) is a true copy of the technical section of our telephone amendment for Hydrocortisone Valerate Cream USP, 0.2%, ANDA No. 74-489.

Regina S. Yeh, MS, RAC
Senior Regulatory Affairs Associate
Copley Pharmaceutical, Inc.

7/9/98

Date

N/FA

ORIG AMENDMENT



COPLEY PHARMACEUTICAL, INC.

25 John Road, Canton, MA 02021

Phone: (781) 575-7828

Fax: (781) 575-7362

FAX

R/S

Fax to Number: (301) 827-4337	From: Regina S. Yeh, RAC Senior Regulatory Affairs Associate
Phone Number: (301) 827-5848	Date: 7/9/98
To: Mr. Joe Buccine, Project Manager Office of Generic Drugs Food and Drug Administration 7500 Standish Place Rockville, MD 20855	Pages: 9 including cover

**RE: Hydrocortisone Valerate Cream USP, 0.2%
ANDA No. 74-489
Telephone Amendment**

Dear Mr. Buccine:

Attached please find a facsimile copy of the telephone amendment for the above subject product. This amendment is regarding the revised Hydrocortisone 21-Valerate data requested by the Agency.

We will also submit a hard copy via Federal Express mail service to the Office of Generic Drugs upon your confirmation of the faxed information.

Please contact Mr. Nudelman (Director of Regulatory Affairs) at (781) 575-7695 should you have any question. Thank You!

**Copley
Pharmaceutical
Inc.**

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

July 9, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
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Metro Park North II
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Hydrocortisone Valerate Cream USP, 0.2%
ANDA No. 74-489**

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The following revisions have been made to Tables II (a) to (e) according to the Agency's request:

- (1) Added expiration dates for the reference products, Westcort® Cream, 45 g - Lots 81F109 and 81E016.
- (2) Recalculated the values for the degradation product, using the response factor.
- (3) Added additional data where available. No additional Westcort® Cream data on other lots were available.

Telephone Amendment
Hydrocortisone Valerate Cream USP, 0.2%
ANDA # 74-489

In addition, corrections were made to the original reported data as follows:

- (1) Table II (a) - eliminated 3 mo./40°C data for lot 81F109. This was a transcription error in the original submitted data. Lot 81F109 was never placed on 40°C accelerated stability storage.
- (2) Tables II (a) to (e) - added clarification to storage conditions to reflect the real time storage relative to stability pull dates and test dates.
- (3) Tables II (a) to (e) - clarified labeling tubes 1 and 2 and sampling locations (top-middle-bottom portions).

Regarding the recalculation of values for the degradation product, using the response factor, we provide the following comments:

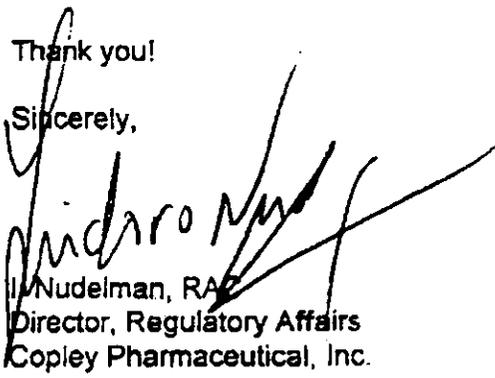
- (1) The standard provided by _____ (manufacturer of drug substance) identified as the _____ was not pure (e.g. two chromatographic peaks were observed). The estimated purity of the principle peak determined to be the _____ was approximately _____. The response factor of 0.79 was derived from the main peak representing the _____ only. Thus, the actual _____ values calculated using the response factor is expected to be lower than the values reported in Tables II (a) to (e). This was the reason that the area percent, not response factor, was used in the original calculations for the _____. The reported data is about 25% higher for _____ when a response factor of 0.79 is used.
- (2) The twenty-four month stability data (real time is 26 months RT) for the ANDA biobatch (lot 679Z02) does not meet the current proposed specifications for _____ using the response factor calculation. The stability studies for the 45 g (STZ/033/93), the 60 g (STZ/034/93) and the 120 g (STZ/035/93) packages of Hydrocortisone Valerate Cream USP, 0.2% exhibit data values for _____ above the proposed specifications listed as follows: [QC87-679 (Dated 4/21/98) provided in Telephone Amendment of April 22, 1998]
 - a) NMT _____ (calculated as the mean of the top, middle, and bottom portions.
 - b) No individual value for Hydrocortisone _____ greater than _____
- (3) It is recommended, based on the issue stated in Comment 2 above, that Copley propose an 18 month expiration date (vs. 24 month).
- (4) The analytical test method for Finished Product (QC83-679) must be revised to include the use of a response factor. In the current test method area percent is employed in the calculation. This revision will be made after the approval of this product.

**Telephone Amendment
Hydrocortisone Valerate Cream USP, 0.2%
ANDA # 74-489**

We believe the information provided in this telephone amendment properly addresses the Agency's requests. Please contact I. Nudelman at (781) 575-7895, should you have any question.

Thank you!

Sincerely,

A handwritten signature in black ink, appearing to read 'I. Nudelman', is written over the typed name and title. The signature is fluid and cursive, with a long horizontal stroke extending to the right.

I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.

TABLE II (a) - Revised 7/8/98

**Summary of Related Substance Stability Data - Reference Product
Westcort® Cream, 0.2% (Westwood Squibb™)**

Lot # Westcort® Cream, 0.2%	Storage Condition	%			Total Other Related Substances (%)	
		[Calculated Using Response Factor = 0.79]				
		Tube No.	Mean	Range (Top-Mid-Bot)		
1. 81F109 (45 g) (Exp. Date 12/96)	RT - Control	(1)	1.4		ND	
	(Test Date 10/94)	(2)	1.4		ND	
	3 Mo. (25°-30°C)	(1)	2.2		ND	
	+	(2)	1.6		ND	
	4 Mo. RT*					
	6 Mo. (25°-30°C)	(1)	1.6		ND	
	+	(2)	1.7		ND	
	1 Mo. RT*					
	12 Mo. (25°-30°C)	(1)	2.0		ND	
	+					
2 Mo. RT*						
18 Mo. (25°-30°C)	(1)	7.4		ND		
	(2)	6.3		ND		
	24 Mo. (25°-30°C)	(1)	8.7		ND	
		(2)	9.5		ND	
	+					
	7 Mo. RT*					
	2. 81E016 (45 g) (Exp. Date 2/95)	RT - Control	(1)	1.1		ND
	3 Mo. /40°C	(1)	15.8		0.9	
(2)		14.7		1.0		

Note:

- (1) The response factor of 0.79 was determined from an authentic standard of _____ provided by _____ (active drug manufacturer). The purity of the standard was estimated to be _____.
- (2) Analyses were conducted using two tubes, testing samples obtained from the top, middle, and bottom portions of each tube. Range is the upper and lower values obtained from top, middle, and bottom testing.
- (3) ND = None Detectable.
- (4) Lot 81F109 (45 g) was stored for 12 months at a target temperature of 27°C ± 2°C, 12 months at a target temperature of 25° ± 3°C (SD) and 7 months at environmental room temperature, prior to testing. The test date for this sample was 10/96, approximately 24 months after the initial control testing was conducted.
- (5) Reference Experiment # 701-105.

* Length of time sample was stored in laboratory after pull, prior to date chromatographed.
HYDROCORTISONE TABLES.DOC

TABLE II (b) - Revised 7/8/98

**Summary of Related Substance Stability Data - Hydrocortisone Valerate Cream USP,
0.2% (Copley)**

Lot # Hydrocortisone Valerate Cream USP, 0.2%	Storage Condition	[Calculated Using Response Factor = 0.79]			Total Other Related Substances (%)
		Tube No.	Mean	Range (Top-Mid- Bot)	
1. 679Z02 (15 g) (Stability # STZ/032/93)	0-Time Control	(1)	ND	ND	ND
	3 Mo./40°C	(1)	23.3		0.6
		(2)	21.4		0.5
		(3)	21.8		ND
		(4)	19.5		ND
		(5)	17.3		ND
	6 Mo. (25°-30°C) +	(1)	1.6	0.3	
		(2)	1.9	0.3	
	1 Mo. RT*	(1)	3.5	0.4	
		(2)	2.8	0.3	
	9 Mo. (25°-30°C)	(1)	2.1	ND	
		(2)	2.1	ND	
	12 Mo. (25°-30°C)	(1)	3.0	ND	
(2)		3.8	ND		
18 Mo. (25°-30°C)	(1)	3.4	ND		
	(2)	5.1	ND		
24 Mo. (25°-30°C) +	(1)		ND		
	(2)		ND		
2 Mo. RT*					

Note:

- (1) The response factor of 0.79 was determined from an authentic standard of _____ provided by _____ (active drug manufacturer). The purity of the standard was estimated to be _____.
- (2) Analyses were conducted using two tubes, testing samples from the top, middle, and bottom portions of each tube. Range is the upper and lower values obtained from top, middle, and bottom testing.
- (3) ND = None Detectable.
- (4) Lot 679Z02 (15 g) was stored for 12 months at a target temperature of 27°C ± 2°C, 12 months at a target temperature of 25°C ± 3°C (SD) and 2 months at environmental RT targeted at 23°C. [Sample test date = 5/15/95].
- (5) Reference Experiment #701-105.

* Length of time sample was stored in laboratory after pull, prior to date chromatographed.
HYDROCORTICRMITABLES.DOC

TABLE II (c) - Revised 7/8/98

Summary of Related Substance Stability Data - Hydrocortisone Valerate Cream USP,
 0.2% (Copley)

Lot # Hydrocortisone Valerate Cream USP, 0.2%	Storage Condition	[Calculated Using Response Factor = 0.79]			Total Other Related Substances (%)
		Tube No.	Mean	Range (Top-Mid- Bot)	
1. 679Z02 (45 g) (Stability # STZ/033/93)	0-Time Control	(1)	ND	ND	ND
	3 Mo./40°C	(1)	5.7		0.4
		(2)	4.6		0.4
	6 Mo. (25°-30°C) +	(1)	1.8		0.3
		(2)	1.8		0.3
	1 Mo. RT*	(1)	3.0		0.3
		(2)	2.1		0.3
	12 Mo. (25°-30°C)	(1)	2.3		ND
		(2)	2.6		ND
	18 Mo. (25°-30°C)	(1)	2.9		ND
		(2)	2.6		ND
	24 Mo. (25°-30°C) +	(1)	6.5		ND
(2)		3.2		ND	
2 Mo. RT*					

Note:

- (1) Control zero time testing was performed 4/29/93 approximately 44 days after packaging. Samples were stored at environmental RT prior to testing.
- (2) The response factor of 0.79 was determined from an authentic standard of provided by active drug manufacturer). The purity of the standard was estimated to be
- (3) Analyses were conducted using two tubes, testing samples from the top, middle, and bottom portions of each tube. Range is the upper and lower values obtained from top, middle, and bottom testing.
- (4) ND = None Detectable.
- (5) 679Z02 (45 g) was stored for 12 months at a target temperature of 27°C ± 2°C, 12 months at a target temperature of 25°C ± 3°C (SD), and 2 months at environmental RT targeted at 23°C.
- (6) Reference Experiment # 701-105.

* Length of time sample was stored in laboratory after pull, prior to date chromatographed.
 HYDROCORTISONE STABILITY DATA

TABLE II (d) - Revised 7/8/98

**Summary of Related Substance Stability Data - Hydrocortisone Valerate Cream USP,
 0.2% (Copley)**

Lot # Hydrocortisone Valerate Cream USP, 0.2%	Storage Condition	[Calculated Using Response Factor = 0.79]			Total Other Related Substances (%)
		Tube No.	Mean	Range (Top-Mid- Bot)	
1. 679Z02 (60 g) (Stability # STZ/034/93)	0-Time Control	(1)	ND	ND	ND
	3 Mo./40°C	(1)	17.4		0.7
		(2)	14.7		0.6
		(3)			
	6 Mo. (25°-30°C) +	(1)	1.9		0.2
		(2)	1.9		0.2
	1 Mo. RT*				
	9 Mo. (25°-30°C)	(1)	2.4		0.3
		(2)	2.2		0.4
	12 Mo. (25°-30°C)	(1)	2.1		ND
(2)		2.1		ND	
18 Mo. (25°-30°C)	(1)	2.9		ND	
	(2)	3.1		ND	
24 Mo. (25°-30°C) +	(1)	4.1		ND	
	(2)	3.8		ND	
2 Mo. RT*					

Note: (1) Additional testing was conducted on three tubes for the 3 mo/40°C samples.

<u>Tube</u>	<u>Mean</u>	<u>Range</u>
(3)	18.4	
(4)	17.0	
(5)	17.9	

- (2) The response factor of 0.79 was determined from an authentic standard of (provided by active drug manufacturer). The purity of the standard was estimated to be
- (3) Analyses were conducted using two tubes, testing samples from the top, middle, and bottom portions of each tube. Range is the upper and lower values obtained from top, middle, and bottom testing.
- (4) ND = None Detectable.
- (5) 679Z02 (60 g) was stored for 12 mos. at a target temperature of 27°C ± 2°C, 12 months at a target temperature of 25°C ± 3°C (SD), and 2 months at environmental RT targeted at 23°C.
- (6) Reference Experiment # 701-105.

* Length of time sample was stored in laboratory after pull, prior to date chromatographed.

TABLE II (e) - Revised 7/8/98

**Summary of Related Substance Stability Data - Hydrocortisone Valerate Cream USP,
 0.2% (Copley)**

Lot # Hydrocortisone Valerate Cream USP, 0.2%	Storage Condition	[Calculated Using Response Factor = 0.79]			Total Other Related Substances (%)
		Tube No.	Mean	Range (Top-Mid- Bot)	
1. 679Z02 (120 g) (Stability # STZ/035/93)	0-Time Control	(1)	ND		ND
	3 Mo./40°C	(1)	5.7		0.4
		(2)	5.6		0.4
	6 Mo. (25°-30°C) +	(1)	1.7		0.3
		(2)	1.8		0.4
	1 Mo. RT*				
	9 Mo. (25°-30°C)	(1)	3.4		0.3
		(2)	3.1		0.4
	12 Mo. (25°-30°C)	(1)	2.8		ND
		(2)	2.5		ND
	18 Mo. (25°-30°C)	(1)	3.4		ND
		(2)	3.3		ND
	24 Mo. (25°-30°C) +	(1)	4.7		ND
		(2)	5.8		ND
2 Mo. RT*					

Note:

- (1) The response factor of 0.79 was determined from an authentic standard of provided by active drug manufacturer). The purity of the standard was estimated to be
- (2) Analyses were conducted using two tubes, testing samples from the top, middle, and bottom portions of each tube. Range is the upper and lower values obtained from top, middle, and bottom testing.
- (3) ND = None Detectable.
- (4) 679Z02 (120 g) was stored for 12 months at a target temperature of 27°C ± 2°C, 12 months at a target temperature of 25°C ± 3°C (SD), and 2 months at environmental RT targeted at 23°C.
- (5) Reference Experiment #701-105.

* Length of time sample was stored in laboratory after pull, prior to date chromatographed.

**Copley
Pharmaceutical
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April 22, 1998

Mr. Douglas Sporn
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Dear Mr. Sporn:

Reference is made to our ANDA # 74-489 for Hydrocortisone Valerate Cream USP, 0.2% submitted March 28, 1994 and to the telephone conferences between J. Buccine, C.S.O., N. Nashed, Ph.D., Reviewing Chemist and P. Schwartz, Ph.D., Team Leader of the Office of Generic Drugs and E. Milano and J. Nudelman of Copley Pharmaceutical, Inc., dated April 21, 1998.

Dr. Schwartz requested that Copley modifies the Finished Product Specifications by listing the Total Known and Unknown Related Substances as follows:

and the Stability Specifications as follows:

Total Known and Unknown Related Substances: NMT Total Known and Unknown
Related Substances
(Calculated as the mean of the Top, Middle, and Bottom portions of the samples
tested)

RECEIVED

APR 23 1998

GENERIC DRUGS

page 2

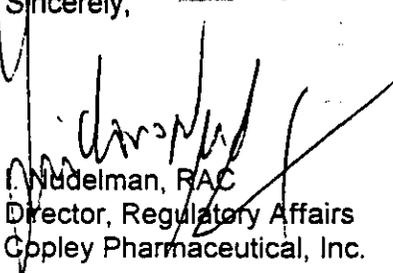
Please refer to the attached documents for additional information with regard to the above limits. Finished Product Specifications (Document No.: QC95-679, dated 4/21/98) and Stability Specifications (Document No.: QC87-679, dated 4/21/98) for Hydrocortisone Valerate Cream USP, 0.2% are provided.

We believe the information provided properly addresses the Agency's requests.

Please feel free to contact I. Nudelman at (781) 575-7695 should you have any questions.

Thank you!

Sincerely,


I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.

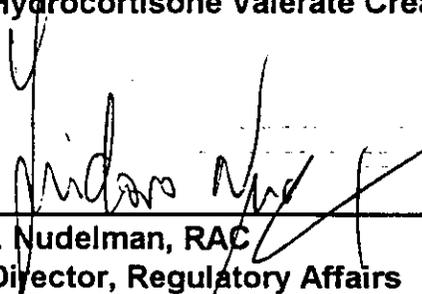


COPLEY PHARMACEUTICAL, INC.

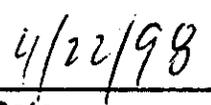
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**I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.**



Date

**Copley
Pharmaceutical
Inc.**

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(617) 821-6111
Mailroom Fax: (617) 821-4068

April 16, 1998

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(A) The following is our understanding of the discussion and of the commitments requested by Dr. Schwartz during the above referenced telephone conference.

Page (s) 2

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

4/15/98

chemistry / mfg

page 4

(B)

FDA's Comment:

Mr. Buccine requested that we eliminate the stability limit of NMT 8.0% for the Individual Assay for Hydrocortisone 21-Valerate included in our submission of March 16, 1998 and propose another specification for Total Impurities (known and unknown).

Copley's Response:

We accept the above request and accordingly we have revised QC87-679 (dated 4/16/98) "Stability Design for Finished Products" and QC95-679 (dated 4/16/98) "Finished Product Specifications" for Hydrocortisone Valerate Cream, 0.2%" (copies attached).

NEW CORRESP

NC

**Copley
Pharmaceutical
Inc.**

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

March 16, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 1507500 Standish Place
Rockville, MD 20855-2773

FACSIMILE AMENDMENT
Response to Facsimile Deficiency of March 2, 1998
Hydrocortisone Valerate Cream USP, 0.2%
ANDA # 74-489

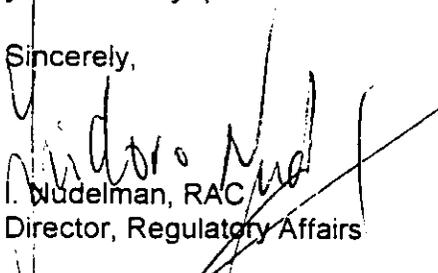
Dear Mr. Sporn:

Reference is made to the above Abbreviated New Drug Application submitted March 28, 1994, to the amendment dated October 31, 1997, and to the Agency's Facsimile Deficiency dated March 2, 1998 (copy attached). Enclosed are Copley's full responses to the Agency's Facsimile deficiency comments.

We have also included in Attachment 1 of this amendment the revised finished product and stability specifications which incorporate the proposed specifications for viscosity and hydrocortisone based on the enclosed responses.

We believe that the data and information enclosed in this submission adequately address the Agency's request. Please contact the undersigned at (781) 575-7695 if you have any question.

Sincerely,


I. Rudelman, RAC
Director, Regulatory Affairs

Enclosures:

Archive Copy (blue folder): 1 copy
CMC Copy (Red folder): 1 copy

RECEIVED

MAR 17 1998

GENERIC DRUGS

ORIG AMENDMENT

N/A



COPLEY PHARMACEUTICAL, INC.

25 John Road, Canton, MA 02021
Phone: (781) 575-7828
Fax: (781) 575-7362

FAX

Regina S. Yeh

Fax to Number: (301) 827-5848	From: Regina S. Yeh Senior Regulatory Affairs Associate
Phone Number: (301) 827-4337	Date: 3/16/98
To: Mr. Joseph Buccine, CSO Office of Generic Drugs Food and Drug Administration 7500 Standish Place Rockville, MD 20855	Pages: 27 including cover

**RE: Facsimile Amendment for Hydrocortisone Valerate Cream USP, 0.2%
ANDA # 74-489**

Dear Mr. Buccine:

Attached please find a copy of the facsimile amendment for the above subject product.

We are also submitting the hard copies (archival and CMC copies) via Federal Express mail service to Office of Generic Drugs according to the Agency's request

Please contact Mr. Nudelman (Director of Regulatory Affairs) at (781) 575-7695 or Regina Yeh at (781) 575-7828 should you have any question regarding the submitted material. Thank You!

**Copley
Pharmaceutical
Inc.**

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

10/31/97

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

FPL
NDA ORIG AMENDMENT

N/AC

**Major Amendment
Response to FDA letters of 6/20/96 and 7/5/96
Hydrocortisone Valerate Cream USP 0.2%
ANDA# 74-489**

Dear Mr. Sporn:

Reference is made to Copley ANDA for Hydrocortisone Valerate Cream 0.2% (ANDA#74-489), and to the Agency's letters of 6/20/96 (CMC) and 7/5/96 (labeling).

This submission includes complete responses to the Agency's letters, including the requested final printed labeling (Attachment 8). In addition to changes related to the Agency's questions, this amendment includes several revisions to the information contained in our original submission. These include:

- i. Revisions to Section VII - Stability of Finished dosage Form (Attachment 3)
 - (a) Product specific stability protocol - addition of tests and specifications requested by the Agency
 - (b) Post approval commitments - Agency requested storage condition
 - (c) Expiration date - 24 months
 - (d) Matrix protocol for long term stability program

- ii. Revision to Section X - Outside Firms Including Contract Laboratories (Attachment 5)
 - (a) deletion of
 - (b) deletion of
 - (c) addition of

RECEIVED

NOV 4 1997

GENERIC DRUGS

- iii. **Revision to Section XI - Proposed Batch Record**
(Attachment 7)
Changes in the quantities of water used in steps 6 and 9 of the process. The total quantity of water used remains the same.

- iv. **Revision to Section XII - In-Process Controls**
(Attachment 6)
 - (a) addition to blend uniformity testing commitment statement
 - (b) clarification of in-process test procedure (QC43-679)

We trust that this information will complete the Agency's needs for additional information and we look forward to an approval of this application in the near future.

Sincerely,



W.E. Brochu, Ph.D.
Director, Regulatory Affairs

Copley Pharmaceutical Inc.
Attention: Bernie Grubstein
Canton Commerce Center
25 John Road
Canton, MA 02021

JUL 5 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated December 15, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocortisone Valerate Cream USP, 0.2%.

Reference is also made to our not approvable letter of June 20, 1996.

The following comments pertain to labeling deficiencies only as discussed in item B of our cited correspondence above.

LABELING DEFICIENCIES

1. GENERAL COMMENT:

Delete the terminal zero throughout your labeling when expressing a strength or a concentration (e.g., 2 mg rather than 2.0 mg).

2. CONTAINER (15 g, 45 g, 60 g, and 120 g)

a. See GENERAL COMMENT

b. Revise the description statement to read,

Each gram contains: 2 mg Hydrocortisone valerate in a hydrophylic base composed of white petrolatum...

3. CARTON (15 g, 45 g, 60 g, and 120 g)

See CONTAINER Comments

4. INSERT

a. DESCRIPTION

Revise paragraph 2 to read,

Each gram of Hydrocortisone Valerate Cream USP,
0.2% contains...

b. PRECAUTIONS

i. Information for Patients

Revise #1 to be one paragraph.

ii. Pregnancy (Category C)

Revise the subheading to read,

Pregnancy: *Teratogenic Effects*, Pregnancy
Category C.

iii. Pediatric Use

Revise paragraph one to read, ...a larger
skin surface area to body weight ratio.

- c. Revise the **Caution** statement to read,
...dispensing without prescription. (delete "a")

Please revise your labels and labeling, and submit in final print with your amendment to our June 20, 1996, letter. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with the differences annotated and explained.

This letter addressed unique issues involving only labeling. Again, we refer you to our letter of June 20, 1996, for the requirements to reopen the file on this application.

Sincerely yours,

/s/

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-489,

Copley Pharmaceutical Inc.
Attention: W.E. Brochu, Ph.D.
25 John Road
Canton Commerce Center
Cantorn, MA 02021

JUN 20 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated March 28, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocortisone Valerate Cream USP, 0.2%.

Reference is also made to your amendments dated October 3, 1994, January 23, October 26, December 15, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies within 10 working days of the date of this letter. Your response must be complete and incorporate ALL deficiencies, including any pending labeling deficiencies.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

- A. The firms-referenced in your application regarding the manufacturing and testing should in compliance with CGMP's at the time of the approval of the application.
- B. Your bio study is under review.
- C. USP is the regulatory method and will prevail in the event of dispute.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MAJOR AMENDMENT and should be plainly marked as such in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Fix) Review under completed

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

Endorsements:

subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

[Signature]
S. Rashmikant W. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

Endorsements:

[Handwritten signature]

ANDA 74-489

Copley Pharmaceutical, Inc.
Attention: W.E. Brochu, Ph.D.
25 John Road
Canton Commerce Center
Canton, MA 02021

DEC 27 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letters dated May 19, 1994, and March 8, 1995, and your amendments dated October 3, 1994, and December 15, 1995.

NAME OF DRUG: Hydrocortisone Valerate Cream USP, 0.2%

DATE OF APPLICATION: March 28, 1994

DATE OF RECEIPT: April 26, 1994

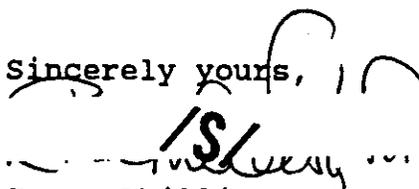
DATE ACCEPTABLE FOR FILING: December 18, 1995

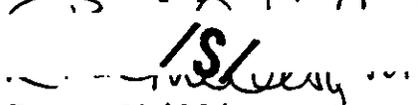
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Anna Marie Weikel
Consumer Safety Officer
(301) 594-1841

Sincerely yours, 


Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

2/27/95

**Copley
Pharmaceutical
Inc.**

25 John Road
Canton Commerce Center
Canton, Massachusetts 02021
(617) 821-6111

Fax:
Canton (617) 821-4068
Boston (617) 268-4394
N.J. (201) 894-1553

October ²⁶ 12, 1995

Charles Ganley, M.D.
Acting Director,
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

NEW CORRESP
N.C.

Re: ANDA# 74-489
Hydrocortisone Valerate Cream 0.2%
Additional External Microbiology Testing Laboratory

Dear Dr. Ganley:

Copley wishes to provide for the addition of an alternate microbiology testing facility to all of its approved and pending product applications. Based on guidance provided by the Agency's Mr. Nuhvich, we are simultaneously submitting supplements to each application (amendments in the case of pending applications) with a cross reference to all affected applications.

We consider these supplements/amendments to be "minor" in nature.

A copy of each of these supplements is also simultaneously being provided to the Boston District Field Office (copy of cover letter attached).

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

RECEIVED
OCT 31 1995
GENERIC DRUGS

ANDA 74-485

Protocol # P94-089

Hydrocortisone Valerate Cream, 0.2%

Reviewer: S. P. Shrivastava

WP # 94089P.094

Close
7-10-94
3-28-94
D.11 B-14-
(Signature)

Copley Pharmaceutical, Inc.

Canton, MA

Submission Date

October 3, 1994

Review of a Protocol

The firm has submitted a protocol for pharmacodynamic study (vasoconstrictor assay) for its product hydrocortisone valerate topical cream, 0.2%. The request was sent to the Division of Topical Drug Products (HFD-540) for consult. The review is attached (Attachment-1).

Deficiency

- 1. The protocol differs in some key respects from the revised guidance, dated June 2, 1995, on Topical Dermatologic Corticosteroids. The firm is advised to follow the guidance closely.

Recommendation

The bioequivalence study protocol submitted by Copley Pharmaceutical on its hydrocortisone valerate cream, 0.2%, comparing it with Westcort^R cream, 0.2% (Westwood/Squibb), has been found unacceptable to the Division of Topical Drug Products, due to the deficiency cited above.

The firm should be informed of the deficiency and recommendation. A copy of the new BE Guidance on Topical Dermatologic Corticosteroids should be sent to the firm for reference.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RNPatnaik

FT INITIALED RNPatnaik

(Signature)

Date 3/21/96

Concur: _____ Date: _____

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Enclosure: Attachment-1

SPS/sps/3-20-96/94089P.094

cc

ANDA 74-489

Copley Pharmaceutical Inc.
Attention: Whe-Yong Lo
25 John Road
Canton Commerce Center
Canton, MA 02021

MAY 9 1995

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated March 28, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocortisone Valerate Cream, USP, 0.2%.

Reference is also made to our "Refuse to File" letter dated May 19, 1994, and your amendment dated October 3, 1994.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

In order for this application to be filed you must provide a vasoconstrictor assay that conforms with the recommendations of the Office of Generic Drugs Interim Guidance dated July 1, 1992, for Topical Corticosteroids: In-vivo Bioequivalence and In-Vitro Release Methods. Therefore, the bioequivalence information submitted with your application is incomplete.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Cecelia Parise
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

Y

3/8/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-489
cc:

Endorsement: