CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-329

CORRESPONDENCE

PERRIGO

March 15, 1999

1713

Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

BIOEQUIVALENCE TELEPHONE AMENDMENT

Faxed to Joseph Buccine @ 301-594-0180

Re: **Miconazole Nitrate Combination Pack - Cream 2%, Suppositories 200 mg ANDA 75-329**

Dear Mr. Sporn:

Reference is made to L. Perrigo Company ANDA 75-329 for Miconazole Nitrate Combination Pack - Cream 2%, Suppositories 200 mg. Further reference is made to the Bioequivalency comments dated March 13, 1999, in which a revision to the dissolution testing requirements is recommended.

We hereby amend this application to provide a Bioequivalence Telephone Amendment to address the following comment. The original amendment is being submitted to the ANDA in addition to a fax copy.

The dissolution testing for the suppository 200 mg will need to be incorporated into your manufacturing controls and stability program.

> *The dissolution testing should be conducted in 900 mL of 0.45% SLS using USP 23 Apparatus 1 at 100 rpm at 40C. The test products should meet the following specifications: Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.*

The recommendation differs from the currently proposed dissolution conditions only in the value of (Q). We have therefore revised the Finished Product Specification and the Stability Specification for the miconazole nitrate suppository, 200 mg, to adopt the "Not less thar [redacted] ' limit. Copies of both revised specifications are enclosed.

As required by 21 CFR 314.94(d)(5), the Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit district office. Perrigo certifies that the amendment contained in the "field copy" is a true copy of the amendment which was submitted to the FDA headquarters.

RECEIVED
MAR 16 1999
GENERIC DRUGS

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

We trust that this amendment now provides all necessary information for the tentative approval of this ANDA. Should you require additional information, please contact me directly by telephone at 616-673-9745, by fax at 616-673-7655, or at the address on this letterhead.

Sincerely,

Brian R. Schuster
Manager, ANDA Submissions
Regulatory Affairs

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-329 APPLICANT: L. Perrigo

DRUG PRODUCT: Miconazole Combination Pack
Cream 2%, Suppositories 200 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing for the suppository 200 mg will need to be incorporated into your manufacturing controls and stability program.

> The dissolution testing should be conducted in 900 mL of 0.45% SLS using USP 23 Apparatus 1 at 100 rpm at 40° C. The test products should meet the following specifications: Not less than of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-329 APPLICANT: L. Perrigo

DRUG PRODUCT: Miconazole Combination Pack
Cream 2%, Suppositories 200 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

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> The dissolution testing should be conducted in 900 mL of 0.45% SLS using USP 23 Apparatus 1 at 100 rpm at 40° C. The test products should meet the following specifications: Not less than ... of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

PERRIGO®

February 26, 1999

Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

BIOEQUIVALENCE
TELEPHONE AMENDMENT

Faxed to Elaine Huie @ 301-594-0181

Re: Miconazole Nitrate Combination Pack – Cream 2%, Suppositories 200 mg
ANDA 75-329

Dear Mr. Sporn:

Reference is made to L. Perrigo Company ANDA 75-329 for Miconazole Nitrate Combination Pack – Cream 2%, Suppositories 200 mg. Further reference is made to two previous Amendments filed on January 12, 1999, for bioequivalence and chemistry issues, to the comments received from the Office of Generic Drugs dated December 14, 1998, and to the Telephone Amendment of February 19, 1999. Additional reference is made to the subsequent telephone conversation with Ms. Elaine Huie on February 22, 1999.

We hereby amend this application to provide a Bioequivalence Telephone Amendment to address the comments provided in the February 22, 1999, telephone contact. The original amendment is being submitted to the ANDA in addition to a fax copy.

-Division of Bioequivalence Comments:

Ms. Elaine Huie called on February 22, 1999 to request the following additional data related to the proposed dissolution test procedure submitted to FDA on February 19, 1999:

1. Multipoint dissolution test results for two unexpired lots of Perrigo product.

2. Multipoint dissolution test results for two unexpired lots of the reference drug.

-Response:

Enclosed with this amendment are the following attachments:

Attachment 1 – Special Assay Report Number 13826 – Multipoint Dissolution Testing of 3 Day Miconazole Nitrate Suppositories. This report contains the results of multipoint dissolution testing of two unexpired lots of Perrigo product, Lot #9A3155V, Exp. 2/01 and Lot #9B1086V, Exp. 2/01. These are the same lots of Perrigo product referenced on Page 9 of the February 19, 1999, amendment.

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Attachment 2 – Special Assay Report Number 13828 – Multipoint Dissolution Testing of 3 Day Miconazole Nitrate Suppositories. This report contains the results of multipoint dissolution testing of two unexpired lots of the Monistat product, Lot #27K862, Exp. 8/00 and Lot #28L410, Exp. 10/01.

Attachment 3 – Special Assay Report Number 13801 – Multipoint Dissolution Testing of 3 Day Miconazole Nitrate Suppositories. This report contains the results of multipoint dissolution testing of the test and reference drug lots used in the bioequivalence study Perrigo product, Lot #5M0520, Exp. 12/97, and Monistat product, Lot #15A156, Exp. 1/98. This report was submitted previously with the 2/19/99 Amendment on Page 7 as Attachment 2 – included here to facilitate easy review.

Attachment 4 – Multipoint Dissolution Testing Comparative Graph – graphic representation of the multipoint dissolution testing data for all six lots tested. The test results for each of the three lots of the Perrigo product and the two unexpired lots of the Monistat product demonstrate a comparable dissolution profile. The proposed dissolution test specification is met by all of the lots presented in the graph.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment which was submitted to the FDA headquarters.

We trust that this amendment now provides all necessary information for the tentative approval of this ANDA. However, should additional information be required, please contact me directly by telephone at 616-673-9745 or by fax at 616-673-7655.

Sincerely,

Brian Schuster

Brian R. Schuster
Manager, ANDA Submissions
Regulatory Affairs

Enc.

PERRIGO®

February 19, 1999

Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

BIOEQUIVALENCE
TELEPHONE AMENDMENT

Faxed to Elaine Huie @ 301-594-0181

Re: Miconazole Nitrate Combination Pack – Cream 2%, Suppositories 200 mg
ANDA 75-329

Dear Mr. Sporn:

Reference is made to L. Perrigo Company ANDA 75-329 for Miconazole Nitrate Combination Pack – Cream 2%, Suppositories 200 mg. Further reference is made to two previous Amendments filed on January 12, 1999, for bioequivalence and chemistry issues, and to the comments received from the Office of Generic Drugs dated December 14, 1998, providing bioequivalency deficiencies. Additional reference is made to the subsequent telephone conversations with Ms. Elaine Hule the week of February 12, 1999.

We hereby amend this application to provide a Bioequivalence Telephone Amendment to address the comments in the December 14, 1998 letter. The original amendment is being submitted to the ANDA in addition to a fax copy.

Comments Received from the Division of Bioequivalence:

"Your proposal of using a disintegration test for Miconazole Nitrate suppository is not acceptable. The Division of Bioequivalence has the following recommendations:

1. There is no standard dissolution method currently available, therefore, you are advised to use various solvent systems and generate the acceptable dissolution profile.

2. The pH of the rectal fluid is with low buffer capacity so phosphate buffer may be a good starting point as a dissolution medium.

3. The Division of Bioequivalence recommends use of surfactants at low concentrations in cases where the drug substance shows low aqueous solubility. You are advised to add some surfactants to the dissolution medium such as SLS, Tween 80, Triton x-100 or CTAP (Hexadecyl trimethyl ammonium bromide) at 1-2%."

117 Water Street
Allegan, Michigan 49010
(616) 673-8451

Response:

The discussions with Elaine Huie of the Division of Bioequivalence during the week of February 12 provided information that enabled our laboratory to develop a dissolution test procedure and proposed dissolution specification for the Miconazole Nitrate suppositories. We have performed tests on several batches of Perrigo product, including the bioequivalence batch, as well as the reference drug. The multipoint dissolution test results indicate excellent comparability between the test and reference product with the proposed specification.

Enclosed with this amendment are the following attachments to document the establishment of a new dissolution test for Miconazole Nitrate Suppositories, 200 mg:

Attachment 1 – Analytical Method and Validation (Dissolution Testing for 200 mg Miconazole Nitrate Suppositories, Procedure No. 1584, and Special Assay Report 13802)
The method specifies the procedure for analysis of the dissolution test samples. Note that procedure 1584 specifies the same analytical column, the same mobile phase, and the same chromatographic conditions as procedure 1406 which is proposed for the assay of Miconazole Nitrate. Validation of the procedure for the analysis of Miconazole Nitrate, Procedure 1406, was submitted with the original application on page 512. A standard recovery analysis was performed using Procedure 1584 to demonstrate linearity with the dissolution media. The validation of the related method 1406 with the additional enclosed linearity document provides documentation for the validation of Procedure 1584.

Attachment 2 – Comparative dissolution analysis of L. Perrigo Miconazole Nitrate suppositories, 200 mg, and the reference listed drug for this ANDA, Advanced Care Products' Monistat® 3 suppositories, is enclosed in Special Assay Report 13801 (Multipoint Dissolution Testing of 3 Day Miconazole Nitrate Suppositories). Also enclosed is a graph of this dissolution data for these batches which were used in the bioequivalence study. Since both the test and reference batches have expired, we undertook testing of additional batches and this data is documented in Special Assay Report 13809.

Attachment 3 – Revised Finished Product Specification – (Miconazole Nitrate Suppositories, 200 mg, Specification No. 06)
The finished product specification has been revised to add the dissolution test and the limits. Please note that the previously proposed test for disintegration has been replaced with the dissolution test.

Attachment 4 – Revised Stability Specification – (Miconazole Nitrate Vaginal Suppositories – 200 mg, Specification No. 04)
The stability specification has been revised to add the dissolution test and the limits. Please note that the previously proposed test for disintegration has been replaced with the dissolution test.

Our preliminary investigations indicate that the proposed dissolution test may be very sensitive to morphological changes induced by the melting, separation, and resolidification of the components of the suppositories stressed under 40°C/75%RH accelerated stability conditions. The Miconazole Nitrate Suppositories, 200 mg, component of the drug product has a melting point below 40°C. The combination pack

product is labeled for storage below 30°C. Stability data submitted in the application indicates no significant changes in morphology, potency or impurities when stored below 30°C. Our investigation further indicates that the potential morphological changes which occur as a result of 40°C storage may result in a significantly decreased dissolution rate of the suppositories. Therefore, Perrigo proposes batches intended for accelerated stability testing will have samples placed at 30°C/60% RH for the purposes of dissolution testing only and additional samples placed at 40°C will be used for all other stability testing. The test results enclosed in Attachment 2 demonstrate that the bioequivalence batch meets the proposed dissolution requirements after being stored at 25°C±2°C for 36 months. This supports the proposed 24 month expiration date.

Accelerated stability testing required to conform to the proposed stability protocol (three months at 40°C/75RH) will be conducted on the first marketed batch following ANDA approval. However, for the dissolution test, 6 months of data will be collected from samples stored at 30°C/60% RH and submitted in the annual report. This is in conformance with the proposed requirements for long term/accelerated testing conditions in the draft Guidance on Stability Testing of Drug Substances and Drug Products, dated June, 1998. Post-approval changes requiring accelerated stability testing will also conform to the conditions described herein as regards dissolution testing of the suppository.

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit District Office. L. Perrigo Company certifies that the amendment contained in the "Field Copy" is a true copy of the amendment which was submitted to the FDA headquarters.

We trust that this amendment now provides all necessary information for the tentative approval of this ANDA. However, should additional information be required, please contact me directly by telephone at 616-673-9745 or by fax at 616-673-7655.

Sincerely,

Brian R. Schuster
Manager, ANDA Submissions
Regulatory Affairs

Enc.

PERRIGO

BIOAVAILABILITY

January 12, 1999

Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

BIOEQUIVALENCE
FACSIMILE AMENDMENT

ORIG AMENDMENT
N/AB

Faxed to Joseph Buccine @ 301-594-0180

Re: **Miconazole Nitrate Combination Pack - Cream 2%, Suppositories 200 mg**
ANDA 75-329

Dear Mr. Sporn:

Reference is made to L. Perrigo Company ANDA 75-329 for Miconazole Nitrate Combination Pack - Cream 2%, Suppositories 200 mg. Further reference is made to the comments received from the Office of Generic Drugs dated December 14, 1998, providing bioequivalency deficiencies, and to the telephone conversation with Mr. Joseph Buccine regarding this amendment on December 18, 1998.

We hereby amend this application to provide a Bioequivalence Facsimile Amendment to address the comments in the December 14, 1998, letter. The original amendment is being submitted to the ANDA in addition to a fax copy.

Comments Received from the Division of Bioequivalence:

> "Your proposal of using a disintegration test for Miconazole Nitrate suppository is not acceptable. The Division of Bioequivalence has the following recommendations:
>
> 1. There is no standard dissolution method currently available, therefore, you are advised to use various solvent systems and generate the acceptable dissolution profile.
>
> 2. The pH of the rectal fluid is ıth low buffer capacity so phosphate buffer ' may be a good starting point as a dissolution medium.
>
> 3. The Division of Bioequivalence recommends use of surfactants at low concentrations in cases where the drug substance shows low aqueous solubility. You are advised to add some surfactants to the dissolution medium such as SLS, Tween 80, Triton x-100 or CTAP (Hexadecyl trimethyl ammonium bromide) at 1-2%."

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JAN 13 1999

117 Water Street
Allegan, Michigan 49010
(616)673-8451

Response:

Both FDA and Perrigo concur that there is no standard methodology or instrumentation currently available to perform a dissolution profile on this drug product. The testing which will be required to establish and validate an appropriate dissolution procedure and specification is expected to require significant research over several months. The comments provided by the Division of Bioequivalence on the use of surfactants will be helpful and will be the starting point for new investigations. In order to avoid unnecessary delay in the tentative and final approval of this ANDA, we propose that the Division of Bioequivalence accept the commitment contained in this amendment to establish the dissolution test on the suppositories following application approval. Our discussion with Mr. Joseph Buccine on December 18, 1998, indicated that the chemistry review division would find such a commitment to be acceptable. This would be consistent with the manner in which our related ANDA 74-395 was approved (Miconazole Nitrate Suppositories, 100 mg). A commitment to attempt to establish a dissolution test post-approval was also provided just prior to final approval of that ANDA.

We are in the process of acquiring the instrumentation needed to perform the analysis and expect to be in a position to begin the development work in the near future. The L. Perrigo Company hereby commits to providing a supplement for Changes Being Effected to add a new test and specification for dissolution of the suppository in this ANDA and to work with the Agency to ensure that an acceptable method is adopted. In the event that this test has not been established at the time of the first annual report, information on the progress made in the period will be included in the report.

Following the approval of the supplement to add the dissolution test to ANDA 75-329, we further commit to provide a similar supplement for Changes Being Effected to approved ANDA 74-395 (Miconazole Nitrate Suppositories, 100 mg) to add a new test and specification for dissolution of the suppository.

These commitments will provide consistency in the test requirements for these two related products. We believe this to be a reasonable approach that will not unnecessarily delay the tentative and final approval of ANDA 75-329.

As required by 21 CFR 314.94(d)(5), the Perrigo Company has provided a true copy of this amendment (including a copy of the 356h form) to the Detroit district office. Perrigo certifies that the amendment contained in the "field copy" is a true copy of the amendment which was submitted to the FDA headquarters.

We trust that this amendment now provides all necessary information for the tentative approval of this ANDA. Should you require additional information, please contact me directly by telephone at 616-673-9745, by fax at 616-673-7655, or at the address on this letterhead.

Sincerely,

Brian R. Schuster
Manager, ANDA Submissions
Regulatory Affairs

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BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 75-329 APPLICANT: L. Perrigo

DRUG PRODUCT: Miconazole Nitrate Combination Pack

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. Your proposal of using a disintegration test for Miconazole Nitrate suppository is not acceptable. The Division of Bioequivalence has following recommendations:

1. There is no standard dissolution method currently available, therefore, you are advised to use various solvent systems and generate the acceptable dissolution profile.

2. The pH of the rectal fluid is 7.2 with low buffer capacity so phosphate buffer (pH 7.2) may be a good starting point as a dissolution medium.

3. The Division of Bioequivalence recommends use of surfactants at low concentrations in cases where the drug substance shows low aqueous solubility. You are advised to add some surfactants to the dissolution medium such as SLS, Tween 80, Triton x-100 or CTAP (Hexadecyl trimethyl ammonium bromide) at 1-2%.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-329 APPLICANT: L. Perrigo

DRUG PRODUCT: Miconazole Combination Pack
Cream 2%, Suppositories 200 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-329 APPLICANT: L. Perrigo

DRUG PRODUCT: Miconazole Combination Pack
Cream 2%, Suppositories 200 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-003

L. Perrigo Company
Attention: Lisa Gould McNeil
117 Water Street
Allegan, MI 49010

Dear Madam:

We acknowledge the receipt of your communication dated January 30, 1998, requesting withdrawal of your abbreviated new drug application for Miconazole Nitrate Vaginal Suppositories USP, 200 mg.

In compliance with your request and in accordance with Section 314.65 of the regulations under the Federal Food, Drug and Cosmetic Act, the application is regarded as withdrawn. This withdrawal does not prejudice any future filing of the application. You may request that the information in this application be considered in connection with any resubmission.

Sincerely yours,

Mark Anderson for / 2/5/98

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