

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40-300

CORRESPONDENCE

MALLINCKRODT

Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

TELEPHONE AMENDMENT

November 24, 1998

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**RE: ANDA 40-300: Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)**

Dear Sir:

The following information is provided in response to a November 23, 1998 telephone conversation with Ray Brown of the Agency requesting the data associated with the in-process content uniformity testing for Master Blend lot MHSC9718. This lot was then used to manufacture Methylphenidate Hydrochloride Tablets, USP exhibit lots MHSC9719 (5 mg), MHSC9720 (10 mg) and MHSC9721 (20 mg).

Step 8b. of the manufacturing instructions for the Methylphenidate HCl Master Blend (page 2412 of the original application) states that ten test samples as well as the normal composite sample for assay are submitted to Quality Control for testing.

Attached are the data for the blending validation assay report for the ten individual samples. The average for the ten individual samples is active in the blend. The specification for the active in the blend is

In addition, a copy of the results of the composite assay as provided on page 2441 of the original application are provided.

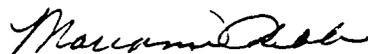
RECEIVED

NOV 25 1998

GENERIC DRUGS

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

A handwritten signature in cursive script that reads "Marianne Robb".

Marianne Robb
Manager, Regulatory Affairs
(314) 654-6258
Fax (314) 654-6496

TELEPHONE AMENDMENT

October 23, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

hm

**RE: ANDA 40-300: Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)**

Dear Sir:

The following information is provided in response to an October 22, 1998 telephone conversation with Ray Brown of the Agency concerning the use of the terms, bisect or score, in documentation for the 5 mg, 10 mg, and 20 mg Methylphenidate Hydrochloride Tablets, USP.

For the purposes of the above referenced application the terms, bisect or score, are used interchangeably for labeling and manufacturing documentation. Labeling will continue to use the term "scored" to be consistent with the labeling of the reference listed drug.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

Marianne Robb
Marianne Robb
Manager, Regulatory Affairs
(314) 654-6258
Fax (314) 654-6496

RECEIVED

OCT 26 1998

GENERIC DRUGS

MALLINCKRODT

*noted KF
9/15/98*

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

**MINOR AMENDMENT
ADDITIONAL INFORMATION**

September 9, 1998

ANDA ORIG AMENDMENT

N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**RE: ANDA 40-300: Methylphenidate Hydrochloride Tablets USP
(5 mg, 10 mg, and 20 mg)**

Dear Madame or Sir:

The following information is provided in response to Comment #5 of a July 20, 1998 facsimile from the Agency for the above referenced application. Drug Master File /as revised on September 4, 1998 in response to an August 19, 1998 deficiency letter. For ease of review a copy of the deficiency response is provided.

On February 27, 1998, pursuant to Section 505(j) of the Food Drug and Cosmetic Act, Mallinckrodt Inc. submitted an abbreviated new drug application (ANDA) seeking approval to market Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg). Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg) are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability at the Hobart facilities. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

This amendment consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

RECEIVED

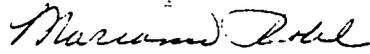
SEP 10 1998

GENERIC DRUGS

*86-51-b
9-15-98*

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

A handwritten signature in cursive script that reads "Marianne Robb".

Marianne Robb
Manager, Regulatory Affairs
(314) 654-6258
Fax (314) 654-6496

MALLINCKRODT

Improving Healthcare and Chemistry

*noted
plus 9/4/98*

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

MINOR AMENDMENT

August 18, 1998

NDA ORIG AMENDMENT

N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**RE: ANDA 40-300: Methylphenidate Hydrochloride Tablets USP
(5 mg, 10 mg, and 20 mg)**

Dear Madame or Sir:

The attached information is provided in response to a July 20, 1998 facsimile from the Agency to the above referenced file. For ease of review your comments have been repeated.

On February 27, 1998, pursuant to Section 505(j) of the Food Drug and Cosmetic Act, Mallinckrodt Inc. submitted an abbreviated new drug application (ANDA) seeking approval to market Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg). Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg) are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability at the Hobart facilities. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

This amendment consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. In addition, twelve copies of final printed labeling are provided in a separate blue folder labeled, "Final Printed Labeling".

SEP 19 1998

*Madame
9.21-90*

Correspondence related to this submission should be addressed to Marianne Robb,
Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions
concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

A handwritten signature in cursive script, appearing to read "Marianne Robb".

Marianne Robb
Manager, Regulatory Affairs
(314) 654-6258
Fax (314) 654-6496

JUL 20 1998

38. Chemistry comments to be Provided to the Applicant

ANDA: 40-300

APPLICANT: Mallinckrodt Inc.

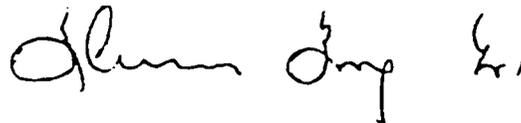
DRUG PRODUCT: Methylphenidate Hydrochloride Tablets USP,
5 mg, 10 mg and 20 mg.

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Your in-process control of Methylphenidate HCl blend of _____ is not correct (p 2388). Please make the necessary correction and resubmit.
2. Please submit certificates of analysis for the 5 mg, 10 mg and 20 mg tablets, executed batch records MHSC9719, MHSC9720 and MHSC9721 respectively.
3. Your stability report sheet(s) should be revised to identify the test specifications along with the test results. Please report all dissolution results.
4. Your reprocessing statement should be revised to describe the reprocessing procedure in accordance with 21 CFR 314.70(b)(2)(x).
5. Drug Master File _____ is currently deficient and the DMF holder has been advised of the deficiencies. A satisfactory resolution of the DMF deficiencies is required by the holder prior to the approval of the application.
6. You have identified Drug Master File _____ as a packaging component manufacturer of the colorant (page 2779). This is incorrect. Please identify the correct number for this DMF and resubmit.

Sincerely yours,



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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-300

APPLICANT: Mallinckrodt

DRUG PRODUCT: Methylphenidate Hydrochloride 5, 10, 20 mg Tablets

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

MALLINCKRODT

Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

TELEPHONE AMENDMENT - BIOEQUIVALENCE

June 8, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA ORG AMENDMENT

N/AB

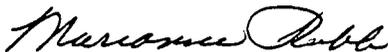
**RE: ANDA 40-300: Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)**

Dear Madame or Sir:

Full chromatograms for Subjects 2, 3, 4, 5, 26, 27, 28, and 29 for Study #97204 and for Subjects 2, 9, 10, 15 and 16 for Study #97247 are provided in response to a June 2 telephone request from Nancy Chamberlin of the Division of Bioequivalence.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,



Marianne Robb
Manager, Regulatory Affairs
(314) 654-6258
Fax (314) 654-6496

RECEIVED

JUN 09 1998

GENERIC DRUGS

MALLINCKRODT

Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

NEW CORRESP

NC

March 11, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**RE: ANDA 40-300: Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)**

Dear Madame or Sir:

Attached is a copy of a signed Patent & Exclusivity Certification which was originally submitted as unsigned for the above referenced application.

I apologize for any inconvenience this may have caused.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,



Marianne Robb
Manager, Regulatory Affairs
(314) 654-6258
Fax (314) 654-6496

Attention: Greg Davis

RECEIVED

MAR 12 1998

GENERIC DRUGS

2.1 signed

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-300

APPLICANT: Mallinckrodt

DRUG PRODUCT: Methylphenidate Hydrochloride 5, 10, 20 mg Tablets

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

ANDA 40-300

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134

MAR 17 1998



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 March 11, 1998 and your correspondence dated March 11, 1998.

NAME OF DRUG: Methylphenidate Hydrochloride Tablets USP, 5 mg,
10 mg and 20 mg

DATE OF APPLICATION: February 27, 1998

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

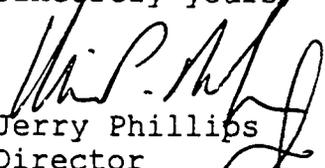
We will correspond with you further after we have had the opportunity to review the application.

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) 827-5849

Sincerely yours,


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

MALLINCKRODT

Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

ORIGINAL APPLICATION

February 27, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

505(j)(ii) OK
3/11/98
[Handwritten signature]

**RE: Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)**

Dear Madame or Sir:

Persuant to Section 505(j) of the Food Drug and Cosmetic Act, Mallinckrodt Inc. hereby submits an abbreviated new drug application (ANDA) seeking approval to market Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg). Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg) are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

In November 1996, Mallinckrodt purchased D.M. Graham Laboratories in Hobart, New York. Methylphenidate Hydrochloride Tablets, USP (5 mg, 10 mg, and 20 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability at the Hobart facilities. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

This application consists of ten volumes. An archival copy is being filed in blue folders and a technical review copy is being filed in red folders. A separate copy of the bioequivalence section is being submitted in an orange folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this ANDA, true copies of the technical sections of the ANDA were sent to the local district offices. These "field copies" are contained in maroon folders.

RECEIVED

MAR 02 1998

GENERIC DRUGS

For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

A handwritten signature in cursive script, appearing to read "Marianne Robb".

Marianne Robb
Manager, Regulatory Affairs
(314) 654-6258
Fax (314) 654-6496