CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75043

CORRESPONDENCE

August 19, 1998

Office of Generic Drugs
Food and Drug Administration
Document Control Room
MPN II
7500 Standish Place, room 150
Rockville, Maryland
USA 20855-2773

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Reference: **ANDA 75-043**
Hydrocortisone Valerate Ointment, 0.2%
Telephone Amendment

Dear Sir:

Reference is made to our ANDA dated 12/23/1996 and our amendments dated 3/26/1997, 4/17/1997, 11/7/1997 and 3/30/1998, 4/16/1998, 6/29/1998 and 7/30/1998 for Hydrocortisone Valerate Ointment, 0.2%.

Reference is also made to the telephone conversation of August 19, 1998 between Dr. A. Rudman of the Agency and Dr. T. Feldman and Lorraine Sachs of Taro Pharmaceuticals Inc. in which the following clarification and information have been requested by the Agency.

Comment 1: Establish in-process specifications for blend uniformity

In-process and bulk specifications for Hydrocortisone Valerate Ointment, 0.2% have been revised to include the test and limits for blend uniformity. Please see **supplementary page 1**.

Comment 2: Establish stability limits for viscosity

Based on the viscosity data collected to date, limits for viscosity have been included in the stability specifications (please see **supplementary pages 2-3**).

Comment 3: Include limits for USP OVI's in the specifications for the

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Comment 4: Since the Packaging Modification Protocol submitted on page 1511 of the original ANDA has been found unacceptable in this case, it should be revised or withdrawn from the file.

We withdraw the Packaging Modification Protocol submitted in the ANDA. The components to be used in packaging of this product will be supplied by ing.

This completes our Telephone Amendment dated August 19, 1998. We hope that all Agency's concerns have been addressed satisfactorily and are looking forward to approval of this ANDA. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532

(914) 345-9001

This Telephone Amendment is being submitted in two copies. In addition a third (Field copy) is enclosed.

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph. D.
V.P., Regulatory Affairs

/Vesna Lucic

cc. Acting Director, FDA, Office of International Programs

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August 21, 1998

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- - FA

TARO PHARMACEUTICALS INC
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Reference: **ANDA 75-043**
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Dear Sir:

Reference is made to our ANDA dated 12/23/1996 and our amendments dated 3/26/1997, 4/17/1997, 11/7/1997 and 3/30/1998, 4/16/1998, 6/29/1998, 7/30/1998 and 8/19/1998 for Hydrocortisone Valerate Ointment, 0.2%.

Reference is also made to the telephone conversation of today between Dr. A. Rudman of the Agency and Lorraine Sachs of Taro Pharmaceuticals Inc. in which the following information have been requested by the Agency:

Comment: Include the limit of for individual unknown degradation products in the stability specifications

Stability specifications for Hydrocortisone Valerate Ointment, 0.2% have been revised to include the limit of or individual unknown degradation products. Please see **supplementary pages 1-2**.

This completes our Telephone Amendment dated August 21, 1998. We hope that all Agency's concerns have been addressed satisfactorily and are looking forward to approval of this ANDA. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
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TARO PHARMACEUTICALS INC.

V. Lucic

for Derek Ganes, Ph. D.
V.P., Regulatory Affairs

/Vesna Lucic

cc. Acting Director, FDA, Office of International Programs

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July 30, 1998

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NDA ORIG AMENDMENT

N/FA

Reference: **ANDA 75-043**
Hydrocortisone Valerate Ointment, 0.2%
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Reference is also made to the telephone conversation between Mr. Buccine of the Agency and Lorraine Sachs of Taro Pharmaceuticals Inc. in which the commitment regarding the blend uniformity specifications has been requested by the Agency.

Taro Pharmaceuticals Inc. hereby commits to establish in-process limits for blend uniformity after approval of the above mentioned ANDA. At that time the established limits will be submitted to the Agency as a Changes Being Effected Supplement.

This completes our Telephone Amendment dated July 30, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our US agent

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
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TARO PHARMACEUTICALS INC.

for Derek Ganes, Ph. D.
V.P., Regulatory Affairs

/Vesna Lucic

cc. Acting Director, FDA, Office of International Programs

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June 29, 1998

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NEW CORRESP.
NDC to FAX

ence: **ANDA 75-043**
Hydrocortisone Valerate Ointment, 0.2%
Facsimile Amendment

Sir:

ence is made to our ANDA dated 12/23/1996 and our amendments dated 3/26/1997, 1997, 11/7/1997 and 3/30/1998 and 4/16/1998 for Hydrocortisone Valerate Ointment, 0.2%.

ence is also made to the Agency's letter dated June 9, 1998 in which the Agency stated that pplication is deficient and, therefore, not approvable under section 505 of the Act for the ving reasons:

DEFICIENCIES

Explain why the original method validation results without the correction factor are not valid.

The original method validation work reported in RD-MV024, dated September 12, 1996 is valid since the only difference between the new (SOP A-106-3) and the original (SOP A-106-2) methods is how the sample calculations are carried out. Therefore, the original validation data (report) was re-evaluated regarding the effect of the proposed volume correction factor on the results reported. Since the volume correction factor is applied only in the sample calculations (it originates from the sample matrix having components -

preparation) only those validation parameters involving sample calculations, i.e. method accuracy and precision, needed to be looked at.

Data originally obtained (pages 3 and 4 of the validation report) were recalculated and are presented in the Analytical Report "Recalculation of Original Validation and Precision Data for HCV Cream and Ointment Using the Volume Correction Factor" (**supplemental pages 1 - 2**). The original and revised formulae used for the calculations are also shown. Please note that the same Report has been submitted to the Agency with our June 15/98 Facsimile Amendment for Hydrocortisone Valerate Cream USP, 0.2%

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2. **Use of a correction factor in an assay method is not appropriate. Develop and provide a validated alternate method without a correction factor, e.g. using an internal standard. The new method should be used for release and stability of all subsequent batches. Please provide the validation data for the new method and compare the results with those of the other (corrected and uncorrected) methods.**

Upon your request we revised our method for the quantitation of hydrocortisone valerate, related impurities and in hydrocortisone valerate cream and ointment (SOP in order to eliminate the use of the volume correction factor and utilize an internal standard method instead. The revised method, is identical to SOP with the exception of the addition of the internal standard, other aspects of the SC including the chromatographic system, conditions, standard and sample preparation/extraction solvents and procedures remain unchanged.

The revised method, SC was fully validated for system and method precision, method accuracy, linearity, limit of quantitation and limit of detection, ruggedness and robustness. Since selectivity was already proven for nd reported in RD-MV024 (dated September 12, 1996), only the aspects affected by the inclusion of the internal standard were evaluated (i.e. it was shown that the internal standard does not interfere with any of the compounds of interest, as well as with any of the unidentified degradants generated in the stability studies).

A copy of the revised method, 4 **(supplemental pages 3 - 7)** and the Validation Report RD-MV060 **(supplemental pages 8 - 36)** are attached.
and the interim version of the Validation Report RD-MV060 (containing data for all validation parameters except for the ruggedness and robustness) have already been submitted to the Agency with our June 15/98 Facsimile Amendment for Hydrocortisone Valerate Cream USP, 0.2% (ANDA

We also acknowledge that the revised method. will be used for both release and stability testing for all future batches of hydrocortisone valerate ointment, 0.2%, manufactured by Taro.

In order to evaluate correlation between data generated using the revised (internal standard, and previous (external standard.
versions of the method and strengthen justification for data calculated using the volume correction factor (as described in a number of experiments were conducted. A copy of the Validation Report RD-MV059 "Validation for the Use & Value of the Volume Correction Factor in & Correlation Between Methods " is presented in **supplemental pages 37 - 44**. Please note that the same Report has been submitted to the Agency with our June 15/98 Facsimile Amendment for Hydrocortisone Valerate Cream USP, 0.2% (ANDA

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3. **If the correction factor method compares favourably with the newly developed alternate method, recalculate all your original validation, stability, and release results using the correction factor.**

The data presented in the Validation Report RD-MV059 (**supplemental pages 37 - 44**) demonstrate excellent correlation between data generated using external (SOP using the volume correction) versus internal ( ) standard methods. Since the data correlate very well we have recalculated all our original validation, stability, and release results using the correction factor.

Data for the original validation are shown with the response to Comment 1 (**supplemental pages 1 - 2**).

Results for release and all stability stations for the exhibit batch up to and including 24 months, recalculated using the volume correction factor are presented as **supplemental pages 45 - 56**.

Taro requests at this time for Agency reconsideration with respect to one of the previous discussed stability limits, specifically the stability limit for the known degradation product, In our Facsimile Amendment date March 30, 1998, Taro agreed to a release limit of In our Telephone Amendment of April 16, 1998, Taro agreed to a stability limit for the same level, . A review of the 24 month stability data shows levels of %. Taro is requesting, based on the 24 month data, that the stability limit for the known degradant, hydrocortisone base, be increased to based on the following considerations:

1. Safety: Hydrocortisone is a known corticosteroid with the lowest potency available under an OTC monograph in topical dosage forms at 1%. The proposed stability limit of equivalent to a formulated level of 0.002% (that is, 1% of the active hydrocortisone valerate present at 0.2%).

2. ICH Considerations: Hydrocortisone would be considered a "qualified degradant" under the ICH Guideline on Impurities in New Drug Products. (Q3A, FR 62, no. 96, p 27454-61). If the "daily dose" for this topical product was as high as 2 g (equivalent of 4 mg of active) then the threshold limit would be 1.0%.

3. Analytical Variability. At both the 18 and 22 month stability times, the levels of hydrocortisone were about The difference between 0.3% and 0.6% is, we believe, a reflection of analytical variability and not a sign of poor stability. For example, analytical variability is allowed (example, RSD of 5% on replicate injections of standard).

4. Level of Hydrocortisone in the Raw Material: The limit established and agreed upon with the Agency for the impurity hydrocortisone in the active raw material is

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5. Comparison with Hydrocortisone Valerate Cream USP, 0.2%. Taro and the Agency have previously agreed to a stability limit of for the known degradant in Hydrocortisone Valerate Cream USP, 0.2%. Considering the strong similarities between the two formulations, we believe that this provides added assurance that the limit of for hydrocortisone in Hydrocortisone Valerate Ointment is appropriate.

We wish to re-state that our request in no way alters our previously agreed to stability limits which are stated below:

	Limits as per April 16/98 Correspondence	June 29/98 Proposed Limits

B. Please note and acknowledge that your new regulatory assay method will need to be validated by an FDA laboratory.

Please note that the revised house method is identical to the method previously evaluated and validated by the FDA Brooklyn District Laboratory, with the exception of the inclusion of an internal standard ( ) in the method, as you requested. The chromatographic system, conditions, standard and sample preparation/extraction procedures did not change.

Based on the above we ask the Agency to consider waiving the re-evaluation/validation of our revised method,

This completes our Facsimile Amendment dated June 29, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our US agent

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532

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This Facsimile Amendment is being submitted in two copies. In addition a third (Field copy) is enclosed.

Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph. D.
V.P., Regulatory Affairs

/Vesna Lucic

cc. Acting Director, FDA, Office of International Programs

TARO PHARMACEUTICALS INC
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April 16, 1998

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TARO PHARMACEUTICALS INC.
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FA

Reference: **ANDA 75-043**
Hydrocortisone Valerate Ointment, 0.2%
Telephone Amendment

Dear Sir:

Reference is made to our ANDA dated 12/23/1996 and our amendments dated 3/26/1997, 4/17/1997, 11/7/1997 and 3/30/1998 for Hydrocortisone Valerate Ointment, 0.2%.

Reference is also made to the telephone conversation of April 16, 1998 between Mr. Buccine, Dr's Schwartz and Nashed of the Agency and Lorraine Sachs and Dr Terry Feldman of Taro Pharmaceuticals in which the Agency requested that the impurity limits for stability be revised as follows:

Degradation Products	Limits proposed by Taro on March 30/1998	Limits suggested by the FDA on April 16/1998

On the basis of the stability data obtained on the product, Taro agrees to adopt the impurity limits suggested by the Agency.

This completes our Telephone Amendment dated April 16, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532

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Derek Ganes, Ph. D.
V.P., Regulatory Affairs

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cc. Acting Director, FDA, Office of International Programs

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ORIG AMENDMENT
N/FA

March 30, 1998

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TARO PHARMACEUTICALS INC.
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Reference: **ANDA 75-043**
Hydrocortisone Valerate Ointment, 0.2%
Facsimile Amendment

Dear Sir:

Please find enclosed Taro Pharmaceuticals' response to a recent deficiency letter from the FDA, dated March 19, 1998, for the above-referenced application.

As required by 21 CFR 314.96(d)(5), Taro is forwarding a copy of the technical data (including 356h form). Taro Pharmaceuticals Inc. certifies that the technical sections contained in this copy are true copies of the same sections submitted to OGD. If there are any questions relating to the information submitted, please contact our US Agent:

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
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Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph. D.
V.P., Regulatory Affairs

Encl. : Field Copy

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March 30, 1998

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Reference: **ANDA 75-043**
Hydrocortisone Valerate Ointment, 0.2%
Facsimile Amendment

Dear Sir:

Reference is made to our ANDA dated 12/23/1996 and our amendments dated 3/26/1997, 4/17/1997 and 11/7/1997 for Hydrocortisone Valerate Ointment, 0.2%.

Reference is also made to the Agency's letter dated March 19, 1998 in which the Agency stated that the application is deficient and, therefore, not approvable under section 505 of the Act for the following reasons:

A. DEFICIENCIES

COMMENT # 1

Please tighten your limits for impurities for the release of the product based on your data.

Response:

Taro has re-examined our previously suggested release limits for impurities in hydrocortisone valerate ointment, 0.2%. We now propose the following:

Impurity Limits		
	Proposed Nov 7/97	Revised March/98

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In addition, based on the Agency's correspondence relative to other ANDA's, please note the following:

> Taro commits to a maximum holding time of s for the bulk product and to generate stability data that would support this timeframe. Taro also commits to generate bulk stability data on the first three validation batches with sampling at 3, 6 and 9 month test stations and to submit such data in a changes-being-effected supplement to the approved ANDA in order to support a holding period of longer than , if the data is supportive.

COMMENT # 2

Your assay method shows that for hydrocortisone and hydrocortisone 21-valerate is achievable. Please explain the reason of having

Response:

The test method for assay and impurities determination has been revised to indicate limits for RSD of or hydrocortisone and hydrocortisone 21-valerate in the system suitability. Revised 06 is submitted as **supplementary pages 1 - 6.**

COMMENT # 3

Please revise your stability limit for degradation products based on your data. In addition, the stability potency limit should be 90.0 - 110.0 %. Your proposed limit of 80 - 110% is unacceptable.

Response:

Since our last response, Taro has completed the 18 month stability station for both the biostudy batch, (L) S139-5590 (three pack sizes) and a second exhibit batch, (L) S139-5591. Updated stability summaries for both batches are included as **supplemental pages 7 - 22.**

In addition, in order to provide data to support a 24 months expiration period with this response, we have elected to conduct testing at a 22 month stability station (because the 24 month station is not due until May/98). The 22 month stability data for two batches of Hydrocortisone Valerate Ointment are submitted in **supplementary pages 23 - 34.**

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With this additional timepoint, we have also updated our graphical trend analysis. Figure 1 shows the formation of hydrocortisone 21- valerate out to 22 months. Figure 2 shows the formation of total impurities out to 22 months. The table 1 summarizes key data.

Figure 1: Taro HCV Ointment - formation of hydrocortisone 21-valerate

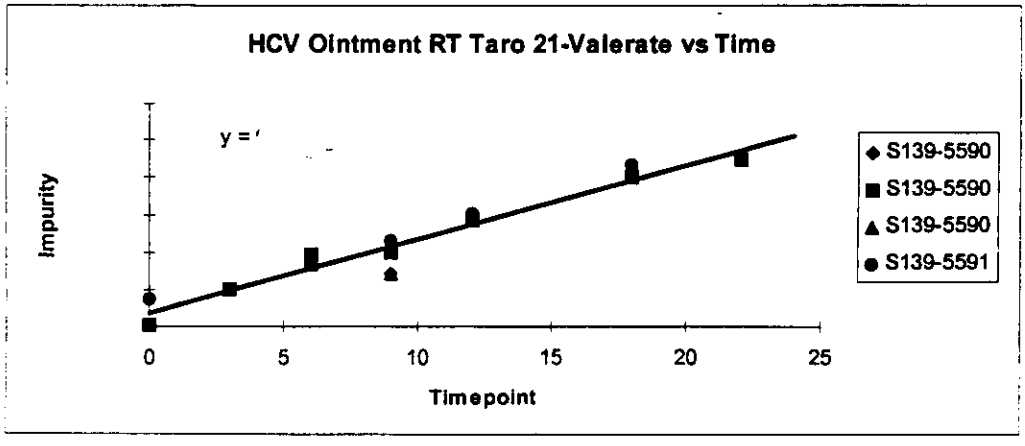

Figure 2: Taro HCV Ointment - formation of total impurities

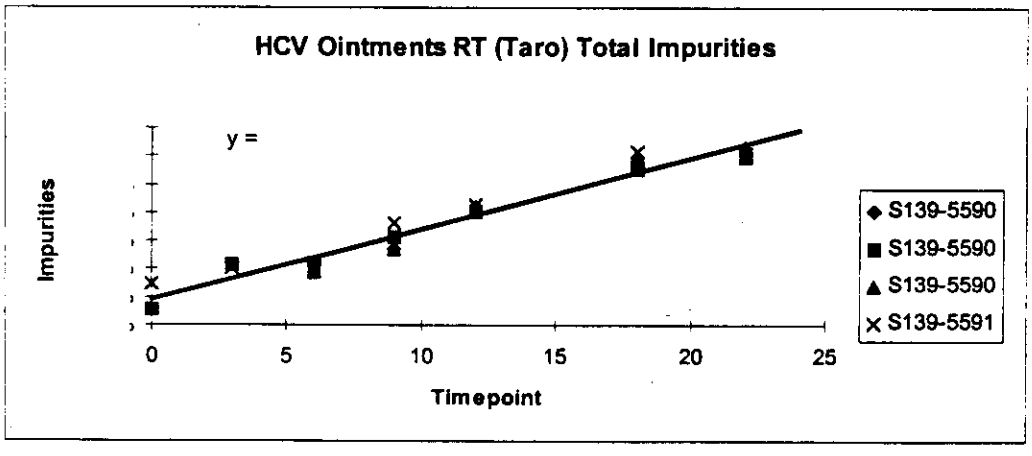

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Table 1: Summary of Key Degradation Parameters

Degradation Products	Taro Limits Proposed Nov 7/97	Taro 18 month data (1)	Taro 22 month data (1)	Taro 24 month projection (2)	Brand Data Near Expiry (3)	Taro Limits Revised Mar/98

(2) Values derived by trend analysis from the data of both Taro batches from initial to 18 months.
(3) Data previously reported to the Agency in Nov/97 amendment, supplemental pages 100-103 and 108-111. Lots tested:

Westcort Ointment (L) 78G022, exp 8/97, tested 3/97 and 9/97
Westcort Ointment (L) 78H19, exp 6/98, tested 9/97 and 3/98

* projected based upon the data including the 18 months time point results

** projected based upon the data including the 22 months time point results

On the basis of the data obtained on Taro's product, and, making reference to the large levels of impurities found in the brand, Westcort Ointment, near expiration, we are proposing to tighten our stability limits for hydrocortisone, hydrocortisone 21-valerate and total degradants as shown in the last column of Table 1.

Stability limits for assay of hydrocortisone valerate have been revised to

COMMENT # 4

Please provide 24 months room temperature stability data.

Response:

The 24 month stability station is not due until May/98. As described in our response to comment 3, in addition to the 18 month data provided in this response, we have also tested all Taro lots at 22 months. Our proposed stability limits are consistent with both the 18 and the 22 month stability data. We suggest that these data fully support a 24 month expiration date for Taro's hydrocortisone valerate ointment, 0.2%

This completes our response to the Agency's deficiency letter dated March 19, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

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V.P., Regulatory Affairs

/Vesna Lucic

cc. Acting Director, FDA, Office of International Programs

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November 7, 1997

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Reference: **ANDA 75-043**
Hydrocortisone Valerate Ointment, 0.2%
Major Amendment

Dear Sir:

Reference is made to our ANDA dated 12/23/1996 and our amendments dated 3/26/1997 and 4/17/1997 for Hydrocortisone Valerate Ointment, 0.2%.

Reference is also made to the Agency's letter dated September 5, 1997 in which the Agency stated that the application is deficient and, therefore, not approvable under section 505 of the Act for the following reasons:

CHEMISTRY COMMENTS

A. DEFICIENCIES

Page(s) 6

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

COMMENT # 1

The firms referenced in your application regarding the manufacturing and testing of the drug product should be in compliance with CGMP's at the time of approval.

Response:

Acknowledged.

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COMMENT # 2

Your bioequivalence study is under review.

Response:

Acknowledged.

COMMENT # 3

The analytical methods for the finished drug product has been submitted for validation by an FDA district laboratory.

Response:

Acknowledged.

LABELING DEFICIENCIES:

COMMENT # 1 GENERAL COMMENTS

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

b. The ointment formulation of this drug product is not the subject of a USP monograph. Revise your labeling to delete "USP" from the established name of your product.

c. You are encouraged to use boxing, contrasting colors, or other means to differentiate the dosage forms of your product.

COMMENT # 2 CONTAINER (15 g, 45 g, 60 g tubes)

See GENERAL COMMENTS.

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905-791-5008

COMMENT # 3 CARTON (15 g, 45 g, 60 g)

See GENERAL COMMENTS.

COMMENT # 4 INSERT

a. GENERAL COMMENT

i. The reference numbers throughout your insert are difficult to read. Revise to enhance their readability.

ii. See GENERAL COMMENTS (1).

b. DESCRIPTION

i. Revise the second sentence of the first paragraph to use "molecular formula" rather than "empirical formula".

ii. Revise the molecular weight to read, 446.59, to be in accord with USP 23.

c. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, and Impairment of Fertility

Revise to delete "and" from the subsection heading.

ii. Pregnancy (Category C)

Revise so that the subsection heading reads, Pregnancy. Teratogenic Effects. Pregnancy Category C.

d. HOW SUPPLIED

You are encouraged to include the NDC codes of your products.

Please revise your labels and labeling, as instructed above, and submit in final print.

TARO PHARMACEUTICALS INC
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Response:

The labels and labeling have been revised as requested by the Agency in the above listed labeling comments. It will be noted that the NDC numbers have not been included in the package insert as requested above. Since the package insert is intended to be used by the manufacturer Taro Pharmaceuticals Inc. and our distributors in the USA, it is Taro's common practice to include the NDC numbers on container and carton labels only.

Final prints of the revised labels are submitted as follows:

- 12 copies of 15 g carton labels (**supplementary pages 150 - 161**)
- 12 copies of 15 g tube labels (**supplementary pages 162 - 173**)
- 12 copies of 45 g carton labels (**supplementary pages 174 - 185**)
- 12 copies of 45 g tube labels (**supplementary pages 186 - 197**)
- 12 copies of 60 g carton labels (**supplementary pages 198 - 209**)
- 12 copies of 60 g tube labels (**supplementary pages 210 - 221**)
- 12 copies of package inserts (plastic pouch with the **supplementary page 222**)

To facilitate review of this major amendment and in accordance with 21 CFR 314.94 (a) (8) (iv) provided on **supplementary pages 131 - 149** is a side-by-side comparison of our proposed labeling with the last submission with all differences annotated and explained.

This completes our response to the Agency's deficiency letter dated September 5, 1997. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532

(914) 345-9001

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This Major Amendment is being submitted in two copies. In addition a third (Field copy) is enclosed.

Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph. D.
V.P., Regulatory Affairs

/Vesna Lucic

cc. Acting Director, FDA, Office of International Programs

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TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

April 17, 1997

Amendment
NJAC

NEW CORRESP

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: ANDA 75-043
Hydrocortisone Valerate Ointment USP, 0.2%
Response to "Refusal to File Letter"

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocortisone Valerate Ointment USP, 0.2% dated December 23, 1996.

Reference is also made to your "Refusal to File" letter dated April 10, 1997, in which you requested the following:

> "The application lacks a comparison of the physical and chemical properties, specifically, pH, viscosity, and partition coefficient, and a discussion of the safety implications for any differences noted, as requested in our letter. Please provide this information."

We acknowledge that we did not provide viscosity, and partition coefficient data in our certificates of analyses which were provided in the last response to refusal to file letter. Please note that pH test was included in our C of As.

Further to our telecon with Ms. Anna Marie H. Weikel on April 16, 1997 and in response to the above referenced refusal to file letter, we are providing a side by side comparison of the physical and chemical properties of our product vs the reference listed drug. During the telecon with Ms. Weikel, we discussed that any differences in these properties will not have any safety implications and therefore do not need to be specifically addressed.

RECEIVED

APR 16 1997

GENERIC DRUGS

TELEPHONE
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1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

Comparison of Physical and Chemical Properties of Taro and RLD, Westcort Ointment

Parameter	Taro	Westcort
pH (1)		
Viscosity (2)		
Macroscopic Appearance		
Microscopic Appearance (3)		
Aqueous phase content (4)		
Oil phase content (5)		

(1) Taro stability limit is Westcort values obtained during stability studies.
(2) viscosity performed using small sample adaptor. Range represents two lots of each of Taro and brand.
(3) identification of crystals performed by visual comparison of
sorbic acid.
(4) Aqueous phase components primarily ol. Taro values are actual; RLD values
measured by Taro for individual contents.
(5) Oil phase content by difference (100% - aqueous phase content = oil phase content)

This response is being submitted in two copies. A copy of the "Refuse to File" letter dated April 10, 1997, and FDA 356h form are also attached.

If you have any questions or require further information, please do not hesitate to contact the undersigned or our US agent at the following address:

Taro Pharmaceuticals USA, Inc.
Attn.: Lorraine W. Sachs
Senior Regulatory Affairs Scientist
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001
Fax: (914) 345-8728

Sincerely,
Taro Pharmaceuticals Inc.

Derek A. Ganes, Ph.D.
Director, Regulatory Affairs

/ Lul Ogbaghebriel

TARO PHARMACEUTICALS INC.
TELEPHONE
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Refuse to File
Anna Marie H. Weibel
4/4/97

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

March 26, 1997

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AC

Reference: ANDA 75-043
Hydrocortisone Valerate Ointment USP, 0.2%
Response to "Refusal to File Letter"

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocortisone Valerate Ointment USP, 0.2% dated December 23, 1996.

Reference is also made to your "Refusal to File" letter dated February 28, 1997, in which you requested the following:

i. Information concerning the level of the inactive ingredient, steareth- our proposed formulation.
ii. A letter of authorization from active drug substance manufacturer, ir agent in granting access to their DMF.
iii. Form 356h and the debarment certification with original signatures.

Our proposed formulation provides for i the inactive ingredient, steareth- We acknowledge that we have failed to provide a quantitative comparison of the amount in our formulation versus the amount in the Reference Listed Drug (RLD), Westcort Ointment 0.2%. However, our qualitative comparison provided on page 1058 of our ANDA indicated that our formulation is qualitatively the same as the RLD.

Steareth- as a nominal chemical structure of $CH_3(CH_2)_{17}(OCH_2CH_2)_{100}OH$. The Handbook of Pharmaceutical Excipients (1) describes polyoxyethylene alkyl ethers as mixtures of polymers of slightly varying molecular weights with, in this particular case, an average chain length of ne repeating units.

RECEIVED
MAR 28 1997
GENERIC DRUGS

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In addition, the stearyl ether portion of the molecule is predominantly C18 but, as is typical for the straight chain alcohols, may contain small amounts of both longer, C20, and shorter, C16 and C18 ethers. Thus, steareth-100, like others of the family, is a mixture with average chain length of 100 and predominantly C18, stearyl, ether.

Taro's present analytical capability does not provide for a method of quantitation of steareth- in Westcort Ointment 0.2%. We believe that Westcort Ointment contains less than 1% of steareth- id the lack of chromophoric groups, the low level and the molecular weight distribution make analytical quantification exceedingly difficult.

To demonstrate that the level of steareth- used in our formulation does not affect the safety of the proposed drug product, the following information is provided:

a. Information on safety of steareth- rom published literature:

We have undertaken a broader literature search to support the safety of 0.6% w/w steareth- literature shows that the material is non-irritating and non-sensitizing. We propose that there are no safety concerns and we direct your attention to the summary provided in **Attachment 1**. A list of references may be found on page 3.

b. A description of the purpose of this inactive ingredient in question:

c. Comparison of Physical and Chemical Properties:

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This response is being submitted in two copies. A copy of the "Refuse to File" letter dated February 28, 1997, and FDA 356h form are also attached.

If you have any questions or require further information, please do not hesitate to contact the undersigned or our US agent at the following address:

Taro Pharmaceuticals USA Inc.
Attention: Timothy A. Anderson, M.Sc., M.B.A.
5 Skyline Drive
Hawthorn, NY 10532

Tel: (914) 345-9001
Fax: (914) 345-8728

Sincerely,

Derek A. Ganes, Ph.D.
Director, Regulatory Affairs

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