CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-232

CORRESPONDENCE

PERRIGO

November 18, 1999

FAX AMENDMENT

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

NEW CORRESP
NC

RE: ANDA 75-232
Loperamide Hydrochloride Tablets USP, 2 mg
Fax Amendment

Dear Sir or Madam:

This fax amendment is in response to the Agency's communication dated November 16, 1999 regarding the L. Perrigo Company's Loperamide Hydrochloride Tablets, 2mg application.

We hereby amend ANDA 75-232 to address the comments delivered in the November 16, 1999 communication.

Chemistry Deficiencies:

If you have any questions or need any additional information, please feel free to contact me by telephone at (616) 686-1749, by FAX at (616) 673-7655, or by email at candrews@perrigo.com.

Respectfully submitted,

Carrie Andrews
Regulatory Affairs

xc: B. Schuster

PERRIGO

December 30, 1999 **TELEPHONE AMENDMENT**

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

RE: ANDA 75-232
Loperamide Hydrochloride Tablets USP, 2 mg
Telephone Amendment

Dear Sir or Madam:

This telephone amendment is in response to the Agency's communication on December 20, 1999 between Kassandra Sherrod and Dr. Rabhika Rajagopalan from the Agency and Carrie Andrews from the L. Perrigo Company regarding the company's Loperamide Hydrochloride Tablets USP, 2mg application.

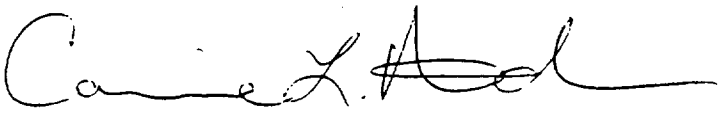
We hereby amend ANDA 75-232 to address the comments delivered in the December 20, 1999 telephone communication.

Chemistry Deficiencies:

As required by 21 CFR 314.94(d)(5), the L. Perrigo Company certifies that a "field copy, which is a true copy of this Fax Amendment submitted to the FDA headquarters, has been submitted to the Detroit District Field Office.

If you have any questions or need any additional information, please feel free to contact me by telephone at (616) 686-1749, by FAX at (616) 673-7655, or by email at candrews@perrigo.com.

Respectfully submitted,



Carrie Andrews
Regulatory Affairs

xc: B. Schuster

Chemistry Comments to be provided to the Applicant:

ANDA: 75-232 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Loperamide Hydrochoride Tablets USP, 2 mg

The deficiencies presented below represent FAX deficiencies.

Deficiencies

1. For method please propose a run time as well as establish system suitability parameters. The loperamide-N-oxide and lopearamide peaks elute very close to each other. A resolution factor is recommended for method

2. We notice your response regarding levels reaching by 3 months under accelerated conditions. The total impurities can remain at during shelf life. However, we request that you lower the levels to

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

PERRIGO

noted
pm 9/30/99

September 23, 1999

MINOR AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
MPN II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N1 pm

Re: Loperamide Hydrochloride Tablets USP (small caplets), 2 mg
ANDA 75-232 Minor Amendment

Dear Mr. Sporn:

Reference is made to ANDA 75-232, Loperamide Hydrochloride Tablets USP (small caplets), 2 mg, filed on February 23, 1998, and to subsequent communication regarding this ANDA as follows:

- FDA's fax dated June 9, 1998, containing comments from the Division of Bioequivalence
- L. Perrigo's response dated July 9, 1998
- FDA's "not approvable" fax dated September 29, 1998, containing comments from the Division of Chemistry and Division of Labeling
- L. Perrigo's response dated January 14, 1999,
- FDA's faxed communication dated July 16, 1999.

We hereby amend this application in accordance with 21 CFR 314.120 to provide the additional information requested in the July 16, 1999, faxed correspondence. This is a minor amendment as indicated in the FDA Fax.

Chemistry Comments:

1 The proposed blend uniformity acceptance criteria are not acceptable. We

Page(s) 1

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

9/23/99

Bioequivalence Comments:

1. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP Section 23.

Response:

Dissolution testing has been incorporated into the stability and quality control programs as noted in the original submission.

In accordance with 21 CFR 314.50, I certify that a field copy, which is a true copy of this amendment, has been mailed to the Detroit District FDA Office.

Should you require additional information, please contact me directly by telephone at 616-673-9367, by fax at 616-673-7655, or at the address on this letterhead.

Sincerely,

Valerie Gallagher
ANDA Regulatory Affairs Administrator

cc: Brian Schuster

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September 23, 1999

Mr. John Dempster
Director, Compliance Branch
Food and Drug Administration
1560 Jefferson Avenue
Detroit, MI 48207

Re: Loperamide Hydrochloride Tablets USP (small caplets), 2 mg
ANDA 75-232 Minor Amendment

Dear Mr. Dempster:

The Perrigo Company has submitted a Minor Amendment dated September 23, 1999, to the Abbreviated New Drug Application 75-232 for Loperamide Hydrochloride Tablets USP (small caplets), 2 mg.

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

Sincerely,

Valerie Gallagher
ANDA Regulatory Affairs Administrator

Cc: G. Boerner
B. Schuster

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

JUL 16 1999

Chemistry Comments to be provided to the Applicant:

ANDA: 75-232 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Loperamide Hydrochoride Tablets USP, 2 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies

1. The proposed blend uniformity acceptance criteria are not acceptable. We recommend a Mean value of with a % RSD Please revise your in-process specifications.

2. We recommend lowering the Total impurities to NMT during shelf life of the product. We request that you report impurities during release and stability as known and unknown impurities and identify them by their retention times or relative retention times. We recommend that the known and unknown impurities be at NMT and respectively during release.

3. We request that you identify the single largest impurity present at (pages 22 and 24 of the amendment).

Sincerely yours,

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-232 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Loperamide Hydrochloride Tablets (small caplets), 2 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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, 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: 75-232 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Loperamide Hydrochloride Tablets (small caplets), 2 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

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BIOAVAILABILITY

ORIG AMENDMENT

N/A

July 9, 1998

Office of Generic Drugs
CDER, FDA
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773
Attention: Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

RE: ANDA 75-232
Loperamide HydrochlorideTablets (small caplets), 2mg
Bioequivalency Amendment

Dear Dr. Conner:

The L. Perrigo Company is submitting this amendment in response to your faxed communication dated June 9, 1998, a copy of which is enclosed. In that fax, the Agency commented on the bioequivalence portion of L. Perrigo Company's ANDA 75-232, Loperamide Hydrochloride Tablets, 2 mg. Attached, in a letter to Perrigo, are responses for comments 1 through 4 and supporting documents from Phoenix International Life Sciences, Inc., the Contract Research Laboratory that performed the bioequivalence study (Protocol #941785) for this ANDA submission. Also included are Perrigo Special Assay reports 12007a & 12009a, which address comment number 5. Please see the attached index and documents for specific information responding to the Agency's comments.

In accordance with 21 CFR 314.96 (b), I certify that a field copy, which is a true copy of this Bioequivalency Amendment, has been provided to the Detroit District Field Office.

Should you require additional information, please contact me directly by telephone at 616-673-9182, by FAX at 616-673-7655, by e-mail at lmcneil@perrigo.com, or at the address on this letterhead.

Respectfully submitted,

Lisa Gould McNeil
Regulatory Affairs

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RECEIVED
GENERIC DRUGS
GENERIC DRUGS

JUN 9 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-232 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Loperamide Hydrochloride Tablets (small caplets) 2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have stated that the original validated method was modified for mode of detection, reconstitution volume, and concentration of internal standard. Since the method was modified, you reassessed within and between batch precision and accuracy, internal standard recovery, specificity and sensitivity of the assay. The submitted supporting data are from the curves GYX33, GYX34, GYX42, GYX50, and GYX57. However, three curves (GYX42, GYX50, and GYX57) are from study sample analyses and are not separate method validation curves. Please Comment.

2. When was the analytical method modified? Before this study or during the study? Were all the study samples assayed using the modified method? If the method was modified before this study, why was it not revalidated before analyzing the study samples?

3. Please submit the validation results of original method.

4. Please state the differences in the mode of detection, reconstitution volume, and concentration of internal standard used in original and modified method. Also, submit

5. Dissolution: Please provide %CV at each sampling time.

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 75-232

APR 02 1998

L. Perrigo Company
Attention: Brian R. Schuster
117 Water Street
Allegan, MI 49010

Dear Sir:

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

Reference is also made to the telephone conversation dated March 6, 1998 and your correspondence dated March 6, 1998.

NAME OF DRUG: Loperamide Hydrochloride Tablets, 2 mg

DATE OF APPLICATION: February 23, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 2, 1998

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:

Kassandra Sherrod
Project Manager
(301) 827-5848

Sincerely yours,

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

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BIOAVAILABILITY

NEW CORRESP

March 6, 1998

Attn: Peter Rickman
FDA, CDER, OPS, Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Abbreviated New Drug Application
Loperamide Hydrochloride Tablets, 2 mg
ANDA 75-232

Dear Mr. Rickman:

In response to your recent phone call concerning the absence of the bioequivalence data sets we are sending that data. Enclosed is a diskette with the data sets from protocol 941785.

If you any questions please feel free to contact me at (616) 673-1404, CBraun@perrigo.com or by fax at (616) 673-7655.

Respectfully submitted,

Chad S. Braun
Regulatory Affairs Administrator

RECEIVED

MAR 0 9 1998

GENERIC DRUGS

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

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-232 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Loperamide Hydrochoride Tablets USP, 2 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies

1. Please verify that there are no other components present in the solution. Is it considered to be clear solution?

2. Your manufacturing process fails to identify the mixing equipment speed in RPM. Please provide and/or justify its ommission from your blank batch records.

3. The total percentage of loperamide hydrocholoride is well of the total components found in your proposed formulation. It is recommended that a blend uniformity analysis be established as an in-process control for all post-approval product batches.

4. The limit which will be observed in your long term room temperature stability studies is not specified in your stability protocol. Please revise and resubmit your stability to include a relative humidity regulatory limit.

5. An individual tablet weight regulatory range should be provided based on the data obtained for the bio batch. In addition, a coating tablet weight gain regulatory range should be also included. Please incorporate the requested analyses as in-process controls.

6. The proposed individual and total impurities release and stability specifications are considered to be too broad. Please revise according to the data obtained for the demonstration batch.

   It is recommended that you justify the individual and total unknown impurities specifications. A comparative impurity profile vs. the RLD should be submitted and include representative chromatograms for the subject study. Were reasonable efforts made to identify individual impurities found in your finished drug product?

7. We noted that your test method uses the peak height to calculate the activity of your finished drug product. We recommend that area units (AU) be used for such purpose instead of the peak height. Please revise your test method calculation formula.

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

is currently under review. If deficiencies are found, these will be directly conveyed to the holder and should be answered satisfactorily before the application can be approved.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 9 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-232 APPLICANT: L. Perrigo Company

DRUG PRODUCT: Loperamide Hydrochloride Tablets (small caplets)
2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have stated that the original validated method was modified for mode of detection, reconstitution volume, and concentration of internal standard. Since the method was modified, you reassessed within and between batch precision and accuracy, internal standard recovery, specificity and sensitivity of the assay. The submitted supporting data are from the curves GYX33, GYX34, GYX42, GYX50, and GYX57. However, three curves (GYX42, GYX50, and GYX57) are from study sample analyses and are not separate method validation curves. Please Comment.

2. When was the analytical method modified? Before this study or during the study? Were all the study samples assayed using the modified method? If the method was modified before this study, why was it not revalidated before analyzing the study samples?

3. Please submit the validation results of original method.

4. Please state the differences in the mode of detection, reconstitution volume, and concentration of internal standard used in original and modified method. Also, submit

5. Dissolution: Please provide %CV at each sampling time.

Sincerely yours,

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

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505(j) 11-7(a) acceptable for filing DA 3/10/98

February 23, 1998

Mr. Douglas Sporn, Director
FDA, CDER, OPS, Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Abbreviated New Drug Application
Loperamide Hydrochloride Tablets, 2 mg

Dear Mr. Sporn:

The L. Perrigo Company is submitting for your review and approval, an ANDA for **Loperamide Hydrochloride Tablets, 2 mg** pursuant to 505(j) of the Federal Food, Drug, and Cosmetic Act. L. Perrigo's **Loperamide Hydrochloride Tablets, 2 mg** is identical in strength, indications, active ingredient, route of administration and dosage form to McNeil's Imodium® A-D product.

Imodium® A-D (NDA 19-860) is listed in the Seventeenth Edition of Approved Drug Products with Therapeutic Equivalence Evaluations as an over-the-counter drug with no patent protection or market exclusivity.

L. Perrigo has an approved ANDA 74-194 for this reference drug, however, this new ANDA is being filed in response to a formulation change by the referenced listed drug to a small caplet form. The new formulation is being filed as a new ANDA application in response to the Policy and Procedure Guide 20-90 dated 5/25/90. The guide states that each application is limited to a common formulation and a separate ANDA is required if a separate bioequivalence study is required due to formulation.

A paragraph I patent certification is enclosed in Section 3. Bioequivalence studies conducted under fasted conditions, sponsored by L. Perrigo, are also included in this ANDA.

Attached is an additional copy of this cover letter. Please stamp the date of receipt on it and return it to me in the attached self-addressed stamped envelope.

Should you require additional information, please contact me directly by telephone at (616) 673-9745, by FAX at (616) 673-7655 or the address on this letterhead.

Respectfully submitted,

Brian R. Schuster

Brian R. Schuster
Regulatory Affairs Manager

RECEIVED
MAR 0 2 1998
GENERIC DRUGS

[illegible] Street
Allegan, Michigan 49010
(616) 673-8451

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-232 SPONSOR: L. Perrigo Company
DRUG: Loperamide Hydrochloride Tablet (small caplet)
DOSAGE FORM: small caplet
STRENGTHS/(s): 2 mg
TYPE OF STUDY: Single Dose, Fasting
STUDY SITE: Phoenix International

STUDY SUMMARY: The 90% confidence intervals for loperamide and desmethylloperamide log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits. The fasting study is acceptable.

DISSOLUTION: The dissolution testing was done by USP method: 900 mL of 0.1N HCl using apparatus 2 (paddles) at 50 rpm. The test product dissolves more than n 30 minutes and meets USP specifications.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: KDhariwal DATE 9/29/98

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: [signature] DATE 10/1/1998

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: DPC DATE 10/27/98

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____
