CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-629

APPROVAL LETTER

ANDA 75-629

MAY 9 2000

Mallinckrodt, Inc.
Attention: Marianne Robb
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Madam:

This is in reference to your abbreviated new drug application dated April 30, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Methylin™ ER Tablets (Methylphenidate Hydrochloride Extended-release Tablets USP), 10 mg and 20 mg.

Reference is also made to your amendments dated July 2, August 30, October 29, and November 17, 1999; and February 14, and April 14, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methylin ER Tablets, 20 mg (Methylphenidate Hydrochloride Extended-release Tablets USP, 20 mg) to be bioequivalent, and therefore therapeutically equivalent, to the listed drug (Ritalin SR Tablets, 20 mg, of Novartis Pharmaceuticals Corp.). The drug product, Methylin ER Tablets, 10 mg (Methylphenidate Hydrochloride Extended-release Tablets USP, 10 mg) can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 5/9/00

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

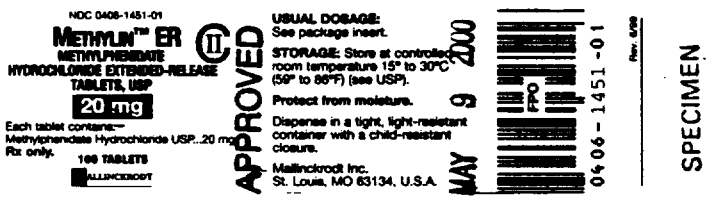
75-629

APPROVED DRAFT LABELING

FINAL PRINTED LABELING

METHYLIN™ ER (METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, USP) 20 mg

100 COUNT BOTTLE LABEL

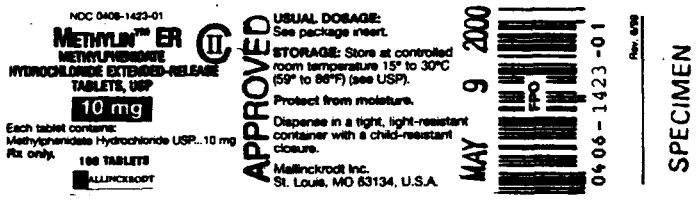


MARGO

FINAL PRINTED LABELING

METHYLIN™ ER (METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, USP) 10 mg

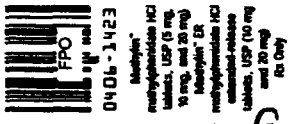
100 COUNT BOTTLE LABEL



APPROVED

MAY 9 2000

SPECIMEN



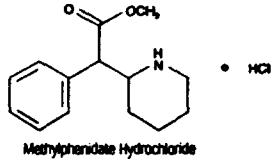
Methylin™ methylphenidate HCl tablets, USP (5 mg, 10 mg, and 20 mg) C II

Methylin™ ER methylphenidate HCl extended-release tablets, USP (10 mg and 20 mg) C II

Rx Only

DESCRIPTION

Methylphenidate hydrochloride is a mild central nervous system (CNS) stimulant, available as tablets of 5 mg, 10 mg, and 20 mg and as extended release tablets of 10 mg and 20 mg. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate Hydrochloride

$C_{14}H_{19}NO_2 \cdot HCl$ MW = 269.77

Methylphenidate Hydrochloride USP is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Each Methylin™ tablet, for oral administration, contains 5 mg, 10 mg, or 20 mg of methylphenidate hydrochloride. In addition, each tablet contains the following inactive ingredients: Lactose Monohydrate NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, and Talc USP. Each Methylin™ ER tablet, for oral administration, contains 10 mg or 20 mg in an extended release formulation. In addition, each extended-release tablet contains the following inactive ingredients: Hydroxypropyl Methylcellulose 2208 USP, Magnesium Stearate NF, Microcrystalline Cellulose NF, and Talc USP.

CLINICAL PHARMACOLOGY

Methylin™ is a mild central nervous system stimulant.

The mode of action in man is not completely understood, but Methylin™ presumably activates the brain stem arousal system and cortex to produce its stimulant effect.

There is neither specific evidence which clearly establishes the mechanism whereby Methylin™ produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Methylphenidate hydrochloride in the ER tablets is more slowly but as extensively absorbed as in the regular tablets. Relative bioavailability of the extended release tablet compared to the immediate release tablet, measured by the urinary excretion of methylphenidate major metabolite (α-phenyl-2-piperidine acetic acid) was 105% (49% to 168%) in children and 101% (85% to 152%) in adults. The time to peak rate in children was 4.7 hours (1.3 to 8.2 hours) for the extended release tablets and 1.9 hours (0.3 to 4.4 hours) for the tablets. An average of 67% of extended release tablet dose was excreted in children as compared to 86% in adults.

In a clinical study involving adult subjects who received extended-release tablets, plasma concentrations of methylphenidate's major metabolite appeared to be greater in females than in males. No gender differences were observed for methylphenidate plasma concentration in the same subjects.

INDICATIONS AND USAGE

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Methylin™ is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Methylin™, since the drug may aggravate these symptoms. Methylin™ is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

WARNINGS

Methylin™ should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Methylin™ in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Methylin™ should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Methylin™ may exacerbate symptoms of behavior disturbance and thought disorder.

Methylin™ should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Methylin™ may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Methylin™ has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Methylin™, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Methylin™ may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that methylphenidate hydrochloride may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Methylin™.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Methylin™ during pregnancy have not been conducted. Therefore, until more information is available, Methylin™ should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Methylin™ should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative. Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Methylin™ should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Methylin™ is usually not indicated.

Long-term effects of Methylin™ in children have not been well established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m² basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m² basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate has not been evaluated in an *in vivo* assay.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Consult with a Certified Poison Control Center regarding treatment for up-to-date guidance and advice.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate before performing gastric lavage. Other measures to detoxify the gut include administration of activated charcoal and a cathartic.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Methylin™ overdosage has not been established.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

ER tablets: Methylin™ ER tablets have a duration of action of approximately 8 hours. Therefore, Methylin™ ER tablets may be used in place of Methylin™ tablets when the 8-hour dosage of Methylin™ ER corresponds to the titrated 8-hour dosage of Methylin™. Methylin™ ER tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over)

Methylin™ should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

ER tablets: Methylin™ ER tablets have a duration of action of approximately 8 hours. Therefore, Methylin™ ER tablets may be used in place of Methylin™ tablets when the 8-hour dosage of Methylin™ ER corresponds to the titrated 8-hour dosage of Methylin™. Methylin™ ER tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Methylin™ should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Each Methylin™ (methylphenidate HCl tablet, USP) 5 mg is available as a round, white unscored tablet debossed with 5 on one side and a boxed "M" on the other side.

Bottles of 100.....NDC 0406-1121-01
Bottles of 1000.....NDC 0406-1121-10

Each Methylin™ (methylphenidate HCl tablet, USP) 10 mg is available as a round, white scored tablet debossed with 10 on one side of the tablet and a M on the other side.

Bottles of 100.....NDC 0406-1122-01
Bottles of 1000.....NDC 0406-1122-10

Each Methylin™ (methylphenidate HCl tablet, USP) 20 mg is available as a round, white scored tablet debossed with 20 on one side of the tablet and a boxed "M" on the other side.

Bottles of 100.....NDC 0406-1124-01
Bottles of 1000.....NDC 0406-1124-10

Protect from light. Dispense in tight, light-resistant container with child-resistant closure.
Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F). (See USP).

Each Methylin™ ER (methylphenidate HCl extended-release tablet, USP) 10 mg is available as a round, white to off-white tablet, debossed with 1423 on one side and a boxed "M" on the other side.

Bottles of 100.....NDC 0406-1423-01

Each Methylin™ ER (methylphenidate HCl extended-release tablet, USP) 20 mg is available as a round, white to off-white tablet, debossed with 1451 on one side and a boxed "M" on the other side.

Bottles of 100.....NDC 0406-1451-01

Note: Methylin™ and Methylin™ ER tablets are color-additive free.
Dispense in tight, light-resistant container with child-resistant closure.
Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F)(see USP).
Protect from moisture.

Mallinckrodt Inc.
St. Louis, MO 63134 U.S.A.

MALLINCKRODT
Printed in U.S.A.
020100

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-629

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-629

3. NAME AND ADDRESS OF APPLICANT
Mallinckrodt, Inc.
Attn: Marianne Robb
675 McDonnell blvd.
PO Box 5840
St. Louis, MO 63134-0840

4. BASIS OF SUBMISSION
Reference Listed drug product: Ritalin-SR® by Novartis (Formerly Ciba-Geigy), approved in NDA #18-029.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

*The firm submitted an amendment for the new 10 mg strength. The basis for this amendment for the 10 mg strength of Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg) is Ritalin-SR® (NDA 18-029) as established by the Citizen Petition, Docket No. 92P-0400/CP1, which may be found on page 13 of the amendment to ANDA 75-629 as submitted on July 30, 1999. Ritalin-SR® owned by Novartis (formerly Ciba-Geigy Corporation, Pharmaceuticals Division).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Methylin™

7. NONPROPRIETARY NAME
Methylphenidate Hydrochloride Extended-release Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

FIRM

Original submission (20 mg strength): 4-30-99
Amendment (Bioequivalence): 7-2-99
Amendment (10 mg strength): 7-30-99
Amendment (Chemistry): 9-7-99
Amendment (Chemistry-subject of this review): 10-29-99
Amendment (Labeling): 11-17-99
Amendment (Labeling): 2-14-00

FDA

Acknowledgement: 5-17-99
Labeling, not acceptable: 11-9-99
Bioequivalence, acceptable 20 mg strength: 7-14-99
Bioequivalence, acceptable 10 mg strength: 9-29-99
Chemistry, not acceptable: 10-7-99
Labeling, not acceptable: 1-24-00

10. PHARMACOLOGICAL CATEGORY
For ADS and narcolepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

is

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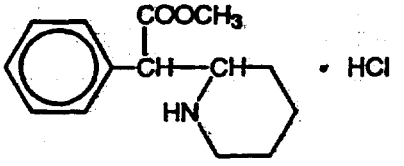
star

13. DOSAGE FORM
Solid Oral- Tablet

14. POTENCY
10 and 20 mg

15. CHEMICAL NAME AND STRUCTURE
Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



[298-59-9]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Bioequivalence acceptable for 10 mg (9/29/99) and 20 mg strengths (7/14/99).
Labeling is pending.
EER is acceptable (11/4/99).
DMF is acceptable (10/6/98).

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER: DATE COMPLETED:
Karen A. Bernard, Ph.D. (review #1) (9-23-99)
Ruth M. Ganunis, Ph.D. (review #2) RGanunis 4-4-00 4/4/00

Page(s) 22

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

Chem Rev 2

~~4/25/00~~

4/4/00

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-629

3. NAME AND ADDRESS OF APPLICANT
Mallinckrodt, Inc.
Attn: Marianne Robb
675 McDonnell blvd.
PO Box 5840
St. Louis, MO 63134-0840

4. BASIS OF SUBMISSION
Reference Listed drug product: Ritalin-SR® by Novartis (Formerly Ciba-Geigy), approved in NDA #18-029.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

*The firm submitted an amendment for the new 10 mg strength. The basis for this amendment for the 10 mg strength of Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg) is Ritalin-SR® (NDA 18-029) as established by the Citizen Petition, Docket No. 92P-0400/CP1, which may be found on page 13 of the amendment to ANDA 75-629 as submitted on July 30, 1999. Ritalin-SR® owned by Novartis (formerly Ciba-Geigy Corporation, Pharmaceuticals Division).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Methylin™

7. NONPROPRIETARY NAME
Methylphenidate Hydrochloride Extended-release Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 4-30-99
Acknowledgement: 5-17-99
Amendment: (new strength):7-30-99
Amendment: 9-7-99

10. PHARMACOLOGICAL CATEGORY
For ADS and narcolepsy

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

s

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star

13. DOSAGE FORM
Solid Oral- Tablet

14. POTENCY
10 and 20 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application contains chemistry deficiencies.
Bioequivalence is pending for the 10 mg strength. The 20 mg strength was found acceptable on 7/14/99 by Sikta Pradhan.

Labeling is pending.
EER is pending.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is unapprovable. Major amendment.

19. REVIEWER: DATE COMPLETED:
Karen A. Bernard, Ph.D. 9-23-99

Page(s) 21

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

Chem Rev 1

9/23/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-629

BIOEQUIVALENCE

Methylphenidate Hydrochloride
10 mg ER Tablet
ANDA # 75-629 (EVA)
Reviewer: Sikta Pradhan
V:\firmsam\Mallinckrodt\ltrs&rev\75629SDA.799.doc

Mallinckrodt Inc.
St. Louis, MO
Submission Date:
July 30, 1999

Review of a Bioequivalence Study and Dissolution Data

I. BACKGROUND:

Methylphenidate Hydrochloride is a mild central nervous system stimulant.

The firm had previously (submission dated April 30,1999) conducted three acceptable bioequivalence studies (a single-dose fasting study, a single-dose fed study, and a multiple-dose study) comparing its Methylphenidate Hydrochloride 20-mg ER tablets, to Ritalin-SR[R], 20-mg tablets of Novartis (formerly CIBA Pharmaceuticals Co.).

Currently no RLD for 10 mg strength of Methylphenidate Hydrochloride ER tablet is available in the market. In this amendment the firm submitted results of a single-dose fasting bioequivalence study conducted on its 10-mg ER Methylphenidate Hydrochloride tablets to the Agency for approval of the test product.

The basis for this amendment for the 10 mg strength of Methylphenidate Hydrochloride ER tablets has been established by the Citizen Petition, Docket No. 92P-0400/CPI (copy of the Citizen Petition and the letter approving the petition is attached).

II. OBJECTIVE:

1. To compare the relative bioavailability of Mallinckrodt's Methylphenidate HCl, 10-mg ER tablets to the reference product, Novartis' Ritalin-SR[R] 20-mg tablets under fasting conditions.

2. Review of the dissolution data for the 10mg strength of the test and 20-mg strength of the reference products.

III. SINGLE DOSE STUDY UNDER FASTING CONDITIONS
(Study Number: 98355)

Study Facility Information:

Clinical Facility: Gateway Medical Research, St. Charles, MO.

Clinic Director:

Principal Investigator: Irwin Plisco, MD.

Clinical Study Dates: May 8 - 16, 1999

Analytical Facility:

Project Director:

Analytical Director: h.D.

Analytical Study Dates: June 9, 1999 to July 8, 1999

The Duration of Maximum Storage Time: About two months

Sponsor: Mallinckrodt Inc.

Study Design: Single dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions.

Subject Selection

Subjects selected for the study met the following acceptance criteria:

1. Age range: 18 to 45 years.
2. Healthy as determined by physical examination, medical history, and clinical laboratory diagnostic tests: blood chemistry, hematology, urinalysis and HIV.
3. Absence of any exclusion criteria determined during physical or laboratory evaluations.
4. Body weight within 15% of their ideal body ``weight according to Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983.

Thirty-two (32) volunteers met all eligibility requirements and were successfully selected for the study.

Subject Restrictions:

1. No antacids- no alcohol-, grapefruit- or xanthine-containing beverages and foods for the 24 hours before dosing and throughout the period of sample collection.
2. No medication (including over-the-counter products) for the 7 days preceding the study.
3. Water intake was prohibited from one hour pre-dose until one hour post-dose.

4. Subjects remained ambulatory or seated upright and were prohibited from smoking. No strenuous activity was permitted at any time during the housing period.

Treatments:

A. 2 x 10 mg Methylphenidate HCl tablet (test product) of Mallinckrodt, Lot #MHSC9921, Lot size 252,700 tablets, Potency 98.2%

B. 1 x 20 mg Ritalin-SR^{R} tablet (Novartis), Lot #1T233346, Exp: September, 1999, Potency 98.8%

Dose Administration:

A single oral dose of 20 mg, (test product or reference product) was administered with 240 mL of water following a 10 hour fast.

Drug Washout Period:	One week
Special Procedures:	Blood pressure and pulse measurements were obtained within 60 minutes pre-dose, and within 30 minutes post-dose, and also at 2, 4, 6 hours post dose.
Housing	Evening prior to each drug administration until 36 hours after dosing

Meal and Food Restrictions:

All volunteers fasted for 10 hours prior to and 2 hours after drug administration. No fluid except that given with drug administration was allowed from 1 hour prior to dose administration until 2 hours after dosing. Standard meal was served at 4 hour post-dose. No caffeine-containing food or beverages were served during the first 24 hours.

Blood Samples Collection:

Blood samples were collected in vacutainers containing EDTA (anticoagulant) at the following times: 0 (pre-dose), 20 and 40 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 24 hours post-dose (18 samples). The plasma samples were separated and stored frozen at $-20^{\circ}C \pm 5^{\circ}C$ until analysis.

Assay Methodology

Plasma samples were analyzed for intact methylphenidate using a

The pre-study and during study assay validations for methylphenidate are presented in Tables 1 & 2 below:

Table 1.Pre-Study Assay Validation

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.75,10.0, 20.0, 50.0	0.25, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0
Inter-day Precision (% CV)	17.6, 3.9, 4.6, 1.9	11.3, 8.9, 10.8, 9.1, 3.5, 2.6, 3.4
Absolute Deviation (% Actual)	9.2, 6.2, 8.1, 9.4	0.80, 1.5, 2.1, 0.28, 1.3, 0.57, 0.36
Intra-day Precision (% CV)	21.9, 1.5, 2.3, 1.9	1) NA, 7.8, 14.4, 4.7, 5.5, 3.6, 2.6 2) 5.8, 6.2, 10.0, 0.29, 0.95, 1.1, 3.0 3) NA, 4.9, 11.4, 17.2, 2.6, 2.3, 5.5
Absolute Deviation (% Actual)	13.8, 8.9, 11.7, 9.4	1) 1.6, 1.5, 0.93, 0.33, 0.27, 0.57, 0.27 2) 5.7, 4.8, 2.5, 1.3, 3.5, 0.07, 0.40 3) 13.0, 10.8, 4.6, 0.83, 0.13, 2.3, 0.93
Linearity (Range of R values)	0.9983 to 0.9995	
Linear Range (ng/mL)	0.25 ng/mL to 25.0 ng/mL	
Sensitivity/LOQ (ng/mL)	0.250 ng/mL	
Stability in Plasma:		
a) Long-term Frozen	10 months	
b) Bench-top at room temperature	6.5 hours	
c) Freeze/Thaw	Stable at least three cycles	
d) Extract Stability	Stable at room temperature for 24 hours during extraction	
Specificity	Specific; no interference from endogenous compounds noted in serum blanks or pre-dose subject serum samples.	

Table 2. During study Assay Validation for Fasting Study #98355

Parameter	QC Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.75, 10.0, 20.0	0.25, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0
Inter day Precision (% CV)	12.3, 10.1, 9.9	10.8, 10.3, 7.5, 6.0, 6.0, 4.2, 5.9
Absolute Deviation (% Actual)	0.81, 0.41, 2.2	3.7, 2.5, 1.5, 7.8, 1.7, 4.4, 0.30
Linearity (Range of R values)	0.9922 to 0.9997	
Linear Range (ng/mL)	0.25 to 25.0	
Sensitivity/LOQ (ng/mL)	0.25	

Results:

Thirty-two (32) volunteers were selected for the study and all 32 volunteers completed the study. The pharmacokinetic and statistical analyses (using SAS-GLM procedure for analysis of variance) were conducted on data obtained from all 32 subjects. During this study six adverse events in six subjects (2 events due test product and 2 for reference products) were reported. However, there was no serious adverse event or any event, which required terminating any subject from the study. No non-zero pre-dose plasma value was observed. The mean plasma concentration versus time data for the test and reference products are summarized in the following table:

Table 3. Arithmetic Mean (N=32) Plasma Concentration (ng/mL) versus Time

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
	Mean	SD	Mean	SD
0	0	--	0	--
0.33	0.0088	0.0495	0.0388	0.1318
0.67	0.8114	0.4914	0.7484	0.8455
1	2.1749	1.1721	1.8541	0.9708
1.5	3.2675	1.2234	2.9466	1.1171
2	4.0019	1.2714	3.9241	1.4213
2.5	4.4188	1.3721	4.4281	1.7432
3	4.6959	1.4053	4.5384	1.5421
4	5.1513	1.7896	4.8097	1.6968
5	5.6775	1.6769	5.7119	1.7775

6	4.6384	1.4075	4.9422	1.7168
7	3.8069	1.3133	4.0894	1.4024
8	3.1966	1.1290	3.5022	1.3298
10	2.0713	0.7864	2.4263	0.9179
12	1.3516	0.6008	1.5828	0.6340
14	0.9262	0.4328	1.0349	0.5101
16	0.5669	0.3727	0.6730	0.3901
24	0.0571	0.1612	0.0570	0.1591

Table 4: Pharmacokinetic Parameter Summary (Means of Untransformed Data)

Parameter	Test Formulation Mean (SD)	Reference Formulation Mean (SD)	Ratio (A/B)
AUCinf (ng-hr/mL)	47.46 (15.94)	49.61 (17.57)	0.96
AUCt (ng-hr/mL)	44.79 (15.17)	46.76 (17.07)	0.96
Cmax (ng/mL)	5.83 (1.69)	5.84 (1.85)	1.00
Kel (1/hr)	0.2133 (0.0484)	0.2134 (0.0408)	1.00
T1/2 (hr)	3.42 (0.82)	3.37 (0.68)	1.01
Tmax (hr)	4.66 (0.90)	4.89 (0.97)	0.95

N = 32

The summary of 90% confidence intervals limits, least squares mean (LSM) ratios and intra-subject variabilities for the critical pharmacokinetic parameters are presented below.

Table 5: Summary of 90% Confidence Limits and Variability

	Ln(AUCinf)	Ln(AUCt)	Ln(Cmax)
90% CI (%)	93.2 - 99.0	93.4 - 99.5	96.8 - 104.6
LSM Ratio (Test/Ref) %	96.1	96.4	100.6
Intra-subject CV (%)	7.14	7.36	9.10

As seen in the above summary table, the 90% confidence intervals for all parameters are within 80 to 125%.

VI. Product Formulation:

The composition of the test formulation is presented in Table 6.

Table 6. Compositions of Mallinckrodt's (Methylin™ ER) Methylphenidate HCl Extended-release 10 mg and 20 mg Tablets

Ingredients	Amounts (mg)/Tablet	Amounts (mg)/Tablet
Methylphenidate	10.000	20.000
Hydroxypropyl Methylcellulose		
Magnesium Stearate		
Microcrystalline Cellulose		
01)		
Purified Water		
Talc		
Total		

VII. In Vitro Dissolution Testing Results:

The firm has conducted dissolution testing using the USP dissolution method for Methylphenidate Hydrochloride ER tablets (USP 23, supplement 5, pg. 3423) as presented below:

The USP method:

Medium: Water, 500 mL
Apparatus: Paddle
RPM: 50
Specifications:

The dissolution data are presented in Table 7.

Table 7. In Vitro Dissolution Testing	
Drug (Generic Name): Methylphenidate hydrochloride	
Dosage Form:	Extended Release Tablet
Dose Strength:	10 mg
I. Conditions for Dissolution Testing:	
Apparatus:	Paddle
Speed:	50 rpm
No. Units	12

Medium:	Water
Volume:	500 ml
Sampling Time:	1, 2, 3.5, 5 and 7 hours
Reference Product:	Ritalin-SR® 20 mg tablets (Ciba-Geigy Corp.)

II. Results of In Vitro Dissolution Testing:

Time (hr)	Test Lot #MHSC9921			Reference (Ritalin-SR[R]) Lot # 1T233346		
	Mean	Range	CV%	Mean	Range	CV%
1	41.82%		7.06%	41.84%		1.67%
2	59.62%		5.74%	58.28%		1.97%
3.5	76.02%		5.46%	74.32%		1.73%
5	86.71%		3.99%	84.88%		1.41%
7	93.60%		2.85%	94.33%		1.73%

The dissolution data are acceptable. The dissolution data of 10-mg and 20-mg tablets of the test product are comparable.

Comments:

1. The results of the single-dose bioequivalence study conducted under fasting conditions demonstrated that at 20 mg dose, the test product, Methylphenidate Hydrochloride Extended-release 10 mg Tablet manufactured by Mallinckrodt Inc. has similar bioavailability as the reference listed drug, Ritalin-SR® 20 mg Tablet.

2. The dissolution data indicate that Mallinckrodt's Methylphenidate Hydrochloride Extended-release Tablets, 10 mg (Methylin™ ER) and the RLD, Ritalin-SR® 20 mg Tablets had comparable dissolution profiles and both met the USP dissolution specifications.

3. The firm had previously conducted three acceptable bioequivalence studies, a single-doe fasting study, a single-dose fed study, and a multiple-dose study, comparing its Methylphenidate Hydrochloride 20-mg ER tablets, to Ritalin-SR[R], 20-mg tablets of Novartis (formerly CIBA Pharmaceuticals Co.).

Recommendations:

1. The single dose bioequivalence study under fasting conditions conducted on the test product, Mallinckrodt's Methylphenidate Hydrochloride ER Tablet, 10 mg, lot # MHSC99921, comparing it to the reference product, Ritalin-SR® Tablet, 20

mg, lot # 1T233346 of Novartis, has been found acceptable by the Division of Bioequivalence. The study demonstrated that at 20 mg dose, Methylphenidate Hydrochloride Extended-release Tablet, 10 mg (Methylin™ ER), lot # MHSC9921 manufactured by Mallinckrodt Inc. has similar bioavailability as the reference listed drug, Ritalin-SR® 20 mg Tablet.

2. The *in vitro* dissolution testing conducted by Mallinckrodt Inc. on its Methylphenidate Hydrochloride ER Tablet, 10 mg, lot # MHSC9921 and Ritalin-SR® Tablet, 20 mg, lot # 1T233346 of Novartis, using USP dissolution method, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should meet the following specifications:

3. The amendment is acceptable.

Sikta Pradhan

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

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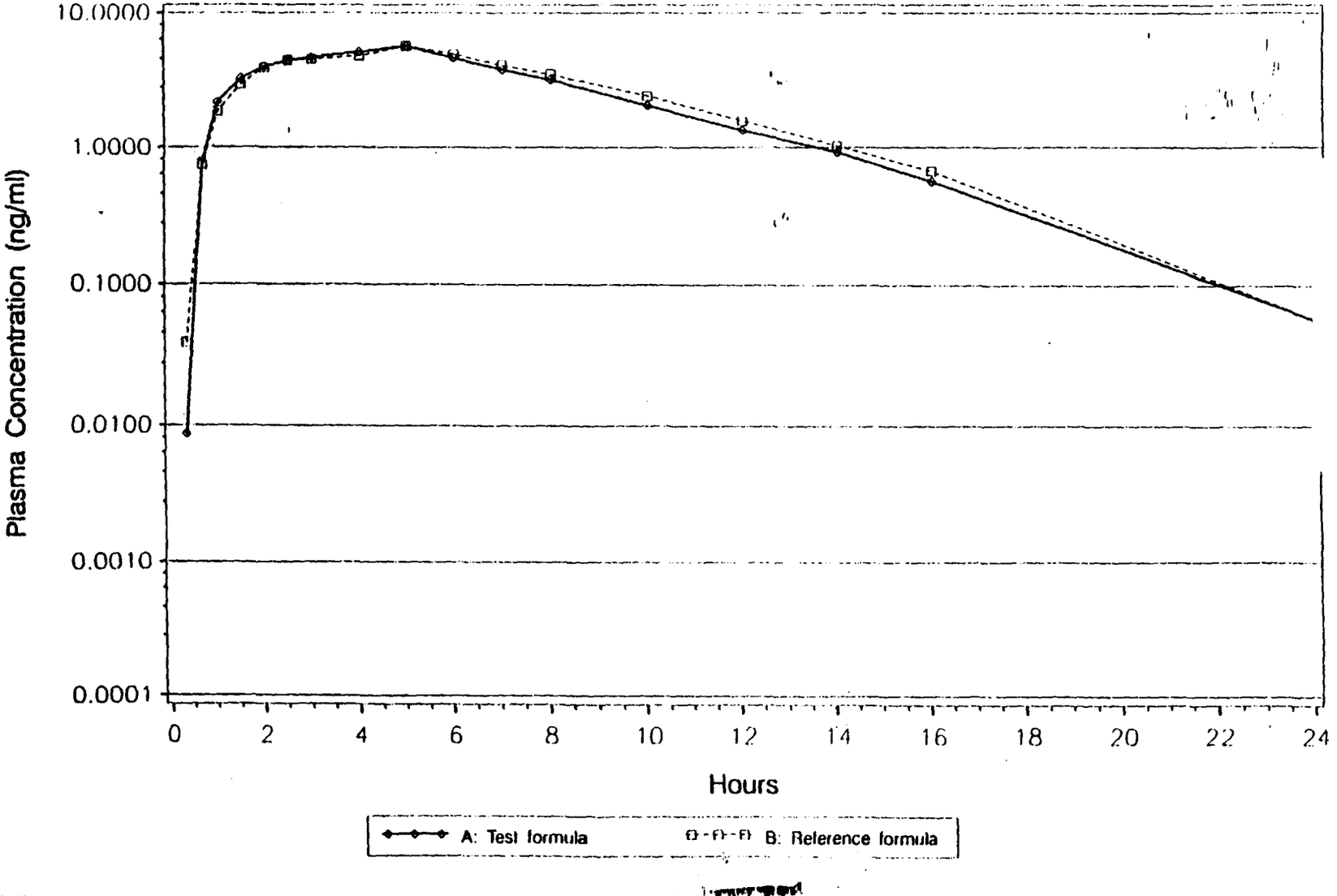
FT INITIALED YCHUANG ---------- 8/20/99

Concur: [signature] Date: 9/9/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Mean Plasma Concentration versus Time

Mallinckrodt Protocol 98355, Methylphenidate HCL ER 10 mg, Tablets (Fasting)



Mallinckrodt Inc.

Methylphenidate Hydrochloride
20 mg ER Tablet
ANDA # 75-629 (EVA)
Reviewer: Sikta Pradhan
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Mallinckrodt Inc.
St. Louis, MO
Submission Date:
April 30, 1999
July 2,1999

Review of Three Bioequivalence Studies and Dissolution Data

I. BACKGROUND:

Methylphenidate Hydrochloride is a mild central nervous system stimulant. The mode of action in man is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate hydrochloride appears to be well absorbed from the GI tract and effects persist for 3-6 hours after oral administration of conventional tablets and about 8 hours after oral administration of extended-release tablets.

The firm has conducted three bioequivalence studies, a single-doe fasting study, a single-dose fed study, and a multiple-dose study, comparing its Methylphenidate Hydrochloride 20-mg ER tablets, to Ritalin-SR^R, 20-mg tablets of Novartis (formerly CIBA Pharmaceuticals Co.). The firm submitted these study data (as an electronic submission) to the Agency for approval of its test product.

RLD: Ritalin-SR^R, 20-mg tablets

II. OBJECTIVE:

1. To compare the relative bioavailability of Mallinckrodt's Methylphenidate HCl, 20-mg ER tablets to the reference product, Novartis' Ritalin-SR^R 20 mg tablets under fasting, fed and multiple dosing conditions.

2. Review of the dissolution data for the 20mg strength of the test and reference products.

III. SINGLE DOSE STUDY UNDER FASTING CONDITIONS
(Study Number: 98260)

Study Facility Information:

Clinical Facility: Gateway Medical Research, St. Charles, MO.

Principal Investigator: Irwin Plisco, MD.

Clinical Study Dates: November 14 - 22, 1998

Analytical Facility:

Project Director:

Analytical Study Dates: 11-30-98 to 12-16-98

The Duration of Maximum Storage Time: About one month

Sponsor: Mallinckrodt Inc.

Study Design: Single dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions.

Subject Selection

Subjects selected for the study met the following acceptance criteria:

1. Age range: 18 to 45 years.
2. Healthy as determined by physical examination, medical history, and clinical laboratory diagnostic tests: blood chemistry, hematology, urinalysis and HIV.
3. Absence of any exclusion criteria determined during physical or laboratory evaluations.
4. Body weight within 10% of their ideal body weight according to Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983.

Thirty-two (32) volunteers met all eligibility requirements and were successfully selected for the study.

Subject Restrictions:

1. No antacids- no alcohol-, grapefruit- or xanthine-containing beverages and foods for the 24 hours before dosing and throughout the period of sample collection.
2. No medication (including over-the-counter products) for the 7 days preceding the study.
3. Water intake was prohibited from one hour pre-dose until one hour post-dose.

4. Subjects remained ambulatory or seated upright and were prohibited from smoking. No strenuous activity was permitted at any time during the housing period.

Treatments:

A. 1 x 20 mg Methylphenidate HCl tablet (test product) of Mallinckrodt, Lot #MHSC9851, Lot size ablets, Potency 96.0%

B. 1 x 20 Ritalin-SR® tablet (Novartis), Lot #1T233345, Exp: November, 1999, Potency 99.0%

Dose Administration:

A single oral dose of 20 mg, (test product or reference product) was administered with 240 mL of water following a 10 hour fast.

Drug Washout Period:	One week
Special Procedures:	Blood pressure and pulse measurements were obtained within 60 minutes pre-dose, and within 30 minutes post-dose, and also at 2,4, 6 post dose hours.
Housing	Evening prior to each drug administration until 36 hours after dosing

Meal and Food Restrictions:

All volunteers fasted for 10 hours prior to and 2 hours after drug administration. No fluid except that given with drug administration was allowed from 1 hour prior to dose administration until 2 hours after dosing. Standard meal was served at 4 hour post-dose. No caffeine-containing food or beverages were served during the first 24 hours.

Blood Samples Collection

Blood samples were collected in vacutainers containing EDTA (anticoagulant) at the following times: 0 (pre-dose), 20 and 40 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 24 hours post-dose (18 samples). The plasma samples were separated and stored frozen at $-20^{\circ}C \pm 5^{\circ}C$ until analysis.

Assay Methodology

Plasma samples were analyzed for intact methylphenidate using a

The pre-study and during study assay validations for methylphenidate are presented in Tables 1 & 2 below:

Table 1.Pre-Study Assay Validation

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.75,10.0, 20.0, 50.0	0.25, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0
Inter-day Precision (% CV)	17.6, 3.9, 4.6, 1.9	11.3, 8.9, 10.8, 9.1, 3.5, 2.6, 3.4
Absolute Deviation (% Actual)	9.2, 6.2, 8.1, 9.4	0.80, 1.5, 2.1, 0.28, 1.3, 0.57, 0.36
Intra-day Precision (% CV)	21.9, 1.5, 2.3, 1.9	1) NA, 7.8, 14.4, 4.7, 5.5, 3.6, 2.6 2) 5.8, 6.2, 10.0, 0.29, 0.95, 1.1, 3.0 3) NA, 4.9, 11.4, 17.2, 2.6, 2.3, 5.5
Absolute Deviation (% Actual)	13.8, 8.9, 11.7, 9.4	1) 1.6, 1.5, 0.93, 0.33, 0.27, 0.57, 0.27 2) 5.7, 4.8, 2.5, 1.3, 3.5, 0.07, 0.40 3) 13.0, 10.8, 4.6, 0.83, 0.13, 2.3, 0.93
Linearity (Range of R values)	0.9983 to 0.9995	
Linear Range (ng/mL)	0.25 ng/mL to 25.0 ng/mL	
Sensitivity/LOQ (-g/mL)	0.250 ng/mL	
Stability in Plasma:		
a) Long-term Frozen	10 months	
b) Bench-top at room temperature	6.5 hours	
c) Freeze/Thaw	Stable at least three cycles	
d) Extract Stability	Stable at room temperature for 24 hours during extraction	
Specificity	Specific; no interference from endogenous compounds noted in serum blanks or pre-dose subject serum samples.	

Table 2. During study Assay Validation for Fasting Study #98260

Parameter	QC Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.75, 10.0, 20.0	0.25, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0
Inter day Precision (% CV)	6.4, 4.7, 10.3	9.7, 8.6, 4.5, 6.4, 3.0, 4.6, 3.3
Absolute Deviation (% Actual)	7.1, 4.3, 2.5	2.2, 5.9, 1.3, 2.6, 2.1, 0.24, 0.06
Linearity (Range of R values)	0.9986 to 0.9999	
Linear Range (ng/mL)	0.25 to 25.0	
Sensitivity/LOQ (ng/mL)	0.25	

Results:

Thirty-two (32) volunteers were selected for the study and 31 volunteers completed the study. Subject#19 completed only the first period of the study. The pharmacokinetic and statistical analyses (using SAS-GLM procedure for analysis of variance) were conducted on data obtained from 31 subjects. During this study, there was no serious adverse event or any event, which required terminating any subject from the study. No non-zero pre-dose plasma value was observed. The mean plasma concentration versus time data for the test and reference products are summarized in the following table:

Table 3. Arithmetic Mean Plasma Concentration (ng/mL) versus Time

TIME (HR)	TEST TREATMENT A			REFERENCE TREATMENT B			RATIO (A/B)
	N	Mean	SD	N	Mean	SD	
0.33	31	0.0479	0.1334	32	0.0095	0.0536	5.0421
0.67	31	0.8074	0.6314	32	0.9133	0.6030	0.8840
1	31	1.9373	1.1761	32	2.2732	1.2664	0.8522
1.5	31	3.3700	1.7691	32	3.6228	1.9784	0.9302
2	31	4.2403	2.0672	32	4.3750	2.2117	0.9692
2.5	31	5.0358	2.7250	32	5.0066	2.7877	1.0058
3	31	5.2532	2.8207	32	5.1922	2.6963	1.0117
4	31	5.7384	3.5698	32	5.6944	3.1958	1.0077
5	31	6.3400	3.7021	32	6.9228	2.8518	0.9158
6	31	5.5761	3.4673	32	5.8541	3.2044	0.9525
7	31	4.7710	3.3926	32	5.0803	2.9477	0.9391
8	31	3.9971	2.8859	32	4.2519	2.6829	0.9401
10	31	2.7706	2.4505	32	3.0216	2.1195	0.9169
12	31	2.0773	2.2746	32	2.0615	1.7531	1.0077
14	31	1.4893	1.8080	32	1.5673	1.4912	0.9502
16	31	1.1551	1.5038	32	1.0342	1.1125	1.1169
24	31	0.3489	0.8040	32	0.2427	0.5348	1.4376

Table 4: Pharmaeokinetic Parameter Summary (Means of Untransformed Data)

Parameter	N	Test Formulation Mean (SD)	N	Reference Formulation Mean (SD)	Ratio (A/B)
AUCinf (ng-hr/mL)	31	63.32 (55.41)	32	63.09 (43.48)	1.00
AUCt (ng-hr/mL)	31	58.14 (47.59)	32	59.28 (39.81)	0.98
Cmax (ng/mL)	31	6.51 (3.66)	32	7.06 (3.09)	0.92
Kel (1/hr)	31	0.17 (0.043)	32	0.19 (0.040)	0.89
T1/2 (hr)	31	4.28 (1.21)	32	3.77 (0.91)	1.14
Tmax (hr)	31	4.65 (0.97)	32	4.67 (0.81)	1.00

The summary of 90% confidence intervals limits, least squares mean (LSM) ratios, inter-subject variability, and intra-subject variability for the critical pharmacokinetic parameters is presented below.

Table 5: Summary of 90% Confidence Limits and Variability

	Ln(AUCinf)	Ln(AUCt)	Ln(Cmax)
90% CI (%)	90.7-98.3	89.3-96.8	82.9-94.5
LSM Ratio (Test/Ref) %	94.4	93.0	88.5
Intra-subject CV (%)	9.42	9.38	15.2
Inter-subject CV (%)	70.9	70.3	52.2

As seen in the above summary table, the 90% confidence intervals for all parameters are within 80 to 125%. These results indicate that the Test and Reference formulations are bioequivalent.

IV. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITION (Study #98259)

Study Information: As mentioned in the fasting study.

Study Design: Single-dose, three-way crossover design

Subject Selection

Subjects selected for the study met the selection and restriction criteria mentioned in the fasting study.

Clinical Study Dates: 11-8-98 to 11-23-98

Analytical Study Dates: 12-28-98 to 2-1-99

The Duration of Maximum Storage Time: Little less than two months

Treatments:

A. 1 x 20 mg methylphenidate tablet (test product) of Mallinckrodt, Lot #MHSC9851, after an overnight fast

B. 1 x 20 mg methylphenidate tablet (test product) of Mallinckrodt, Lot #MHSC9851, thirty minutes after initiation of a high fat breakfast preceded by an overnight fast.

C. 1 x 20 mg Ritalin-SR^R tablet (reference product), Lot #IT233345, thirty minutes after initiation of a high fat breakfast preceded by an overnight fast.

Dose Administration:

A single oral dose of 20mg (methylphenidate, test or reference) tablet was administered with 240 mL of water.

Drug Washout Period: One week between doses

Meal and Fluid Restrictions:

For treatments A, subjects fasted for 10 hours before drug administration.

For treatments B and C, subjects received a standard high fat breakfast 30 minutes before dosing.

In all treatments, water was given ad lib after 2 hour of dosing. All volunteers fasted for 4 hours after drug administration. Standard meal was served during the in-house confinement period. No caffeine-containing food or beverages were served during the study. All subjects were confined from 12 hours pre-dose to 36 hours post-dose.

Blood Samples Collection Similar as mentioned in the fasting study.

Assay Methodology: Same as discussed in the fasting study

The pre-study assay validations have been presented in Table 1 before.
The during study assay validations have been presented in Table 6 below:

Table 6. Assay Validation for Food Effects Study #98259

Parameter	QC Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.75, 10.0, 20.0	0.25, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0
Inter-day Precision (% CV)	5.8, 5.3, 15.6	8.4, 9.7, 10.6, 6.6, 3.8, 4.7, 4.0
Absolute Deviation (% Actual)	1.7, 0.09, 0.48	0.29, 7.1, 1.1, 4.3, 1.4, 2.1, 0.44
Linearity (Range of R values)	0.9977 to 0.9998	
Linear Range (ng/mL)	0.25 to 25.0	
Sensitivity/LOQ (ng/mL)	0.25	

Results:

Of the 24 healthy, adult subjects enrolled in the study, all 24 successfully completed all three phases of the study. Ten adverse events (6 events due to test and 4 events due to reference products) were reported in 8 subjects. One of the events was judged likely to be drug related, 6 were judged to be unrelated to study medications, and 3 had an inaccessible relationship. Five of the events were of mild severity and required no intervention, while 5 events were considered of moderate severity and one required intervention. Nine adverse events resolved prior to dismissal from the clinical study site (i.e. exit exam) and one was resolved on follow-up. The mean plasma concentrations versus time data for the test and reference products have been summarized below:

Table 7. Arithmetic Mean Plasma Concentration (ng/mL) versus Time

TIME (HR)	FED TEST (A)			FED REFERENCE (B)			FASTING TEST (C)			RATIO A/B	RATIO A/C
	N	Mean	STD	N	Mean	STD	N	Mean	STD		
0	24	0.0000	0.0000	24	0.0000	0.0000	24	0.0000	0.0000	0.0000	0.0000
0.33	24	0.0843	0.1832	24	0.0000	0.0000	24	0.0468	0.1326	0.0000	1.8013
0.67	24	1.1192	1.0264	24	0.6625	0.4746	24	0.8717	0.5096	1.6894	1.2839
1	24	1.9599	1.2955	24	1.8315	0.9407	24	1.8870	0.7605	1.0701	1.0386
1.5	24	3.0830	1.3444	24	2.8883	1.2358	24	2.6163	0.7097	1.0674	1.1784
2	24	3.8304	1.2111	24	3.8333	1.3421	24	3.2479	0.7184	0.9992	1.1793
2.5	24	4.6842	1.4355	24	4.5754	1.3895	24	3.7900	0.8730	1.0238	1.2359
3	24	5.1183	1.3984	24	4.9754	1.4799	24	3.9954	0.8144	1.0287	1.2810
4	24	5.4367	1.4589	24	5.5321	1.0681	24	4.1813	0.7055	0.9828	1.3002
5	24	5.6675	1.5702	24	6.2988	1.2897	24	4.3300	0.7014	0.8998	1.3089
6	24	4.6033	1.3877	24	5.3225	1.1278	24	3.6767	0.6391	0.8649	1.2520
7	24	3.8888	0.8807	24	4.4513	0.8872	24	3.2238	0.7888	0.8736	1.2063
8	24	3.2142	0.8864	24	3.6917	0.7585	24	2.6513	0.5776	0.8707	1.2123
10	24	2.2600	0.5705	24	2.5725	0.6781	24	1.7967	0.4719	0.8785	1.2579
12	24	1.5653	0.5130	24	1.5179	0.3262	24	1.2345	0.4311	1.0312	1.2680
14	24	1.1372	0.3978	24	0.9861	0.2650	24	0.9594	0.3477	1.1532	1.1853
16	24	0.7670	0.3026	24	0.6273	0.2408	24	0.6319	0.2637	1.2227	1.2138
24	24	0.1111	0.1640	24	0.0309	0.1049	24	0.0789	0.1260	3.5955	1.4081

The pharmacokinetic parameters for each formulation, calculated from the untransformed data, have been presented in Table 10 below:

Table 8: Pharmacokinetic Parameter Summary

PK PARAMETER	N	FED TEST TREATMENT B (SD)	N	FED REFERENCE TREATMENT C (SD)	N	FASTING TEST TREATMENT A (SD)	RATIO B/C	RATIO B/A
AUCinf (ng-hr/mL)	24	51.12 (9.69)	24	51.29 (8.10)	24	41.19 (7.71)	1.00 (1.20)	1.24 (1.26)
AUCt (ng-hr/mL)	24	47.44 (9.70)	24	48.55 (7.35)	24	37.96 (6.94)	0.98 (1.32)	1.25 (1.40)
Cmax (ng/mL)	24	6.21 (1.27)	24	6.64 (1.19)	24	4.59 (0.79)	0.94 (1.07)	1.35 (1.61)
Kel (1/hr)	24	0.17 (0.06)	24	0.23 (0.05)	24	0.17 (0.05)	0.74 (1.20)	1.00 (1.20)
T1/2 (hr)	24	4.44 (1.45)	24	3.21 (1.00)	24	4.38 (1.30)	1.38 (1.45)	1.01 (1.12)
Tmax (hr)	24	4.15 (1.21)	24	4.38 (1.09)	24	4.17 (0.95)	0.95 (1.11)	1.00 (1.27)

Results indicated that food increases both AUC and Cmax (similar results were also observed in other methylphenidate-ANDAs submitted to the agency).

The summary of 90% confidence intervals limits, least square mean (LSM) ratios, inter-subject variability, and intra-subject variability for the critical pharmacokinetic parameters are presented in Table 9 below.

Table 9: Confidence Limits (90%) and Variability for Test Fed and Reference Fed

	Ln(AUCinf)	Ln(AUCt)	Ln(Cmax)
90% CI (%)	95.4 to 103.3	92.7 to 101.3	87.9 to 99.0
LSM Ratio (Test/Ref) %	99.8	99.2	96.3
Intra-subject CV (%)	8.06	8.96	11.97
Inter-subject CV (%)	26.6	27.4	25.5

As seen in Table 9 above, the LSM Ratios for the AUCt, AUCinf, and Cmax are within 80% to 120%. These results indicate that the Test and Reference formulations are bioequivalent.

V. MULTIPLE DOSE BIOEQUIVALENCE STUDY

Study #98258

Objective: Study - to evaluate the bioavailability of the test preparation of Methylphenidate sustained release 20 mg tablet in comparison with Ritalin-SR^R as reference preparation under steady state conditions in 32 healthy male volunteers.

Study Investigators and Contract Laboratory: Identical to fasting study.

Clinical Study Dates: 11-02-98 to 11-19-98

Analytical (assay) Dates: 12-11-98 to 01-13-99

The Duration of Maximum Storage Time: Less than 10 weeks

Study Design: An open, multiple-dose, randomized, two-way crossover design with 32 healthy male non-smoking subjects.

Subject Selection Criteria: Similar to the previous studies.

Subject Restrictions: Similar to the previous studies.

Drug Treatments :

1. Test Product A : Methylphenidate 20mg tablet (Mallinckrodt), Lot #MHSC9851, one 20-mg tablet every 8 hours on days 1-3, and one tablet on 4th day after over night fast.

2. Reference Product B : Ritalin-SR^R Tablet, 20mg (Novartis), Lot #IT233345, one 20-mg tablet every 8 hours on days 1-3, and one tablet on 4th day after over night fast.

Therefore, during each period subjects were administered one tablet every 8 hours for a total of ten doses.

Washout Period: 10 days

During each period of the study, 10 mL blood samples were collected at the following intervals: prior to the first dose (baseline), within 30 minutes prior to doses 2 to 10 (trough levels). Blood samples (10 mL each) were also collected at the following times: after the tenth (last) dose: 20 and 40 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7,

and 8 hours post-dose. The samples were collected into pre-chilled Vacutainer tubes containing EDTA anticoagulant. The blood samples were centrifuged at 4°C, and the plasma samples were kept frozen at –20°C untill analysis.

Assay Methodology: Same as that mentioned in the fasting study.

The during-study assay validations for Methylphenidate have been presented below:

Table 11. Assay Validation for Multi-Dose (Steady State) Study #98258

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	0.75, 10.0, 20.0	0.25, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0
Inter-day Precision (% CV)	9.5, 9.4, 10.1	10.3, 10.6, 9.7, 5.1, 5.1, 2.8, 3.8
Absolute Deviation (% Actual)	1.6, 0.15, 2.4	0.04, 0.33, 0.03, 0.71, 1.0, 0.24, 0.03
Linearity (Range of R values)	0.9979 to 0.9997	
Linear Range (ng/mL)	0.25 to 25.0	
Sensitivity/LOQ (ng/mL)	0.25	

Results of the Multi-Dose Study:

Of the 32 subjects who began the study, all 32 completed both periods. Seventy-three (73) adverse events (29 events due to test product, 41 events due to reference products, and 3 at pre-dose) were reported by 22 of the volunteers during the study. Fifty-two of the events were judged likely to be drug related, 18 were judged to be unrelated to study medications, and 3 had an unassessable relationship. Sixty-seven of the events were of mild severity and required no intervention, and 5 of the events were considered of moderate severity and none required intervention. One of the adverse events was considered severe and required intervention. Sixty-eight adverse events resolved prior to dismissal from the clinical study site (i.e. exit exam) and the other 5 were resolved on follow-up Based on the dose (20 mg) and the dosing interval (q8hr), the number of adverse events is not regarded as unusual for this drug.

The mean plasma concentration versus time data for the test and reference products are summarized in Table 12:

Table 12. Arithmetic Mean Plasma Concentrations (ng/mL) versus Time

TIME		TEST TREATMENT A			REFERENCE TREATMENT B			RATIO (A/B)
(DAY)	(HR)	N	Mean	STD	N	Mean	STD	
1	0	32	0.00	0.00	32	0.00	0.00	0.00
	7.5	32	2.99	1.06	32	3.24	1.24	0.92
	15.5	32	4.20	2.00	32	4.17	1.66	1.01
2	0	32	5.02	2.63	32	4.90	2.17	1.02
	7.5	32	4.01	1.58	32	4.07	1.38	0.99
	15.5	32	4.55	2.19	32	4.50	2.05	1.01
3	0	32	5.04	2.17	32	5.00	2.29	1.01
	7.5	32	4.20	1.81	32	4.43	1.84	0.95
	15.5	32	4.18	1.95	32	4.13	1.72	1.01
4	0	32	4.51	1.85	32	4.69	2.10	0.96
	0.33	32	4.16	1.70	32	4.16	1.90	1.00
	0.67	32	4.72	1.86	32	4.72	1.86	1.00
	1	32	5.51	2.07	32	5.78	1.94	0.95
	1.5	32	6.42	2.40	32	6.61	2.30	0.97
	2	32	6.58	2.25	32	6.85	2.61	0.96
	2.5	32	6.85	2.68	32	7.15	2.85	0.96
	3	32	6.78	2.67	32	7.03	2.94	0.96
	4	32	6.43	2.33	32	6.84	2.52	0.94
	5	32	6.47	2.71	32	6.77	2.35	0.96
	6	32	5.34	2.35	32	5.59	2.01	0.96
	7	32	4.46	2.11	32	4.47	1.57	1.00
	8	32	3.74	1.69	32	3.86	1.44	0.97

Statistical Analysis: Standard non-compartmental pharmacokinetic techniques were applied to the analysis of the plasma level data for the study. The pre-dose samples for the first dosing on each day were assigned nominal sampling times of zero. The pre-dose samples from the second and third dosing intervals on each day (days 1 to 3) were assigned nominal sampling times of 7.5 hours and 15.5 hours to more closely correspond to the actual draw times.

Achievement of Steady-State:

Statistical procedures were applied to the data from days 2-4 to examine whether steady-state had been achieved by the tenth dose. An analysis of variance was performed, using the three "zero-time" plasma concentration values (obtained early in the morning of days 2-4). The results of the ANOVA on the "zero-time" trough data (page 4871) demonstrated no significant effect of time, drug (i.e. Treatment A versus

Treatment B) or drug* time interaction ($p>0.4544$ for all tests). This indicated that steady-state drug concentrations had been achieved.

The arithmetic mean and standard deviation pharmacokinetic parameters for each formulation, calculated from the untransformed data, are presented in Table below.

Table 13: Arithmetic Means of Pharmacokinetic Parameters

Parameter	Test Formulation Mean (SD)	Reference Formulation Mean (SD)	Ratio (A/B)
$AUC_{0-\tau}$ (ng-hr/mL)	45.58 (17.56)	47.31 (16.96)	0.96 (1.04)
Cmax (ng/mL)	7.43 (2.96)	7.74 (2.89)	0.96 (1.02)
Cmin (ng/mL)	3.74 (1.69)	3.86 (1.44)	
Tmax (hr)	2.95 (1.15)	3.16 (1.32)	0.93 (0.87)
FLUX1[a](%)	64.74	65.65	
FLUX2[b](%)	98.66	100.52	

$AUC_{0-\tau}$ = $AUC_{72\text{-}80hr}$.
Cav = $AUC_{0-\tau}$ /8 = 5.70 for Test
Cav = $AUC_{0-\tau}$ /8 = 5.91 for Reference
a FLUX1=(Cmax-Cmin)*100/($AUC_{0-\tau}$ /8)
b FLUX2=(Cmax-Cmin)*100/Cmin=Swing (%)
FLUX1 and FLUX2 are the Arithmetic Means of all subjects' flux1 and flux2, respectively.

The summary of 90% confidence interval limits, least square mean (LSM) ratios, inter-subject variability, and intra-subject variability for the critical pharmacokinetic parameters is presented in Table 14 below.

Table 14: Summary of 90% Confidence Limits and Variability

	Ln(AUCτ)	Ln(Cmax)
90% CI (%)	93.4 - 98.5	92.1 - 99.3
LSM Ratio (Test/Ref) %	95.9	95.6
Intra-subject CV (%)	6.17	8.83
Inter-subject CV (%)	52.9	53.1

VI. Product Formulation:

The composition of the test formulation is presented in Table 15 below.

Table 15. Composition of Mallinckrodt's Methylin™ ER (Methylphenidate HCl Extended-release Tablets, USP (20 mg)

Ingredients	Amounts (mg) /Tablet
Methylphenidate	20.000
Hydroxypropyl Methylcellulose	
Magnesium Stearate	
Microcrystalline Cellulose	
Purified Water	
Talc	
Total	

VII. In Vitro Dissolution Testing Results:

The firm has conducted dissolution testing using the USP dissolution method for Methylphenidate Hydrochloride ER tablets (USP 23, supplement 5, pg. 3423) as presented below:

The USP method:

Media: Water, 500 mL
Apparatus: Paddle
RPM: 50
Specifications:

The dissolution data are presented in Table 16.

Table 16. In Vitro Dissolution Testing						
Drug (Generic Name): Methylphenidate hydrochloride Dosage Form: Extended Release Tablet Dose Strength: 20 mg						
I. Conditions for Dissolution Testing: Apparatus: Paddle Speed: 50 rpm No. Units 12 Medium: Water Volume: 500 ml Sampling Time: 1, 2, 3.5, 5 and 7 hours Reference Product: Ritalin-SR® 20 mg tablets (Ciba-Geigy Corp.)						
II. Results of In Vitro Dissolution Testing:						
Time (hr)	Test Lot #MHSC9851			Reference (Ritalin-SR®) Lot # 1T233345		
	Mean	Range	CV%	Mean	Range	CV%
1	37.67%		5.07%	40.92%		2.07%
2	53.79%		4.36%	57.13%		2.28%
3.5	70.23%		4.00%	73.64%		1.74%
5	81.33%		3.99%	84.28%		1.97%
7	90.55%		2.80%	93.11%		1.96%

The dissolution data are acceptable.

Comments:

1. The steady-state drug concentrations were achieved by the tenth dose, as the results of the ANOVA on the "zero-time" trough data demonstrated no significant effect of time, drug (i.e. Treatment A versus Treatment B) or drug*time interaction ($p > 0.4544$ for all tests).

2. The results of the single-dose bioequivalence studies conducted under fasting and fed conditions, and the multiple-dose study conducted under the steady-state conditions, demonstrated that Methylphenidate Hydrochloride Extended-release Tablets, 20 mg (Methylin™ ER) manufactured by Mallinckrodt Inc. are bioequivalent to the reference listed drug, Ritalin-SR® 20 mg Tablets.

3. The dissolution data indicate that Mallinckrodt's Methylphenidate Hydrochloride Extended-release Tablets, 20 mg (Methylin™ ER) and the RLD, Ritalin-SR® 20 mg Tablets had comparable dissolution profiles and both met the USP dissolution specifications.

Recommendations:

1. The single dose bioequivalence studies (under fasting and fed conditions) and the multiple dose study (under fasting condition), conducted on the test product, Mallinckrodt's Methylphenidate Hydrochloride ER Tablet, 20 mg, lot # MHSC9851, comparing it to the reference product, Ritalin-SR® Tablet, 20 mg, lot # 1T233345 of Novartis, have been found acceptable by the Division of Bioequivalence. These studies demonstrated that Methylphenidate Hydrochloride Extended-release Tablets, 20 mg (Methylin™ ER), lot # MHSC9851 manufactured by Mallinckrodt Inc. are bioequivalent to the reference listed drug, Ritalin-SR® 20 mg Tablets.

2. The *in vitro* dissolution testing conducted by Mallinckrodt Inc. on its Methylphenidate Hydrochloride ER Tablet, 20 mg, lot # MHSC9851 and Ritalin-SR® Tablet, 20 mg, lot # 1T233345 of Novartis, using USP dissolution method, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should meet the following specifications:

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- 7/8/99

Concur: ---------- Date: 7/14/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-629

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 75-629

DRUG PRODUCT: Methylphenidate Hydrochloride Extended-release Tablets, USP

FIRM: Mallinckrodt, Inc

DOSAGE FORM: Tablets **STRENGTH:** 10 and 20 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification is provided on pages 1728-9, Vol. 3.4. Acceptable EER dated 11/4/99.

BIO STUDY: 20 mg strength acceptable, 7/14/99 (vol. 2.1).
10 mg strength acceptable, 9/29/99 (vol. 3.1).

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both USP. The firm is using the USP testing methods with the following exceptions: The firm has developed their own method for Assay and Related Substances for the bulk drug substance, and their own method for Identification, Assay, Related Compounds, Blend Uniformity, Uniformity of Dosage Units, and Dissolution for the finished drug product.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: Acceptable 4/20/00.

STERILIZATION VALIDATION (IF APPLICABLE): Not-applicable

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): The exhibit batches used for stability and bio-studies were manufactured with bulk drug substance from Mallinckrodt. The size of the 20 mg exhibit batch #MHSC1-9851 was tablets. The size of the 10 mg exhibit batch #MHSC-9921 was tablets.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): see above.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch size for the 10 mg strength is tablets, and for the 20 mg strength is tablets. The manufacturing process described in the master production record is the same as that described in the exhibit batch record.

CHEMIST: Ruth Ganunis [signature] **DATE:** 4/4/00 4/24/00
SUPERVISOR: Richard Adams R.C. Adams **DATE:** 4/5/00 4/25/00

CC:

Endorsements: (Final with Dates)
HFD-652/ S Pradhan SP
HFD-650/ Y. Huang YLH 7/8/99
HFD-617/ E. Hu EH 7/14/99
HFD-650/ D. Conner DHC 7/14/99

V:\FIRMSAM\ **Mallinckrodt** \LTRS&REV\75629S3D.499

Printed in final on 6/24/99

BIOEQUIVALENCY		Submission date: 4/30/99
1.	Fasting Study (STF) OIC	Strength: 20 mg **Outcome: AC**
2.	Fed Study (STP) OIC	Strength: 20 mg **Outcome: AC**
3.	**Multiple Dose** Study (STM) OIC	Strength: 20 mg **Outcome: AC**
4.	~~**Multiple Dose**~~ Study Amendment (STA) OIC	Submission date: 7/02/99 **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT

ANDA Number: 75-629

Dates of Submission: July 30, 1999
August 30, 1999
November 17, 1999

Applicant's Name: Mallinckrodt Inc.

Established Name: Methylin ER (Methylphenidate Hydrochloride Extended-release Tablets, USP) 10 mg and 20 mg

Labeling Deficiencies

1. CONTAINER

The dark blue background on the principal display panel makes it difficult to see the established name. Please improve the contrast and clarity.

2. INSERT

a. CLINICAL PHARMACOLOGY

i. Revise the second sentence of the fourth paragraph to read, "...of the extended release tablet compared to the immediate release tablet, ...excretion of methylphenidate major metabolite..."

ii. Replace "ER" with "extended release" in the last two sentences of the fourth paragraph.

iii. Replace "receive" with "received" in the first sentence of the last paragraph.

b. ADVERSE REACTIONS

Replace "abdominal" with "abnormal" in the fifth sentence of the first paragraph.

c. HOW SUPPLIED

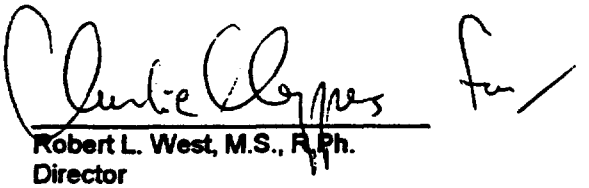
Add "(see USP)" after the storage temperature statement for the immediate release tablets.

Please revise your labels and labeling, as instructed above, and submit twelve final printed copies of the container labels and package insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-629 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Methylphenidate Hydrochloride Extended-release Tablets
20 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

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT

ANDA Number: 75-629

Dates of Submission: July 30, 1999
August 30, 1999
November 17, 1999

Applicant's Name: Mallinckrodt Inc.

Established Name: Methylin ER (Methylphenidate Hydrochloride Extended-release Tablets, USP) 10 mg and 20 mg

Labeling Deficiencies

1. CONTAINER

The dark blue background on the principal display panel makes it difficult to see the established name. Please improve the contrast and clarity.

2. INSERT

a. CLINICAL PHARMACOLOGY

i. Revise the second sentence of the fourth paragraph to read, "...of the extended release tablet compared to the immediate release tablet, ...excretion of methylphenidate major metabolite..."

ii. Replace "ER" with "extended release" in the last two sentences of the fourth paragraph.

iii. Replace "receive" with "received" in the first sentence of the last paragraph.

b. ADVERSE REACTIONS

Replace "abdominal" with "abnormal" in the fifth sentence of the first paragraph.

c. HOW SUPPLIED

Add "(see USP)" after the storage temperature statement for the immediate release tablets.

Please revise your labels and labeling, as instructed above, and submit twelve final printed copies of the container labels and package insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for the label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. MODEL LABELING – Ritalin – SR: Novartis Pharmaceuticals Corporation; revised 9/97, and approved February 20, 1998 (18-029/S-022), FPL dated May 14, 1998, found acceptable on October 26, 1998.

2. INACTIVE INGREDIENTS
Consistent with the inactive ingredients listed on page 1650 in the firm's amendment dated July 30, 1999 for the 10 mg extended-release tablet and on page 5178 of the April 30, 1999, submission.

3. PATENTS/EXCLUSIVITIES

No patents and exclusivities listed. Paragraph II cited. Firm is correct.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - NDA: Do not store above 86°F (30°C). Protect from moisture.
   - ANDA: Store at controlled room temperature 15° to 30°C(59° to 86°F).

5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight, light-resistant container as defined in USP.
   - ANDA: Dispense in a tight, light-resistant container with a child-resistant closure.

6. PACKAGE CONFIGURATION
   - NDA: 100's
   - ANDA: 100's

7. CONTAINER/CLOSURE
   - Container: HDPE
   - Closure: CRC

8. FINISHED DOSAGE FORM
   - NDA: Not scored.
   - ANDA: Not scored. Descriptions of the tablets are consistent with the application. See page 2490 of the amendment dated July 30, 1999, for the 10 mg extended release tablets and page 6144 of the original submission dated April 30, 1999 for the 20 mg extended release tablets.

Date of Review: November 2, 1999 | Dates of Submission: July 30, 1999, August 30, 1999, November 17, 1999

Primary Reviewer: Koung Lee | Date:

Team Leader: Charlie Hoppes | Date:

---

cc:

the package size, strength(s), and date of submission for approval):

nted Labels and Labeling?

e Insert Labeling:
ost-approval:

AL:

proval based upon a petition?	NO
RLD on the 356(h) form:	Ritalin SR
nber:	18-029
rug Name:	Ritalin SR
Firm:	Novartis Pharmaceuticals Corporation
e of Approval of NDA Insert and supplement #:	2/20/98, S-022 (FPL acceptable 10/26/98)
as this been verified by the MIS system for the NDA?	YES
Was this approval based upon an OGD labeling guidance?	NO
Basis of Approval for the Container Labels:	Side by Side
Basis of Approval for the Carton Labeling:	Not Applicable

Other Comments:

Combined insert labeling with ANDA 40-300. Firm is currently using the tradename "Methylin" for the immediate release tablets however, it should be noted that the tradename was not approved.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PI?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	X		
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-629 Date of Submission: April 30, 1999

Applicant's Name: Mallinckrodt Inc.

Established Name: Methylphenidate Hydrochloride Extended-release Tablets, USP

Labeling Deficiencies:

1. GENERAL

   a. Your proposed proprietary names "Methylin" and "Methylin ER" have been forwarded to the Office of Post-Marketing Drug Risk Assessment (OPDRA) for review and comment. We defer final comment on your proposed proprietary name pending notification of OPDRA's findings.

   b. Add "(see USP)" after the storage temperature statement.

2. CONTAINER

   a. See comments 1.a. and 1.b.

   b. Increase the prominence of "Rx only".

3. INSERT

   a. GENERAL

      See comments 1.a. and 1.b.

   b. DESCRIPTION

      i. Revise the first sentence of the first paragraph to read "of 5 mg, 10 mg, and 20 mg and as extended release tablets of 10 mg and 20 mg".

      ii. Revise the third sentence of the third paragraph to read "Each...tablet, for oral administration, contains 10 mg or 20 mg in an extended release formulation.

      iii. Revise the fourth sentence of the third paragraph to read "In addition, each extended-release tablet contains the following inactive ingredients:"

   c. CLINICAL PHARMACOLOGY

      i. Add "%" after "49" and "85" in the second sentence of the third paragraph.

      ii. Add the following as the last paragraph.

      In a clinical study involving adult subjects who receive extended-release tablets, plasma concentrations of methylphenidate's major metabolite appeared to be greater in females than in males. No gender differences were observed for methylphenidate plasma concentration in the same subjects.

   d. WARNINGS

      Relocate the first sentence of the third paragraph to the end of the second paragraph.

e. PRECAUTIONS (Carcinogenesis, Mutagenesis, Impairment of Fertility)

Revise the second paragraph to read "Methylphenidate did not cause any increases in"

f. HOW SUPPLIED

i. Relocate the parenthesis such that the part that is trademarked is within it.

ii. The description of your Methylphenidate Hydrochloride Tablet USP, 10 mg is inconsistent with the tablet description in your approved labeling for ANDA 40-300. Please revise and/or comment.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies of the container labels and package insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling?
- Container Labels:
- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

• Was this approval based upon a petition?	NO
• What is the RLD on the 356(h) form:	Ritalin SR
• NDA Number:	18-029
• NDA Drug Name:	Ritalin SR
• NDA Firm:	Novartis Pharmaceuticals Corporation
• Date of Approval of NDA Insert and supplement #:	2/20/98, S-022 (FPL acceptable 10/26/98)
• Has this been verified by the MIS system for the NDA?	YES
• Was this approval based upon an OGD labeling guidance?	NO
• Basis of Approval for the Container Labels:	Side by Side
• Basis of Approval for the Carton Labeling:	Not Applicable

Other Comments:

Combined insert labeling with ANDA 40-300. Firm is currently using the tradename "Methylin" for the immediate release tablets however, it should be noted that the tradename was not approved.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PI?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	X		
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR	[redacted]	[redacted]	[redacted]
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive ingredients: (FTR: List page # in application where inactives are listed)	[redacted]	[redacted]	[redacted]
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)	[redacted]	[redacted]	[redacted]
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)	[redacted]	[redacted]	[redacted]
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. MODEL LABELING – Ritalin – SR: Novartis Pharmaceuticals Corporation; revised 9/97, and approved February 20, 1998 (18-029/S-022), FPL dated May 14, 1998, found acceptable on October 26, 1998.

2. INACTIVE INGREDIENTS
Consistent with the inactive ingredients listed on page 1650 in the firm's amendment dated July 30, 1999 for the 10 mg extended-release tablet and on page 5178 of the April 30, 1999, submission.

3. PATENTS/EXCLUSIVITIES

No patents and exclusivities listed. Paragraph II cited. Firm is correct.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - NDA: Do not store above 86°F (30°C). Protect from moisture.
   - ANDA: Store at controlled room temperature 15° to 30°C(59° to 86°F).

5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight, light-resistant container as defined in USP.

- ANDA: Dispense in a tight, light-resistant container with a child-resistant closure.

6. PACKAGE CONFIGURATION
   - NDA: 100's
   - ANDA: 100's

7. CONTAINER/CLOSURE
   - Container: HDPE
   - Closure: CRC

8. FINISHED DOSAGE FORM
   - NDA: Not scored.
   - ANDA: Not scored. Descriptions of the tablets are consistent with the application. See page 2490 of the amendment dated July 30, 1999, for the 10 mg extended release tablets and page 6144 of the original submission dated April 30, 1999 for the 20 mg extended release tablets.

Date of Review: November 2, 1999 Date of Submission: April 30, 1999, for the 20 mg
July 30, 1999, for the 10 mg

Primary Reviewer: Koung Lee Date: 11/9/99

Team Leader: Charlie Hoppes Date:

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cc:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-629

CORRESPONDENCE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-629

CORRESPONDENCE

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 314.654.2000 www.mallinckrodt.com

TELEPHONE AMENDMENT TO A PENDING APPLICATION
FINAL PRINTED LABELING

April 14, 2000

NDA ORIG AMENDMENT
N/AF

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 75-629: Methylin™ ER (methylphenidate HCl extended-release tablets, USP 10 mg and 20 mg)

Dear Sir or Madam:

The following information is provided in response to the telephone request from Charles Hoppes of the Agency in reference to ANDA 75-629 as filed on April 30, 1999 and amended July 30, 1999, September 7, 1999, November 17, 1999, and February 14, 2000. Pursuant to Section 505(j) of the Food Drug and Cosmetic Act, Mallinckrodt Inc. submitted ANDA 75-629 seeking approval to market Methylin™ ER (methylphenidate HCl extended-release tablets, USP 10 mg and 20 mg). Methylin™ ER (methylphenidate HCl extended-release tablets, USP) are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

Methylin™ ER (methylphenidate HCl extended-release tablets, USP 10 mg and 20 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability at the Hobart, New York facilities. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

Twelve copies of the package insert as final printed labeling are provided in an archival copy (in blue folder).

MALLINCKRODT

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

MAJOR AMENDMENT TO A PENDING APPLICATION
LABELING RESPONSE

November 17, 1999

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 75-629: Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg)

Dear Sir or Madam:

The following information is provided in response to the November 9, 1999 facsimile letter from the Agency in reference to ANDA 75-629 as filed on April 30, 1999 and amended July 30, 1999 and September 7, 1999. Pursuant to Section 505(j) of the Food Drug and Cosmetic Act, Mallinckrodt Inc. submitted ANDA 75-629 seeking approval to market Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg). Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP) are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

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

For ease of reference, the entire amendment is numbered sequentially in the bottom right corner so that both text and attachments bear consecutive numbering. If necessary, the pagination uses alphabetical sequencing following a number.

Four copies of the draft labeling are provided in both an archival copy (in blue folder) and a technical review copy (in red folder). In addition, to facilitate review and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the proposed labeling with that submitted in the July 30, 1999 submission with all differences annotated and explained is provided.

Correspondence related to this proposal 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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-629 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Methylphenidate Hydrochloride Extended-release Tablets
10 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

MALLINCKRODT

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

MAJOR AMENDMENT TO A PENDING APPLICATION

October 29, 1999

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 75-629: Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg)
CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

Dear Sir or Madam:

The following information is provided in response to the October 12, 1999 facsimile letter from the Agency in reference to ANDA 75-629 as filed on April 30, 1999 and amended July 30, 1999 and September 7, 1999. Pursuant to Section 505(j) of the Food Drug and Cosmetic Act, Mallinckrodt Inc. submitted ANDA 75-629 seeking approval to market Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg). Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP) are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

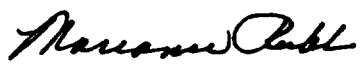
Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability at the Hobart, New York facilities. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt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

For ease of reference, the entire amendment is numbered sequentially in the bottom right corner so that both text and attachments bear consecutive numbering. If necessary, the pagination uses alphabetical sequencing following a number. Whenever the text references an attachment, a \ cross-reference will be provided to the section where the attachment can be found. If an attachment is referred to more than once, it will only be included once in the submission.

Three copies of the amendment are filed: an archival copy (in blue folder), a technical review copy (in red folder), and field copies (in maroon folders). The technical review copy and the field copies are identical to the archival copy and a certification attesting to this is provided in the Field Copy Certification.

Correspondence related to this proposal 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

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-629 APPLICANT: Mallinckrodt, Inc.

DRUG PRODUCT: Methylphenidate Hydrochloride Tablets Extended-Release USP, 10 and 20 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. We recommend that you lower your Single and Total Impurity limits you have established for your Related Substance testing of Methylphenidate Hydrochloride, USP to be more in line with the actual data observed.

2. Your testing for Magnesium Stearate, NF does not appear to be in full accordance with current compendia. See USP 23. Supp. 10.

3. We note that you have stated that the amount of Magnesium Stearate quantity for the ten granulations is calculated and the amount of magnesium stearate needed for blending is adjusted accordingly (approximate Please clarify if you intend to make adjustments to your formulation provided in the Components and Composition statement.

4. We also note that you are proposing a holding time on the tablets stored in a bulk container. Please clarify how this affects your expiration dating calculation for the product. Itis recommended that computation of the expiration dating period of the drug product should begin no later than the time of quality control release of that batch, and the date of release should generally not exceed 30 days from the production date. We define the date of production as the date that the first step of manufacture is performed which involves the combining of an active ingredient, antioxidant, or preservative, with other ingredients in the production of a dosage form. Please provide assurance that your expiration dating policy is in accordance with this recommendation.

5. Since this drug is less than ıctive, we request that you adopt the final blend homogeneity specification recommended by the Office of Generic Drugs. A specification of (mean) with an RSD is recommended. The use of a Stage II testing criteria is unacceptable.

6. Although the USP 23 includes a large allowable impurities specification for the single and total impurities for this product, based on the data you have supplied for both exhibit lots, you are requested to lower your impurities limits for the drug product on release.

7. It is unclear why you express your Hardness specification in Kg. Tablet hardness is generally expressed as a force per unit area, such as in Kp.

8. We also believe that the stability data provided do not justify the Related Substances limits you have established for stability testing also. We recommend that you also lower these limits to be more inline with the data you have provided. This is especially true of the specification set for the Threo-α-phenyl-2-piperidineacetic Acid Hydrochloride.

9. Although you propose to include a specification for Moisture on stability, a limit of igh. We recommend that this also be lowered.

Sincerely yours,

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: 75-629 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Methylphenidate Hydrochloride Extended-release Tablets
20 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

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134 Phone: (314) 654-2000 Fax: (314) 654-6496

AMENDMENT TO A PENDING APPLICATION

September 7, 1999

NDA ORIG AMENDMENT

N/A

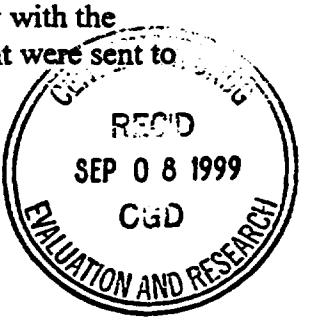
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 75-629: Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits an amendment to the above referenced application under 21 C.F.R.§314.60(a). ANDA 75-629 is for Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP), a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). The purpose of this amendment is to provide updated documentation which reflects the deletion of the term "tentative" for product specifications for tablet thickness, hardness, and moisture. In addition, stability limits for tablet moisture have been established and the limits for Total Related Substances have been reduced based on the data for the exhibit lots. Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 20 mg and 10 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability at Mallinckrodt Inc. in Hobart, New York. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

The archival (blue folders) and technical review copies of this amendment consists of one volume. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this amendment, true copies of the technical sections of the amendment were sent to the local district offices. These "field copies" are contained in maroon folders.



For more detailed information on the organization of this amendment, 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,

/Marianne Robb/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-629 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Methylphenidate Hydrochloride Extended-release Tablets
10 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

CC:

Endorsements: (Final with Dates)
HFD-652/ S Pradhan
HFD-650/ Y. Huang 8/30/99
HFD-617/ E. Hu 9/29/99
HFD-650/ D. Conner 9/29/99

V:\FIRMSAM\ **Mallinckrodt** \LTRS&REV\75629SDA.799

Printed in final on 8/9/99

BIOEQUIVALENCY AMENDMENT

Submission date: 7/30/99

1. Fasting Study (STF)

Strength: 10 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

...ES MANAGEMENT BRANCH MAR 22 1993

93 MAR 24 PM 2:10

MD Pharmaceutical Inc.
Attention: Eugenia Vajadaffy
3501 West Garry Ave.
Santa Ana, California 92704

Docket No. 92P-0400/CP1

Dear Madam:

This is in response to your petition filed on October 20, 1992, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following product: Methylphenidate Hydrochloride Extended-release Tablets USP, 10 mg. The listed drug product to which you refer in your petition is Methylphenidate Extended-release Tablets USP, 20 mg, manufactured by MD Pharmaceutical Inc.

We have revieved your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act), and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced product.

Your request involves a change in strength from that of the listed drug product (i.e., from a 20 mg extended-release tablet to a 10 mg extended-release tablet). The change you request from is the type of change that is authorized under the Act.

Under Section 505(j)(2)(C)(i) of the Act the Agency must approve petitions seeking a strength which differs from the strength of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing strength.

The Agency has determined that a change in strength from a 20 mg extended-release tablet to a 10 mg extended-release tablet for this specific product does not pose questions of safety or effectiveness and concludes, therefore, that investigations are not necessary in this instance. The basis for this determination is that the proposed product will have the same uses, doses, and route of administration as the listed drug. The approved labeling of the reference listed drug recommends that doses of extended-release tablets may be used in place of immediate-release tablets when the eight hour dose of extended-release tablets corresponds to the titrated eight hour dose of the immediate-release tablets. The change in strength will allow

92P-0400

PAV1

smaller doses of extended-release tablets to be administered, thus facilitating dosage adjustment and reducing the dosing interval for certain patients. In addition, if shown to meet the bioavailability requirements, the proposed product can be expected to have the same therapeutic effect as the listed reference drug product.

The approval of this petition to allow an ANDA to be submitted for the above-referenced product does not mean that the Agency has determined that and ANDA will be approved for the product. The determination that an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

To permit review of your ANDA submission you must submit all information required under Section 505(j)(2)(A) and (B) of the Act. To be approved, the product will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you contact the Acting Director, Division of Bioequivalence at (301) 295-8355 to determine the specific requirements for this product. During the review of your application, the Agency may require the submission of additional information.

The listed drug product to which you refer in your ANDA must be the one upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, HFD-305, Park Building, 12420 Parklawn Drive, Room 1-23, Rockville, MD 20857.

Sincerely yours,

3/17/99

Roger Williams, M.D.
Director
Office of Generic Drug
Center for Drug Evaluation and Research

cc:

HFD-1 (Chron. File)
HFD-650 (Wu)
HFD-360
HFD-224

Correspondence related to this proposal 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 James Baker, Ph.D. at (314) 654-5729

Sincerely,

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

MALLINCKRODT

labeling received drafted 4/19/00 C. Vezza

Mallinckrodt Inc. 675 McDonnell Boulevard P.O. Box 5840 St. Louis, MO 63134 Phone: 314-654-2000 www.mallinckrodt.com

AMENDMENT TO A PENDING APPLICATION
FINAL PRINTED LABELING

ORIG AMENDMENT

NDA

:bruary 14, 2000

)ffice 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 75-629: Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg)

Dear Sir or Madam:

The following information is provided in response to the January 24, 2000 facsimile letter from the Agency in reference to ANDA 75-629 as filed on April 30, 1999 and amended July 30, 1999, September 7, 1999, and November 17, 1999. Pursuant to Section 505(j) of the Food Drug and Cosmetic Act, Mallinckrodt Inc. submitted ANDA 75-629 seeking approval to market Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg and 20 mg). Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP) are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

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

Twelve copies of the final printed labeling are provided in an archival copy (in blue folder). In addition, to facilitate review and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the proposed labeling with that submitted in the November 17, 19999 amendment with all differences annotated and explained is provided.

CENTER FOR DRUG EVALUATION AND RESEARCH RECD FEB 15 2000 OGD

Correspondence related to this proposal 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 James Baker, Ph.D. at (314) 654-5729

Sincerely,

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

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134 Phone: (314) 654-2000 Fax: (314) 654-6496

AMENDMENT TO A PENDING APPLICATION

July 30, 1999

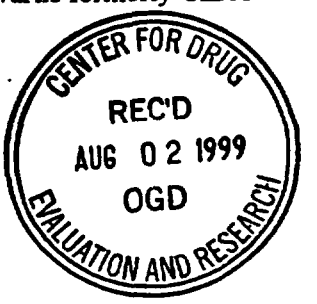
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 75-629: Methylin™ ER
(Methylphenidate Hydrochloride Extended-release Tablets, USP)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits an amendment to the above referenced application un 21 C.F.R.§314.60(a). ANDA 75-629 is for Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP), a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). This amendment provides for an additional strength, Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg), to be manufactured, processed, packaged, labeled, and tested for release and stability at Mallinckrodt Inc. in Hobart, New York. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

To support the filing of this amendment an exhibit/stability lot of Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg) was manufactured. Documentation is provided for a classical two-way crossover bioequivalence study. In addition, a multi-point dissolution profile study was performed in the application medium, comparing the proposed drug product, Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 10 mg), to that of the reference listed drug, Ritalin-SR® (20 mg), manufactured by Novartis formerly CIBA Pharmaceutical Company a Division of CIBA-Geigy Corporation.



The archival copy (blue folders) of this amendment consists of five volumes and the technical review copy consists of three volumes (Sections I through V, and VII through XXI in red folders). A separate copy of the bioequivalence section is being submitted in orange folders (Sections I through VII; three volumes). This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this amendment, true copies of the technical sections of the amendment were sent to the local district offices. These "field copies" are contained in maroon folders.

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

In addition, an electronic submission will arrive within 30 days of this paper application. In the event review of the paper submission is initiated before the electronic submission is received and processed, it is understood that the review will be completed using the hard copy only.

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
Phone: (314) 654-6258
Fax: (314) 654-6496

ANDA 75-629

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd
P.O. BOX 5840
St. Louis MO 63134-0840

MAY 17 1999

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.

NAME OF DRUG: Methylphenidate Hydrochloride Extended-release Tablets USP, 20 mg

DATE OF APPLICATION: April 30, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 3, 1999

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

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

Robert L. West, M.S., R.Ph.
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

TELEPHONE AMENDMENT

July 2, 1999

NDA ORIG AMENDMENT
N/A8

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 75-629: Methylin™ ER 20 mg
(Methylphenidate Hydrochloride Extended-release Tablets, USP)

Dear Sir:

The following information is provided in response to a June 22, 1999 request from Elaine Hu of the Agency for values or statistical anaysis for several pharmacokinetic parameters which are unique to multi-dose (steady state) studies. These include Cmin, Cav, Flux1, and Flux2 along with analysis of variance of the estimates.

Correspondence related to this amendment 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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 06 1999
OGD

MALLINCKRODT

Click for S. Mitchell 5/13/99

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

ORIGINAL APPLICATION

April 30, 1999

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: Methylin™ ER
(Methylphenidate Hydrochloride Extended-release Tablets, USP 20 mg)

Dear Madame or Sir:

Pursuant 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 Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 20 mg). Methylphenidate Hydrochloride Extended-release Tablets, USP are a Schedule II prescription drug indicated for the treatment of narcolepsy and Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children).

Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 20 mg) will be manufactured, processed, packaged, labeled, and tested for release and stability at Mallinckrodt Inc. in Hobart, New York. The packaged product will be held and distributed by Mallinckrodt Inc. at Mallinckrodt & Second Streets in St. Louis, Missouri.

To support the filing of this application an exhibit/stability lot of Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 20 mg,) was manufactured. Documentation is provided for a classical two-way crossover bioequivalence study, a three-way crossover food effects study, and a two-way crossover fasting study at steady state (multi-dose).

In addition, a multi-point dissolution profile study was performed in the application medium, comparing the proposed drug product, Methylin™ ER (Methylphenidate Hydrochloride Extended-release Tablets, USP 20 mg), to that of the reference listed drug, Ritalin-SR®, (20 mg,) manufactured by Novartis formerly CIBA Pharmaceutical Company a Division of CIBA-Geigy Corporation.

The archival copy (blue folders) of this application consists of thirteen volumes and the technical review copy consists of four volumes (Sections I through V, and VII through XXI in red folders). A separate copy of the bioequivalence section is being submitted in orange folders (Sections I through VII; ten volumes). This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of the 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.

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.

In addition, an electronic submission will arrive within 30 days of this paper application. In the event review of the paper submission is initiated before the electronic submission is received and processed, it is understood that the review will be completed using the hard copy only.

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
Phone: (314) 654-6258
Fax: (314) 654-6496