CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76005

CORRESPONDENCE

ANDA 76-005

Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532

NOV 30 2000

Dear Madam:

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 the telephone conversation dated November 16, 2000 and to your correspondence dated November 21, 2000.

NAME OF DRUG: Econazole Nitrate Cream, 1%

DATE OF APPLICATION: October 10, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 11, 2000

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:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

/S/ for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

June 22, 2001

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

BIO

ORIG AMENDMENT

N/AB

Re: **Econazole Nitrate Cream, 1%**
ANDA # 76-005
Telephone Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on October 10, 2000 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Econazole Nitrate Cream, 1%. Reference is also made to a telephone call on June 18, 2001 from Krista Scardina of the Agency in which she requested the following:

Question 1:
Case Report Forms for patient No. 159 and 763.

Response 1:
Attached please find Case Report forms for patient No. 159 and 763.

Question 2:
Information on other medication used during the study, as well as data collected on compliance.

Response 2:
Please note that any other medications used during the study are indicated on the Case Report forms (section labeled "Concomitant Medications List dose and dates taken"). Please also note that information regarding patient compliance is located on the Case Report Forms.

This concludes our response to the Agency's telephone call of June 18, 2001. If you have any questions or require additional information, please do not hesitate to contact the undersigned at (914) 345-9001 x298.

Sincerely,

6/22/01

Kalpana Rao
Vice President, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 25 2001
OGD

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

November 6, 2002

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 20857
USA

ORIG AMENDMENT

N/AM

RE: ANDA: 76-005 – Econazole Nitrate Cream, 1%
Telephone Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product submitted October 10, 2000 and to our Minor Amendments of August 20, 2001 and May 17, 2002.

Reference is also made to the telephone conversation of November 6, 2002 between Ms. Sarah Ho, Dr. Paul Schwartz, Dr. Nashad and Dr. James Fan of the Agency and Mrs. Kalpana Rao of Taro Pharmaceuticals USA Inc., in which the following comments were made:

1. **Please revise the finished product release and stability specifications to include the test and limits for Yeasts and Molds.**

Response

As part of our normal Preservative Efficacy Test (PET) procedure this product was tested at a range of dilutions to identify any antibacterial or antifungal properties that may affect the results of the PET. This test is referred to as a Lowest Countable Dilution Test.

The results of this test for Econazole Nitrate Cream showed the product to be inhibitory to both *C.albicans* and *A.niger* at dilution levels up to 1:10000. This was expected since the product is an antifungal.

These results show that the minimum dilution usable for this product to isolate Yeasts & Molds would be 1:10000 which would make the lowest measurable plate count 10,000 c.f.u./g. This level is well above what would be reasonably expected to be a suitable specification for the product.

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As the product is a cream and is not suitable for testing by membrane filtration there is no practical alternative to a standard Yeast & Mold Count.

The product is sufficiently antifungal that it is unlikely to be susceptible to contamination by fungi.

In **supplementary pages 3 – 8**, presented is the Preservative Efficacy Preparatory Testing Report for Econazole Nitrate Cream 1%, ANDA exhibit batch S123-51820.

2. **Please revise your finished product release specifications to include test and establish limits of % LC for the top, middle and bottom of the tube.**

Response

In addition to the R&D data presented in the ANDA, Taro has generated results on three process validation batches, packaged into 4 pack sizes and tested at 0, 3, 6, and 9 months stability test points, a total of 192 individual assay values. The data (presented in **supplementary pages 9 - 16**) show that all assay results obtained from the top, middle or bottom of the tube for all batches in all pack sizes and at all test stations are between % LC. This data clearly shows tight patterns at both release and throughout 9 months RT stability (to date). Taro suggests, therefore, that the inclusion of testing at release does not provide added assurance of product quality. Taro will continue to monitor the of the product during the stability study.

3. **Please tighten the viscosity limits in the finished product release and stability specifications, based on your data.**

Response

Taro has manufactured both process validation and additional batches of this product. A total of 59 lots of bulk cream, packaged into 54 lots of 15, 30 or 85 g tubes have been tested for viscosity at release and 3 lots on stability. The range of observed values at release is 52,667 cps to 168,000 cps (**supplementary page 17**) and on stability is 80,000 cps - 152,000 cps (**supplementary pages 24 - 25**). Based on these data finished product specifications (in-process, release and stability) have been revised to tighten the viscosity limits

from **30,000 – 250,000 cps** to **30,000 – 200,000 cps.**

The revised specifications are presented in **supplementary pages 18 - 23.**

This concludes the Telephone Amendment. We trust the information provided is complete and sufficient for your review. Should you have additional questions please contact us at:

Taro Pharmaceuticals U.S.A. Inc.
ATT. Kalpana Rao
Vice President, Regulatory Affairs U.S.A.
5 Skyline Drive,
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,
TARO PHARMACEUTICALS INC.

Vesna Lucic
Director, Regulatory Affairs

September 13, 2002

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
NIAM

Re: ***Expedited Review Requested***

Econazole Nitrate Cream, 1%
ANDA # 76-005
Minor Amendment

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 Econazole Nitrate Cream, 1% dated October 10, 2000 and to a telephone call between Gary Buehler of the Agency and Avraham Yacobi of Taro on September 11, 2002.

As per this conversation, Gary Buehler advised us that our biostudy issues have been resolved and the Agency will move forward with the review of the CMC part of the application.

Following this conversation, Sarah Ho (Agency) requested from Kalpana Rao (Taro) on September 13, 2002, that we resubmit our most recent Minor Amendment (originally submitted on May 17, 2002). As such, enclosed, please find a copy of this amendment and we request that the Agency will expedite the review of the enclosed copy.

If there are any questions regarding this application, or if additional information is required, please contact me at (914) 345-9001 x 298.

Sincerely,

9/13/02

Kalpana Rao
Vice President, Regulatory Affairs

RECEIVED
SEP 16 2002
OGD / CDER

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

505(b)(2)(A) OK
30-NOV-2000

TARO

October 10, 2000

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA for Econazole Nitrate Cream, 1%**
This application also includes a CMC electronic submission

Dear Sir/Madam:

Taro Pharmaceuticals USA Inc. submits today an original Abbreviated New Drug Application (ANDA) seeking approval to market Econazole Nitrate Cream, 1% that is bioequivalent to the listed drug, Spectazole® Cream, manufactured by Ortho-McNeil Pharmaceutical pursuant to NDA 19-579.

This ANDA consists of four volumes. Taro Pharmaceuticals USA Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in orange folders. The diskette with the biostudy data is included in the archival copy, section VI "Bioavailability and Bioequivalence".

This application also includes a CMC electronic submission ESD. The electronic files have been provided in duplicate on 3.5" virus-free diskettes in the archival copy of the ANDA (blue jackets). The information provided in these files is identical to the hard copy ANDA submission.

Taro Pharmaceuticals USA Inc. hereby certifies that, the field copy of this ANDA submission contained in burgundy folders is a true copy of the technical sections of the ANDA. The field copy also contains a copy of the signed 356h form and a certification that the contents are a true copy of the technical sections of the ANDA.

CENTER FOR DRUG
REC'D
OCT 11 2000
OGD
EVALUATION AND RESEARCH

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 www.taropharma.com

If there are any questions regarding this application, or if additional information is required, please contact us at:

Taro Pharmaceuticals USA, Inc.,
Attn: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001

Sincerely,
Taro Pharmaceuticals Inc.

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

/Vesna Lucic

Enclosures:

Archival Copy (1 set):
All Sections (I - XX), 4 volumes (Blue)
Review Copies:CMC (Sections I-V and VII-XX), 2 volumes (Red)
Bioequivalence (Sections I-VII): 2 volumes (Orange)
Field Copy (1 set)
CMC (Sections I-V and VII-XX), 2 volumes (Burgundy)

August 20, 2001

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 20857
USA

ORIG AMENDMENT

RE: ANDA: 76-005 - Minor Amendment
Econazole Nitrate Cream, 1%

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product. Reference is also made to the agency correspondence of March 9, 2001. The MINOR deficiencies presented in the agency's correspondence have been restated and are followed by Taro's response.

A. Deficiencies
Comment 1
Drug Master File No. ' is deficient. The holder of the DMF, , has been notified of the DMF deficiencies. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

Response
Taro has been notified by , the DMF holder, that they have submitted a response with respect to their DMF deficiencies. Their initial response was submitted on May 9, 2001 (see Attachment 1 for a copy of the cover letter to their response). Amendments to this response were also submitted by on July 23, 2001 and August 1, 2001.

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AUG 2 1 2001
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Comment 2

Please separate the individual impurities into known and unknown impurities, and set appropriate limits for the drug substance. Known impurities should be identified. If the manufacturer does not use Organic Volatile Impurities (OVIs) in the manufacture of econazole nitrate, such a certification statement should be included in your specification sheet.

Response

Individual impurities have been separated into individual known and individual unknown impurities and limits for each have been established. The impurities specified and the limits established have been harmonized with those of the supplier. These changes have been incorporated into the current specifications for the drug substance included in Attachment 2.

In establishing specifications for the three (3) individual known impurities, characterized as *synthetic* impurities, Taro has developed and validated a method for the quantitation of econazole and related impurities in the drug substance. The method, and the corresponding validation presented in Research Report RD-MV110 are included in Attachment 3.

The drug substance manufacturer certifies the absence of Organic Volatile Impurities (OVIs) and a certification statement to that effect has been included in Attachment 2. Taro's specifications for the drug substance, also in Attachment 2, have been revised to indicate there is no potential for OVIs to be present.

Comment 3

You should revise your proposed specifications for particle size specification to include The limits should be established to be close to the observed values for lot #8358-R, which was used in the bio batch.

Response

The histogram for (L) 8358-R of Econazole Nitrate, USP, included in the ANDA on page 881, and provided herein as Attachment 4, included statistical particle size results as These listed statistical results are output parameters which were arbitrarily predefined by the operator. The output readings do not represent release criteria for the drug substance and were not intended to be used as proposed limits. The two stage limit established for Taro's Econazole Nitrate USP specification, (95%< 50 μm, 80% < 25 μm) sufficiently characterizes the drug substance for its use in the topical cream.

Comment 4
Please establish specifications for Residual Solvents based on the current manufacturer's Certificate of Analysis (COA), and provide test results for lot #8358-R based on a validated analytical method. A validation report should be submitted.

Response
Taro has developed and validated a method for the testing of residual solvents in the active drug substance. Taro's Method and the validation for this method are provided in Attachment 5. Specifications for Residual Solvents have been established and are provided on the current drug substance specifications (Attachment 2). Test results for lot #8358-R based on Method are provided in on page 12 of the validation report included in Attachment 5.

Comment 5
Please provide blank batch records for filling and packaging, which are missing in the submission.

Response
Blank batch records for the filling and packaging of the 15 g, 30 g, 85 g and 120 g tubes are provided in Attachment 6.

Comment 6
Regarding your in-process specifications, please establish limits for homogeneity and viscosity. RSD for test should be at %.

Response
The in-process specifications (Attachment 7) were revised to include limits for homogeneity and viscosity. The RSD for the test was established at NMT %.

Comment 7
Please specify the maximum holding time for the bulk before packaging.

Response
The maximum holding time for the bulk before packaging has been established as six (6) months. Nine (9) months of bulk stability data obtained on the product packaged in 5L HDPE pails and stored at 25±2°C/60±5% RH to support the six month holding time is included in Attachment 8.

Comment 8
Please establish specifications for degradation products, viscosity and homogeneity in your finished product specifications. Known impurities should be included in the specifications.

Response

The finished product specifications have been revised to include specifications for unknown and total degradation products (there are no known degradants), viscosity and homogeneity. In addition, the specification for benzoic acid has been removed from the finished product specifications since this test is performed on the bulk product. The revised finished product specifications are provided in Attachment 9.

Comment 9

Please explain why is included under Benzoic Acid Assay on page 1206.

Response

Page 1206 of the ANDA erroneously lists under Benzoic Acid Assay. This page has been revised to remove the statement and the corrected page has been included in Attachment 10.

As indicated in the response to Comment 8, testing for Benzoic Acid is performed on the bulk product and is not intended for the packaged finished product. Page 1206 has been revised to indicate Benzoic Acid Assay testing will be performed on the bulk product.

Comment 10

Please establish specifications for degradation products, viscosity and homogeneity in your stability specifications.

Response

Limits for unknown and total degradation products (there are no known degradants), viscosity and homogeneity have been established in the stability specifications. Established limits are based on 24 months of room temperature stability data. The revised stability specifications are included in Attachment 11.

Comment 11

Please add preservative effectiveness test to the stability specifications. This test should be performed at time zero and just prior to the proposed expiration date.

Response

In a telephone conversation on April 3, 2001, between Kalpana Rao of Taro Pharmaceuticals U.S.A. Inc. and Paul Schwartz, Shing Liu, and Elaine Hue of the FDA, clarification was requested regarding the FDA's expectations for Preservative Challenge Testing in connection with Taro's ANDA 76-005 for Econazole Nitrate Cream, 1%.

During that conversation Taro was advised that one iteration of Preservative Challenge Testing was sufficient and that it was acceptable to perform this test on one

validation batch.

Also, considering that the 28 day test typically takes up to six (6) weeks from the time that the sample is drawn to the time when a full report is available, the test should be performed a month and half or two months before the expiration date.

Based on the agency's recommendation, preservative effectiveness testing has been added to the stability specifications at time zero and prior to expiry for the first validation batch. The revised stability specifications are included in Attachment 11.

Comment 12
Regarding the Tube Uniformity test in the stability specifications, the RSD value of NMT % should be tightened.

Response
The RSD value in the test in the stability specifications has been tightened to NMT % (Attachment 11).

Comment 13
Please add a test for Butylated Hydroxytoluene (BHT) assay in the stability test protocol and establish a specification.

Response
Taro has recently completed an extensive investigation into the role of BHT in its Econazole Nitrate Cream formulation. Our conclusion is that the BHT is not protective of the econazole nitrate, and therefore Taro believes that a test for BHT in our stability program is not meaningful. Please see attached summary of this investigation presented in Attachment 12.

Comment 14
Please clarify whether you intend to include total yeast and Mold count under the total aerobic count.

Response
Econazole Nitrate Cream 1% is highly antifungal and is not at risk for spoilage or contamination by yeast and mold. Therefore, there is no reason for Taro to include Total Yeast and Mold Count under total aerobic count.

Comment 15
Please provide the missing pages of the three-page Preservative Challenge Test report (see p. 1285). Only the first page of the report is found in the ANDA.

Response
The complete three-page Preservative Challenge Test report for Econazole Nitrate Cream 1%, (L) S123-51621, the product formulated at 80% preservative level, is provided in Attachment 13.

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 ANDA must be in compliance with cGMPs at the time of approval.

Response
We acknowledge that the firms referenced in our ANDA must be in compliance with cGMPs at the time of approval.

Comment 2
Please submit all available room temperature stability data.

Response
24-months of room temperature stability data for the biolot (L) S123-51820 in 15 g, 30 g, 85 g and 120 g tubes is provided in Attachment 14.

Comment 3
The bioequivalence information, which you have provided, is under review. Comments, if any, will be communicated to you under a separate cover.

Response
We note that the bioequivalence information is under review

Comment 4
The labeling information, which you have provided, is under review. Comments, if any, will be communicated to you under separate cover.

Response
Taro has revised the labeling based on comments received from the Division of Labeling and Program Support. Labels and labeling have been submitted in final print in Attachment 15. Also provided in this attachment is a side-by-side comparison of the proposed labeling with the labeling of the last submission with all differences annotated and explained.

Comment 5
The acceptance of your proposed 24 month expiration dating period is contingent upon you providing the requested stability specifications.

Response
We acknowledge that acceptance of the proposed 24 month expiration dating period is contingent upon the provided stability specifications.

Comment 6
Please be advised that in the event of regulatory dispute, the USP methods for Econazole Nitrate USP will prevail.

Response
Taro acknowledges that in the event of regulatory dispute, the USP methods for Econazole Nitrate USP will prevail.

Comment 7
We requested the Northeast Regional Laboratory to conduct method validation on your finished product. Please provide samples when requested.

Response
At the request of the Northeast Regional Laboratory, samples and analytical data for methods validation were submitted to them on March 16, 2001. A copy of Taro's cover letter, which accompanied the samples and analytical data, is included in Attachment 16.

This concludes the amendment to this ANDA. We trust the information provided is complete and sufficient for your review. Should you have additional questions please contact us at:

Taro Pharmaceuticals U.S.A. Inc.
ATT. Kalpana Rao
Vice President, Regulatory Affairs U.S.A.
5 Skyline Drive,
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

August 10, 2001

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

Re: **ANDA for Econazole Nitrate Cream, 1%**
ANDA #76-005
Telephone Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application, submitted on October 10, 2000, under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream, 1%. Reference is also made to a telephone conversation on August 10, 2001 between myself (Kalpana Rao of Taro) and Harvey Greenburg of FDA, in which the following was requested:

Comment no.1:

In clinical Section, please provide a diskette containing raw patient data.

Response no. 1:

Enclosed please find a diskette in which we have included the patient raw data.

If there are any questions regarding this application, or if additional information is required, please contact the undersigned.

Sincerely,
Taro Pharmaceuticals U.S.A., Inc.

8/10/01
Kalpana Rao
Vice president, Regulatory Affairs.

CENTER FOR DRUG
AUG 13 2001
EVALUATION AND RESEARCH

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

ARCHIVE COPY

June 7, 2002

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 20857
USA

NC

NEW CORRESP

RE: **ANDA 76-005**
Econazole Nitrate Cream, 1%
Minor Amendment

Dear Sir/Madam,

Reference is made to our Abbreviated New Drug Application for Econazole Nitrate Cream 1%. Reference is also made to Taro's Response to the "Not Approvable" Letter of May 24, 2002 (copy attached) and the telephone conversation of June 6, 2002 between Ms. Sara Ho of the Agency and Mrs. Kalpana Rao of Taro Pharmaceuticals U.S.A. Inc.
As per the above mentioned teleconference, and in order to restart the CMC review of the above application at the OGD, please find attached a copy of our Minor Amendment, originally submitted on May 17, 2002.

If there are any questions with regards to this amendment, please do not hesitate to contact us at:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Kalpana Rao
VP, Regulatory Affairs U.S.A.
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

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

TARO PHARMACEUTICALS INC.

Vesna Lucic
Director, Regulatory Affairs

RECEIVED
JUN 10 2002
OGD / CDER

cc. Acting Director, FDA, Office of International Programs

acknowledged
forward to
DBE
6/5/02

May 24, 2002

Gary J. Buehler
Director, Office of Generic Drugs (HFD-600)
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

Taro Pharmaceuticals U.S.A., Inc.

NEW CORRESP

RE: ANDA 76-005
Econazole Nitrate Cream, 1%
Response to "Not Approvable" Letter; Intent to Amend
Request for Meeting

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application dated October 10, 2000, submitted pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Econazole Nitrate Cream, 1%. Reference is also made to the Agency's dated May 16, 2002 "not approvable" letter, dated May 16, 2002 in which the following was stated:

Comment:
Your product does not meet the standard bioequivalence criteria for a generic to be substitutable. Your analyses are consistent with those of Agency and demonstrate that your product is not bioequivalent to the reference, but has a higher overall cure rate.

Your application can be substituted as 505 (b) (2) application. Please refer to the draft guidance "Applications covered by Section 505(b)(2)" for more information (http://www.fda.gov/cder/guidance/index.htm). If you decided to submit a 505 (b) (2) application, you should send a meeting request and a briefing package to the Division Dermatologic and Dental Drug Products in the Office of New Drugs (301-827-2250)

Response:
We intend to amend our abbreviated new drug application with additional information to address the issues raised in the "not approvable" letter. We anticipate that we will be able to submit the amendment within 180 days.

By this letter, we wish to indicate our desire to schedule a meeting with the appropriate agency representatives to discuss the issues and underlying policies concerning our application. We will be sending you a meeting request letter within the next few days listing potential dates and requesting that certain agency officials be available to attend the meeting.

Thank you for your attention to this matter.

Sincerely,
Taro Pharmaceuticals USA., Inc

Kalpana Rao 5/24/02
Vice president, Regulatory Affairs

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MAY 28 2002
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TARO

May 17, 2002

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 20857
USA

NEW CORRESP
NC

RE: ANDA: 76-005 – Econazole Nitrate Cream, 1%
MINOR AMENDMENT

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product submitted October 10, 2000 and to our Minor Amendment submitted August 20, 2001.

Reference is also made to the agency's correspondence of March 6, 2002 designated as a MINOR AMENDMENT letter.

The agency's comments presented in this correspondence have been restated and are followed by our response.

A. Deficiencies:

1. *Drug Master File No is deficient. The holder of the DMF, has been notified of the DMF deficiencies. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.*

Response
Provided in Attachment 1 is a copy of March 13, 2002 response to the FDA regarding the DMF deficiencies of DMF

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5/22/02

2. *Please justify the proposed limits for the individual unknown and total degradants in the finished product release and stability. Please also establish the limit for individual known degradant(s), unless you can prove that there are no known degradants.*

Response

Taro has reviewed the degradant data generated on the finished product release and during stability for two batches of Econazole Nitrate Cream 1%: the biobatch (L) S123-51820 and a second exhibit batch (L) S123-52534. Twenty-four (24) months of room temperature stability data for the biobatch (L) S123-51820 and twelve (12) months of room temperature stability data for the second batch (L) S123-5234 have been included in Attachment 2.

We note that in the stability summaries for the biobatch (L) S123-51820 presented in the Minor Amendment of August 20, 2001, placebo peaks were erroneously reported as impurities/degradants for the 24 month room temperature station. We have provided in Attachment 2 the corrected stability summaries for the (L) S123-51820 as well as a report regarding an investigation of placebo peaks in the cream.

In addition to reviewing stability data for our product, we have reviewed degradant data for two (2) lots of the innovator product tested at expiry. The results for degradation products are tabulated below and the full certificates of analysis are provided in Attachment 3:

Table 1: Degradants Found in Two (2) Lots of Spectazole® Cream 1%

	(L) 28H833A, Expiry: July/01 - Test Date: July 2001		(L) 28M471A Expiry: Nov/01 - Test Date: Nov 2001	
	RRT	**% Degradant**	**RRT**	**% Degradant**
Individual Degradants:	0.22	0.13	0.28	0.14
	0.24	0.20	0.29	0.31
	0.29	0.24	0.44	0.07
	0.57	0.13	0.68	0.07
	1.29	0.07	0.77	0.07
	1.51	0.08	0.86	0.06
			1.27	0.06
			1.36	0.06
Total Degradants:		0.85		0.84

Based on the observed release and stability degradant data for our own product and the results observed for the innovator product, the release specifications of

NMT % for individual degradants and NMT % for total degradants are justified.

In addition, based on the observed data for our product, the stability specification of NMT % for individual degradants is justified. We have, however, tightened the stability specification for total degradants from NMT % to NMT %.

The established limits for degradants can be summarized as follows:

Table 2: Finished Product Release and Stability Specifications for Degradants

	Release	Stability
Individual Unknowns:	**NMT %**	**NMT %**
Total:	**NMT %**	**NMT %**

Please note, there are no known degradants for the finished product. During the validation of the method for the quantitation of degradants in the finished dosage form, Taro demonstrated through product stressing that all degradants generated were unknown. Provided in Attachment 4 is the Validation Report MV-076, originally submitted in Section XV of the ANDA. Section 4 of this report provides details regarding the degradants generated during stressing. In addition, the levels of individual degradants observed during stability do not necessitate identification and qualification.

The revised in process/bulk product, finished product release and stability specifications are included in Attachment 5.

Please note, the presence of placebo peaks observed during the assay have warranted a revision to method Assay of Econazole Nitrate and Related Impurities in Econazole Nitrate Raw Material and Econazole Nitrate Cream, 1%. The revision includes a placebo peak identification table and sample chromatograms. The revised method is provided in Attachment 6.

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

Your response to the bioequivalence deficiencies is under review. Comments, if any, will be communicated to you under a separate cover.

Response

We note and acknowledge that our response to the bioequivalence deficiencies is under review and that comments, if any, will be communicated to us under a separate cover.

Additional Information:

Revisions to Release and Stability Specifications

The in process/bulk product specifications and the finished product release specifications have been revised to reflect a change in viscosity limits from 30,000-150,000 cps to 30,000-250,000 cps. The stability specification for viscosity has also been revised from 20,000 – 200,000 cps to 30,000 – 250, 000 cps. These limits are based on measured in process/bulk product and finished product release viscosity data from several lots of production scale Econazole Nitrate Cream, 1% as provided in Attachment 7. Results have been summarized below:

Table 3: Measured In Process/Bulk Product and Finished Product Release Viscosity Data from Production Scale Batches of Econazole Nitrate Cream 1%

	In Process Bulk (13 batches)	Finished Product Release (3 batches)
Average Viscosity	132,239 cps	132,167 cps
RSD	13.579	19.454
Max	170,000 cps	174,000 cps
Min	96,000 cps	71,000 cps

The revised in process/bulk product, finished product release and stability specifications are included in Attachment 5.

Revisions to Manufacturing Process

Taro wishes to amend the application to provide for the following minor changes in the manufacturing process for the proposed commercial batch size of kg:

Provided in Attachment 8 is the master formula and manufacturing directions (Formula No. E010500B.03U, November 8, 2001) for the proposed commercial kg batch.

This concludes the minor amendment. We trust the information provided is complete and sufficient for your review. Should you have additional questions please contact us at:

Taro Pharmaceuticals U.S.A. Inc.
ATT. Kalpana Rao
Vice President, Regulatory Affairs U.S.A.
5 Skyline Drive,
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,

for Kalpana Rao
Vice President, Regulatory Affairs U.S.A.

/jh

April 11, 2002

Taro Pharmaceuticals U.S.A., Inc.

Gary Buehler
Director
Office of Generic Drugs (HFD-600)
Food and Drug Administration
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

NC TO BIO

RE: REQUEST FOR FORMAL DISPUTE RESOLUTION
ANDA No. 76-005
Econazole Nitrate Cream, 1%

Dear Mr. Buehler:

In accordance with 21 CFR §10.75 and the Food and Drug Administration's ("FDA's") "Guidance for Industry – Formal Dispute Resolution: Appeals Above the Division Level," Taro Pharmaceuticals USA, Inc. ("Taro") hereby requests "Formal Dispute Resolution" regarding the Office of Generic Drugs' ("OGD's") determination that Taro's comparative clinical study fails to demonstrate the bioequivalence of Taro's Econazole Nitrate Cream, 1% drug product to the reference listed drug ("RLD") identified in Taro's abbreviated new drug application ("ANDA"), Spectazole® Cream, 1% (Ortho McNeil Pharmaceuticals).

The cause of this dispute is application of FDA's bioequivalence policy developed for systemically bioavailable drug products to topical, locally acting generic drug products. OGD's Division of Bioequivalence (the "Division") has taken the position that it cannot deviate from policy stated in a 12 year old draft guidance document entitled "Draft Guidance for the Performance of a Bioequivalence Study for Topical Antifungal Products" (1990) (the "Draft Guidance"). While we recognize the virtue in maintaining a consistent bioequivalence policy, we believe that, in this instance, the Division's dogmatic approach is inconsistent with FDA's role as a science-based agency. As described below and in the enclosed medical opinions, Taro's comparative clinical study demonstrates that its drug product is clinically equivalent to the RLD. The only significant "problem" cited by the Division is that Taro's drug product produced mycological cures in a slightly, but insignificantly higher proportion of subjects than the RLD. In reaching this conclusion, the Division has redefined one of the key effectiveness measures for the study and has arbitrarily applied rigid and inappropriate statistical criteria to assess the study results. When one considers the discretion that the Federal Courts and Congress have entrusted to FDA for finding scientifically-based criteria for bioequivalence of non-systemically absorbed drug products, the arbitrary and non-scientific approach adopted by the Division is of great concern. See Schering Corp. v. FDA, 51 F.3d 390 (3rd Cir. 1995). We respectfully request that this dispute be reconsidered from a scientific perspective. We believe that when the agency does so, there will be a consensus that Taro's drug product is bioequivalent to the RLD.

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Our conversations with agency representatives suggest to us that OGD may believe that the applicable statutes and regulations compel the agency to apply the ± 20% of 90% CI statistical

approach to Taro's drug product. We therefore begin by reviewing the agency's obligations with respect to bioequivalence determinations.

As you know, the Federal Food, Drug, and Cosmetic Act ("FD&CA") requires that a drug be "bioequivalent" to a listed drug in order to be the subject of an approved ANDA. See FD&CA §505(j)(2)(iv). Although the statute defines "bioequivalent" drugs in general terms (i.e., no significant difference in the rate and extent of absorption), it does not specify what methods may be used to prove the requisite "bioequivalence." Nor does it specify the degree of "difference" between drugs that would preclude a conclusion of bioequivalence. See FD&CA §505(j)(8)(B). Therefore, these issues are left to FDA's discretion. See Schering Corp., 51 F.3d at 399. FDA's regulations implementing the FD&CA also define "bioequivalence" in general, although using slightly more descriptive terms (i.e., absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of action). See 21 CFR §320.1(e). Additionally, the regulations specify what methods may be used to prove bioequivalence. See 21 CFR §320.24. Among the accepted methods is use of "comparative clinical studies for topical drug products." See 21 CFR §320.24(b)(4). The regulations, however, do not specify a particular statistical method for evaluating clinical studies. It therefore follows that neither the FD&CA nor FDA regulations specifically require that the results from a comparative clinical study meet the ± 20% of 90% CI requirement. Accordingly, FDA has ample authority to evaluate Taro's clinical study using alternative, scientifically sound criteria.

In a further effort to assist the industry, FDA issued the Draft Guidance in 1990, which recommends, but does not mandate, the ± 20% of 90% CI approach. The Draft Guidance, however, has never been finalized and, like all other guidance documents, does not legally bind FDA or Taro. In fact, FDA acknowledged in the Preface to the "Orange Book" that alternative statistical methods "are sometimes used when bioequivalence is demonstrated through comparative clinical trials. . .". While we appreciate the agency's desire to maintain consistency through uniform application of policies stated in guidance documents, in this case, the substantial body of scientific knowledge clearly necessitates a reconsideration of the Draft Guidance. Presumably, one of the reasons for issuing the Draft Guidance as a "guidance," rather than a "regulation," was to provide FDA with flexibility to adapt quickly and keep pace with the advance of science. The results of Taro's study provide compelling support for exercising that flexibility and recognizing that the Draft Guidance cannot be uniformly applied in all instances.

A review of the administrative record in this matter will reveal that the results of Taro's clinical study meet any reasonable interpretation of the statutory requirements for bioequivalence. See 21 U.S.C. §355(j)(8). Even when the agency changed the criteria for mycological cure from those in the original Taro protocol, there was no statistically significant difference between the cure rates produced by Taro's product and the RLD. The only issue is the slightly higher proportion of mycological cures produced by Taro's drug product compared to the RLD when mycological "cure" is redefined and the comparison based solely on mycological testing results at 6 weeks. This interpretation drives the upper limit of the 90% CI for the Taro product – RLD mycological cure rate difference beyond 20%. When mycological "cure" is defined as negative test results at both 4 and 6 weeks (as stated in Taro's original protocol), the mycological cure rates for Taro's product and the RLD are identical. Nevertheless, the Division continues to assert that the single mycological test point (i.e., at 6 weeks) result must be used rather than results from two test points (i.e., 4 and 6 weeks) and that the additional "cures" produced by Taro's product are evidence of a lack of bioequivalence. For the reasons described below, we disagree strongly with this conclusion.

As the agency knows, demonstration of bioequivalence for topical drug products is considerably more difficult than for systemically absorbed products because of the high degree of variability and consequent imprecision in the available clinical assays. Furthermore, clinical studies are expensive to conduct because of the need for a large number of subjects, and the outcomes are less certain than the outcomes of simple pharmacokinetic "biostudies." In fact, FDA has long recognized that assessing the bioequivalence of topical drugs with comparative clinical studies is less precise than the relatively simple blood/plasma level studies used for systemically absorbed drug products. See 21 CFR §320.24(b)(4). Yet, under the policy set forth by the Division, which ignores the statement in the regulation about precision of these studies, generic firms can spend considerable time and money conducting difficult clinical studies, only to obtain results that fail to satisfy inappropriately stringent criteria and therefore get nothing for their efforts. Such a policy is in clear contrast to Congress' vision for generic drugs when it enacted the Hatch-Waxman Act. Congress intended to advance the availability of affordable generic products. One cannot square the noble policy objectives of the statute and the agency's regulations with the Division's decision to review all topical drug studies in a manner that will deny public access to generic products because they cure an insignificantly greater proportion of patients.

BACKGROUND

Taro's ANDA for Econazole Nitrate Cream, 1% was submitted to FDA on October 10, 2000. Taro's proposed drug product is labeled for the same indications for use as the RLD, namely topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T. rubrum, T. mentagrophytes, T. tonsurans, M. canis, M. audouini, M. gypseum,* and *E. floccosum*; in the treatment of cutaneous candidiasis; and in the treatment of tinea versicolor. Because both Taro's product and the RLD are topical, locally acting, drug products, Taro could not use the typical blood-level biostudy to demonstrate the bioequivalence of its product to the RLD. Rather, Taro conducted a 6 week comparative clinical efficacy study, in accordance with the Draft Guidance, employing 453 subjects with clinical signs and symptoms of tinea pedis. The study had three treatment arms: (1) test (Taro's product), (2) reference (the RLD), and (3) placebo (the Taro vehicle without active ingredient). All subjects were randomized into one of the three treatment groups. Of the 453 enrolled subjects, two elected not to participate and 199 were deemed ineligible due to lack of positive mycological culture for any of the specified organisms. Thus, the study was conducted with 252 eligible subjects.

Taro's protocol called for treatment with the active or placebo products for 4 weeks, and described three study endpoints: clinical, therapeutic, and mycological. A "clinical" cure was defined as no evidence of infection (by appropriate measures) at a 6 week (2 weeks after completion of study drug dosing) evaluation. A "mycological" cure was defined as no evidence of fungal infection (10% KOH prep and fungal culture negative) at both the 4 and 6 week evaluations. A "therapeutic" cure, defined in the protocol as a combination of both a "clinical" and "mycological" cure, was a secondary effectiveness measure, and is not mentioned in the Draft Guidance.

Results of Taro's study, when considered according to the protocol definitions of the applicable "cures," clearly demonstrate the bioequivalence of its drug product and the RLD. See Letter from Dr. Thomas Garvey to Taro, attached as Exhibit 1. Taro submitted results of its study to FDA on October 10, 2000. Yet, on January 28, 2002, Taro received a deficiency letter from the

Division which stated that the clinical study failed to demonstrate bioequivalence between Taro's product and the RLD (enclosed as Exhibit 2). Taro responded to each of the issues raised by the Division in a letter dated February 8, 2002 (enclosed as Exhibit 3). It is now our understanding that the Division has deemed our response to be inadequate and has recommended that the ANDA be denied.

ISSUES TO BE RESOLVED

1. **Whether the ± 20% bioequivalence policy should be strictly applied to deny approval of Taro's ANDA when a scientific analysis of the data strongly supports the bioequivalence of Taro's product to the RLD.**

2. **Whether, from a scientific and public policy perspective, it makes sense to deny ANDA approvals for topical drug products on the basis that the generic product produces a statistically insignificantly greater "cure rate."**

3. **Whether FDA is going to base its decision on a single mycological test at week 6 when all of the scientific evidence supports the increased reliability and accuracy of "cure" defined on the basis of results at both weeks 4 and 6.**

POSSIBLE SOLUTIONS

We believe that there are three possible ways to reach a consensus on the issues in this dispute.

1. Rely on the lack of statistical significance

FDA could take the position that, regardless of the 90% confidence intervals, the differences between the test and reference product are not statistically significant and, therefore, do not present a bar to approval. This approach would be consistent with the agency's usual practice of discounting any data differences that do not rise to the level of statistical significance. For example, Taro is not suggesting that the slight differences between the proportion of cures produced by its product and that produced by the RLD would support a "superiority" claim. It is well established that such claims must be supported by clinical differences that are statistically and in many cases, clinically significant. The same approach should be taken with respect to topical drugs for which the upper 90% confidence limit for the difference from the RLD exceeds 20% and for which the absolute difference between the cure rates for the test drug and the RLD is not significant. These differences simply do not rise to a level sufficient to justify a conclusion of "bio-inequivalence". See Garvey letter (Exhibit 1).

2. Recognize that the ± 20% approach is not appropriate for all comparative clinical studies

FDA could recognize that the ± 20% of 90% CI as a statistical standard is inappropriate for analysis of studies of non-absorbed topical products. This would require an acknowledgement that a certain amount of flexibility is needed when determining bioequivalence via clinical studies. The ± 20% bioequivalence standard is a relatively easy, effective and clinically relevant means of determining equivalence when measuring blood levels of a systemically bioavailable

active moiety. However, FDA has recognized that when conducting clinical studies, other statistical approaches may be more appropriate. See FDA Electronic Orange Book, Preface, "Statistical Criteria for Bioequivalence". This is particularly true when, as is the case with Taro's product, the proportion of cures with the test product is slightly higher than the corresponding proportion for the reference product with the result that the upper 90% confidence limit for the difference between the test drug and the RLD exceeds the upper limit of the confidence interval range chosen for analysis of pharmacokinetic parameters.

We have engaged to review our clinical study. A copy of written opinion is enclosed as Exhibit 4. We believe that opinion is representative of the medical community in general in that he believes that the notion of a topical drug being deemed "non-equivalent" because of a "greater than 20% superiority difference" is "patently absurd." See also letter (Exhibit 1) (referring to such a policy as "medically untenable"). As the opinions of point out, a comparative clinical study of a topical product is vastly different from a blood/plasma level study of a systemically absorbed drug. Obviously, relatively high levels of an absorbed drug in the systemic circulation can present significant safety issues. This is simply not the case with a topical antifungal agent, which has virtually no systemic bioavailability. As such, there is no medical, scientific or public policy rationale for denying approval of topical drug products because they appear to be slightly more effective in the context of a comparative clinical study.

3. Recognize that the most appropriate definition of "mycological cure" for Taro's study requires negative test results at both the 4 and 6 week evaluations

As described in detail in analysis (see Exhibit 1), treatment with Taro's drug product produced virtually the same proportions of "mycological cures" and "mycological failures" as treatment with the RLD when one uses the protocol definition of "mycological cure" – i.e., negative test results at both 4 and 6 weeks, and a corresponding definition of "mycological failure," i.e., a positive test result at either 4 or 6 weeks, respectively – see table below.

	Patient with two negative mycologic results	Patient with one negative and one positive mycologic result	Patient with two positive mycologic results
Taro	54/81 (67%)	14/81 (17%)	13/81 (16%)
Ortho	54/81 (67%)	13/81 (16%)	14/81 (17%)
Control	22/85 (26%)	21/85 (25%)	42/85 (49%)

Given the inherent inaccuracies in clinical studies in general, and mycological testing in particular, it should be obvious that a definition of cure based on results for two testing points is more accurate than basing such a definition on results for only one time point. Accordingly, FDA could resolve this dispute by simply acknowledging that Taro's drug product is bioequivalent to the RLD when one relies on results for multiple, rather than single, mycological test points.

LIST OF DOCUMENTS

To facilitate review of this matter, we have enclosed copies of the following documents:

1. Letter to Taro from dated April 11, 2002.
2. Deficiency letter from FDA to Taro dated January 28, 2002.
3. Taro's Response to FDA Deficiency letter dated February 8, 2002
4. Letter from dated March 4, 2002.

Please direct any questions concerning this request to my attention.

Thank you in advance for your prompt attention to this matter.

Sincerely,

4/11/02

Avraham Yacobi, Ph.D.
President
Taro Research Institute
Tele: 914-345-9001 Ext. 342
Fax: 914-593-0078

Enclosure(s)

cc: Janet Woodcock, M.D.
Helen Winkle
Robert Temple, M.D.
Dale Conner, Pharm. D.
James Leyden, M.D.
Thomas Garvey, M.D.

February 08, 2002

Taro Pharmaceuticals U.S.A., Inc.

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CDR/OGD

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
AB

Re: Econazole Nitrate Cream, 1%
ANDA # 76-005
Bioequivalence Amendment

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 Econazole Nitrate Cream, 1% dated October 10, 2000 and to the bioequivalence deficiency letter dated January 28, 2002.

Background:

Taro has conducted a clinical bioequivalence study in 453 patients and concluded that the Taro product and the reference product are bioequivalent. In response to the Agency's deficiency letter, we have performed a thorough re-analysis of our data, both from the perspective of the original protocol and the issues raised by the Agency. We are uncertain of the statistical analyses method used by the Agency, which led to a conclusion that the Taro product is not bioequivalent to the brand. However, based on these data, Taro and an independent statistical consultant reached the following conclusions:

- **The Taro product and the reference product are statistically significantly different from the placebo (Taro vehicle).**
- **Depending upon the statistical method used, the definition of cure, and the patient population selected, the Taro product either falls within a 90% confidence interval of ± 20% or is somewhat more effective than the reference. In no instance is there a statistically significant difference between the Taro product and the reference product (mean difference in all cases ranged from -8.9 to 16%).**
- **The Taro product is safe and effective for the labeled indications.**

Agency's Introductory Remarks:
Your clinical endpoint study fails to demonstrate bioequivalence between your product, Econazole Nitrate Cream, 1%, and the reference listed drug (RLD), Spectazole Cream, 1% (Ortho McNeil Pharmaceuticals) in the treatment of tinea pedis due to the following reasons:

FEB 12 2002
OGD
EVALUATION AND RESEARCH

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-[illegible]0001 1-888-TARO-[illegible] Fax: 914-345-8728 www.taro.com

Taro's Response:
We would like to begin our response to the agency's bioequivalence deficiency letter with a review of the patient accountability table (see Table 1).

Four hundred fifty-three (453) patients with clinical signs and symptoms of tinea pedis were enrolled into the study during the 5 months from January 17 to May 30, 2000. All patients were randomized to one of the 3 treatment groups at enrollment. Of the 453 enrolled patients, two elected not to participate in the study and 199 patients were determined to be ineligible at baseline due to lack of positive mycological culture for any of the specified organisms. Thus 252 eligible patients participated in the study.

Five of the 252 patients did not return for the six-week visit. These patients are now included in the modified intention to treat population (MITT) (see Table 2). The remaining 247 patients were included in Taro's "original per protocol population". For the 6-week visit, Taro's protocol required a return between 42 – 49 days following the initiation of treatment. The FDA, in comment # 3 (below), refers to a window of 42 ± 3 days. Seven patients returned after day 45 and thus are outside the 42 ± 3 day window.

Based upon our understanding of the deficiency letter, the study can be viewed as comprising four possible patient populations.

- The **"full intention to treat (FITT) population"** includes all randomized individuals, n=453.

- The **"modified intention to treat (MITT) population"** consists of all 252 eligible patients who were treated with the Taro or Ortho products, or placebo. The five patients who were lost to follow up at the 6-week visit were included as therapeutic failures.

- The **"original per protocol population"** consists of 247 patients who returned in the window period of days 42 – 49 for the 6-week visit, as specified in the protocol.

- The **"modified per protocol population"** consists of the 240 patients returning between days 39 – 45 (42 ± 3 days) referred to in comment 3 below.

Comment #1:
The therapeutic cure should be based on mycological and clinical cure rate at week 6, and not on a mycological cure rate based on outcomes at week 4 and 6.

Taro's response:
In our previous submissions and approvals, our protocols have used the demanding definition of mycological cure, requiring culture and KOH results to be negative at both the 4 and 6 week visits. Using this definition the Taro product falls within the 90% confidence intervals of ± 20% (see Table 3).

When the 6 week data alone are used in evaluating the four populations described above, the results are summarized as follows:

- Using the **"full intention to treat (FITT) population"** (all randomized individuals, n=453) the therapeutic, clinical and mycological cure rates of the Taro product falls within the 90% confidence intervals of ± 20% (see Table 4).

- Using the **"modified intention to treat (MITT) population"** (all 252 eligible patients who were treated with either the Taro, the Ortho product or placebo, the clinical cure for the Taro product falls within the 90% confidence intervals of ± 20%. With respect to mycological and therapeutic cures, the Taro product is somewhat more effective than the reference, however, the difference is not statistically significant (see Tables 4 & 5).

- The **"original per protocol population"** consists of 247 patients who returned in the window period of days 42 – 49 for the 6-week visit. In this population, the clinical cure for the Taro product falls within 90% confidence intervals of ± 20%. With respect to mycological and therapeutic cures, the Taro product is somewhat more effective than the reference, however, the difference is not statistically significant (see Table 4 & 5).

- The **"modified per protocol population"** consists of the 240 patients returning between days 39 – 45 (42 ± 3 days). In this population, the clinical cure for the Taro product falls within the 90% confidence interval of ± 20%. With respect to mycological and therapeutic cures, the Taro product is somewhat more effective than the reference; however, the difference is not statistically significant (see Table 4 & 5).

Comment #2:
A modified intent to treat (MITT) population, omitting patients lost to follow-up after visit 1, was used for the comparison of the active treatment groups with the placebo arm.

Taro's Response:
For the therapeutic, clinical, and mycological cures, in every analysis of every population described above (including the MITT population, omitting patients lost to follow-up after visit 1), the Taro product and the reference product are significantly superior to the vehicle alone ($p < 0.01$) (See Table 5).

Comment #3:
The evaluable population was used for the comparison of test and reference groups in the determination of bioequivalence. Patients who did not return after visit 2 or were outside the visit window of ± 3 days for visit 3 were not included in this population.

Taro's Response:
Comment #3 appears to direct Taro to do a bioequivalence determination using the MITT population defined above. This analysis is part of the response to Comment #1 and can be found in Tables 3 & 4. We have used the definition of mycological cure based only on the six-week data. We have performed bioequivalence analyses in each of the above patient populations using this definition of mycological cure. There are four possible populations (FITT, MITT, original

per protocol and modified per protocol) and three endpoints for each population; therapeutic, clinical and mycological cure. In all 12 analyses, the Taro product either falls within the 90% confidence interval of ± 20% or is somewhat more effective than the reference (see Table 4), but is never statistically significantly different (see Table 5).

Comment #4:
The comparison between the active treatment arms and the vehicle (placebo) arm was done using the MITT population. The 90% confidence interval method is not the correct method for this analysis.

Taro's Response:
We acknowledge that we did not use the correct statistical test to determine whether the cure rates for active vs. placebo were significantly different from each other. Using the 2 one-sided continuity corrected Z test on the 252 patients in the MITT population, the Taro product and the reference product are each statistically significantly superior to vehicle ($p < 0.01$), for each definition of cure (see Table 5).

Comment #5:
The 90% confidence interval for the difference in therapeutic cure rate between the test and reference drug did not meet the bioequivalence criteria.

Taro's Response:
Taro's understanding is that one of the criterion for clinical bioequivalence studies of topical antifungal products is that the difference in response should be within ± 20% and that the 90% confidence interval will be ± 20%; however, if the test product appears to be better than the reference the upper limit of the 90% confidence interval may be >20%. There are four possible populations and three endpoints; therapeutic, clinical and mycological cure. In all 12 analyses, the Taro product either falls within 90% confidence interval of ± 20% or is somewhat more effective than the reference; but is never statistically significantly different.

It is our belief that these multiple analyses actually support the finding of safety, efficacy and bioequivalence. We also believe that the automatic application of the 90% confidence interval within 80-120%, without regard to the therapeutic implications or the underlying clinical results, will exclude safe and effective products from commerce in the United States. Taro's Econazole Nitrate topical product is a good example of a product being rejected solely on the basis of the automatic application of statistical criteria as described in the guidance without an adequate clinical or scientific rationale. In the final analysis, Taro's Econazole Nitrate Cream is a safe and effective product whose deficiency is a cure in more patients than that observed for the reference product.

Conclusion:
On the basis of a clinical bioequivalence study in 453 patients, we have concluded that the Taro product and the reference product are bioequivalent. In response to the Agency's deficiency letter, we have performed a thorough re-analysis of our data, described above. Taro and an independent statistical consultant reached the following conclusions:

- **The Taro product and the reference product are statistically significantly different from the placebo (Taro vehicle).**
- **Depending upon the statistical method used, the definition of cure, and the patient population selected, the Taro product either falls within a 90% confidence interval of ± 20% or is somewhat more effective than the reference. In no instance is there a statistically significant difference between the Taro product and the reference product.**
- **The Taro product is safe and effective for the labeled indications.**

Therefore, we are concerned about the Agency's deficiency letter and would request an opportunity to appeal the Agency's decision on the grounds of clinical and scientific rationale, as Taro's product is clearly a safe and effective topical antifungal product.

If there are any questions regarding this application, or if additional information is required, please contact me at (914) 345-9001 x 298.

Sincerely,

2/8/02

Kalpana Rao
Vice President, Regulatory Affairs, USA

January 25, 2002

TARO

Taro Pharmaceuticals U.S.A., Inc.

Gary Buehler, Director
Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Econazole Nitrate Cream, 1%
ANDA # 76-005
Gratuitous Amendment

NEW CORRESP
NC/FAX

Dear Gary:

Reference is made to our Abbreviated new Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Econazole Nitrate Cream, 1% dated October 10, 2000 and to the teleconference between yourself, Dr. Daniel Moros and me on January 23, 2002.

Many thanks for returning our call on January 23, 2002. We reflected on the Agency's issues with our clinical study supporting the above referenced ANDA. You brought several points to our attention. We have conducted an in depth review of all of our clinical data and performed additional statistical analyses based on your comments.

- Using the definition of mycological cure as defined in the protocol [culture and KOH negative at the four and six week visits] our product was bioequivalent to the reference-listed product. We have re-analyzed our data based only on the culture and KOH results at the six- week visit. Our product performed better than the Reference Listed Product but the difference is not significantly different; therefore, under this definition our product remains bioequivalent. Similarly, for therapeutic cure, our product performed better than the Reference listed product but again the difference is not significant. (See attached Table-1)
- In the re-analyses, we included only those patients returning between days 39-45 (i.e., 42 ±3 days). In this re-analysis, 240 of the original 247 patients qualified (see attached Table – 2).

For your consideration, we are attaching the results in tabular form. We believe that these results strongly support the bioequivalence of Taro's product with the Reference Listed Product. We hope to see the formal deficiency letter soon and we would like to request that you grant us a meeting to review the data together with the Agency.

If there are any questions regarding this application, or if additional information is required, please contact me at (914) 345-9001 x342.

Sincerely,

A. Yacobi

Avraham Yacobi, Ph.D.
President, Taro Research Institute

Cc: Krista Scardina

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 28 2002

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

December 6, 2001

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMEND
N/AF

Re: **Econazole Nitrate Cream, 1%**
ANDA # 76-005
Telephone Amendment – Final Printed Labeling

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on October 10, 2000 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Econazole Nitrate Cream, 1%. Reference is also made to a telephone call on December 6, 2001 between Lillie Golson of the Agency, and Kalpana Rao of Taro in which it was requested:

Comment 1:
Please provide 12 Final Printed Labels of the Package Insert for Econazole Nitrate Cream, 1%.

Response 1:
Attached please find 12 Final Printed Labels of the Package Insert for Econazole Nitrate Cream, 1%.

This concludes our response to the Agency's telephone call of December 6, 2001. If you have any questions or require additional information, please do not hesitate to contact the undersigned at (914) 345-9001 x298.

Sincerely,

Kalp
12/6/01
Kalpana Rao
Vice President, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 07 2001
OGD

Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 1-888-TARO-USA Fax: 914-345-8728 www.taro.com

October 2, 2001

DRUG ASSOCIATE
N/AB

TARO

Taro Pharmaceuticals U.S.A., Inc.

Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **Econazole Nitrate Cream, 1%**
ANDA # 76-005
Telephone Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on October 10, 2000 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Econazole Nitrate Cream, 1%. Reference is also made to September 26th, 2001 telephone conversation between Harvey Greenburg (RA Support Branch) and Helen Li (Statistician) of the Agency, and Kalpana Rao, Jackie Castaldo and Derek Ganes of Taro, as well as faxes dated September 24 and 26, 2001 in which the following was requested:

Comment 1:
The Add.data is a WordPerfect document and could not be opened.

Response 1:
We acknowledge this comment, however to our knowledge, we did not provide any WordPerfect documents and the diskette that is enclosed today will hopefully be able to open without difficulty.

Comment 2:
FDA only has SAS version 6.12 and could not open the Alldat.sas7dat that might be a SAS version 7 data. Please send either SAS version 6 transport file or version 6 SAS data.

Response 2:
The diskette enclosed has transport files "elig.xpt" and "inelig.xpt" in SAS version 6. File "elig.xpt" replaces "Alldat.sas7dat" and contains the data for eligible patients who had positive baseline cultures at screening. For completeness, we include file "inelig.xpt" which contains data for patients who had negative baseline cultures at screening.

Comment 3:
The Contents.txt is the text file and could be opened. However, several key variables are missing. The Valid code showed the subject belongs to Intent-to-treat population (ITT) or Protocol population (PP). The Exclusion reason showed the reason that the subject was excluded from the PP population. The AE and compliance information.

OCT 0 3 2001

EVALUATION RESEARCH

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Response 3:

We have added the requested key variables to the data set "elig", as shown in the "contents_eligible.lst" file, and summarized below:

Variable	Label
ITT	Included in Intent-to-Treat Population
PP	Included in Per Protocol Population
REASON	Reason Excluded from Per Protocol Population
AE	Drug Related Adverse Event
COMPLY	Assessment of Patient Compliance

Please note that there were no drug related adverse events for this study. We are enclosing the hard copies along with the diskettes to facilitate the review process.

Comment 4:

There is no CRF.xls file in the diskette as the sponsor mentioned in their file readme.txt.

Response 4:

We have confirmed that the diskette enclosed has the CRF.xls file. Please also find a hard copy the laboratory culture report form, which is not included in the CRF.xls file.

This concludes our response to the Agency's telephone call of September 26, 2001 and faxes of September 24 and 26, 2001. If you have any questions or require additional information, please do not hesitate to contact the undersigned at (914) 345-9001 x298.

Sincerely,

10/2/01

Kalpana Rao
Vice President, Regulatory Affairs