CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-419

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I

NDA:	21,419
Brand Name:	Methylin®; [redacted]
Generic Name	Methylphenidate Hydrochloride (MPH HCl)
Dosage form and Strength:	Oral solution, 5mg/5ml (or 1mg/ml), 10mg/5ml (or 2mg/ml)
Route of administration:	Oral
Indication:	Attention Deficit Disorders and narcolepsy
Sponsor:	Mallinckrodt Inc.
Type of submission:	New NDA [505(b)(2)]
Clinical Division:	HFD-120/Neuropharmacological Drug Products
OCPB Division:	HFD-860/DPEI
Priority:	Standard
Submission date:	07/31/01; 10/16/01 (electronic submission of 2 BE studies); 05/07/02 (Response to FDA questions)
OCPB Consult date:	08/14/01
Reviewer:	Wen-Hwei Chou, Pharm.D., Ph.D.
Team leader:	Ramana Uppoor, Ph.D.

Executive summary

This is a 505 (b)(2) NDA submission for Methylin [redacted] oral solution (5mg/5ml, and 10mg/5ml). The sponsor submitted two BE studies (one pivotal in fasted condition and another in fed condition) using higher strength solution against reference listed drug, Ritalin® tablet. The sponsor requested waiver of BE study on lower strength (5mg/5ml). The approvability of this NDA is based on the two BE studies submitted. No clinical trials were conducted with Methylin [redacted]

Overall, the sponsor has submitted sufficient information to support the approval. This is based on the bioequivalence of the 10mg/5ml and granting of biowaiver for the lower strength (5mg/5ml) based on the proportional similarity in composition of two oral solution strengths and the fact that there is no excipient that is known to significantly affect the drug absorption.

The proposed label text is essentially the same as the reference listed drug product Ritalin® tablet except the text that reflects change from reference listed product Ritalin® to an oral solution dosage form. However, relevant clinical pharmacology information is lacking in current Ritalin® label. In the forty-five days filing meeting, we have requested the sponsor to update label from available sources. Unfortunately, during a teleconference dated April 15, 2002, the sponsor indicated that the firm has [redacted] From the Office of Clinical Pharmacology and Biopharmaceutics perspective, it is important to modify and incorporate current knowledge of methylphenidate in the Methylin [redacted] labeling. The sponsor will be requested to update label from literature and/or other available resources. Based on available information from current submission including the two studies and literature, we have suggested some relevant PK information below to be incorporated in the label.

Recommendation:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed this NDA and finds it acceptable. Please forward "comments to the sponsor" to the sponsor. These labeling comments should be adequately addressed by the sponsor.

Comments to the sponsor:
Labeling:
We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the pharmacokinetics of methylphenidate is lacking in the current label for the reference listed drug Ritalin® as well as your proposed label for Methylin [redacted] We request you to update the labeling of Methylin [redacted] to incorporate the above information from literature and/or other available resources. Based on available information from current submission including the two studies and literature, we suggest following relevant PK information should be added to the "Clinical Pharmacology" section of the label:

(H)

Number of Pages Redacted 1

❖❖❖

Draft Labeling
(not releasable

[redacted]

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT Initialed by Ramana Uppoor, Ph.D. _____

cc: NDA21-419 Methylin® [redacted] HFD-120, HFD-860 (Mehta, Marroum, Uppoor, Chou), Central Documents Room (Biopharm-CDR)

Table of contents

Summary of clinical pharmacology and biopharmaceutics findings

Methylphenidate is indicated for the treatment of Attention Deficit Disorder and narcolepsy. The daily dose for adults is on average 20 to 30mg daily administered in divided doses 2 or 3 times daily preferably 30 to 45 minutes before meals. Some patients may require 40 to 60 mg daily. In others, 10 to 15mg daily will be adequate. In children 6 years of age and older, treatment should start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dose of above 60mg is not recommended. Adverse reactions include nervousness, insomnia, palpitations, blood pressure and pulse changes, hypersensitivity, anorexia, nausea, dizziness, headache, dyskinesia, tachycardia.

This is a 505 (b) (2) NDA submission for Methylin [redacted] oral solution (5mg/5ml, 10mg/5ml). The sponsor submitted two BE studies (one pivotal in fasted condition and another in fed condition) using higher strength against reference listed drug, Ritalin® tablet. The sponsor requested waiver of BE study on lower strength (5mg/5ml). The approvability of this NDA is based on the two BE studies submitted.

Overall, the sponsor has submitted sufficient information to support the approval. This is based on the bioequivalence of the 10mg/5ml and granting of biowaiver for the lower strength (5mg/5ml) based on the proportional similarity in composition of two oral solution strengths and the fact that there is no excipient that is known to significantly affect the drug absorption.

The Division of Scientific Investigation (DSI) was requested to audit the clinical study site and analytical site for the pivotal BE study (#610). A form 483 was issued by DSI at the analytical site (1) indicating that the sponsor failed to demonstrate the proposed bench-top stability at 6.5 hours of the drug in EDTA-plasma under the conditions described for the quality control samples and for the subject plasma samples, and (2) indicating that the quality control (QC) samples and subject samples were handled differently (i.e. generally speaking, on average, subject samples were exposed to room temperature 1.5- 2.5 hours longer than QC samples). In light of these issues, we have requested the sponsor to submit additional bench-top stability around 2.5 and 4 hours for QC samples to support the bench-top stability of subject samples.

Subsequently, the sponsor submitted additional benchtop plasma stability study at 1, 3, 4, and 6 hours. These results support the bench-top stability at 4 hours since the percent deviations from original theoretical value up to 4 hours were acceptable ($\leq$15%) except three values [16% and 16.8% at 0.75ng/ml (lowest QC) at 1, 3 hours respectively, 15.5% of 20ng/ml at 4 hours]. In addition, the sponsor indicated that the maximum time that samples sat at room temperature in the analytical sites for both studies (#610 and #722) was 3 hours, therefore, these additional data support the bench-top stability of subject samples at 3 hours that the original submission failed to address.

In addition to the bioanalytical LC-MS/MS assay validation on the EDTA-treated plasma, the sponsor submitted a report on the partial validation of assay for methylphenidate in heparinized plasma against EDTA-treated plasma. This report has not been reviewed here. We will review the validity of this partial validation for heaprinized plasma when the sponsor submits any biostudy where the plasma sample is treated with heparin.

Question based review

(1) What are the proposed dosage strengths, formulation composition, indication, dosing regimen and age ranges for Methylin [redacted]

Methylin [redacted] oral solution has two strengths (5mg/5ml, and 10mg/5ml). Methylin [redacted] is indicated for the treatment of Attention Deficit Disorder and narcolepsy. The daily dose for adults is on average 20 to 30mg daily administered in divided doses 2 or 3 times daily preferably 30 to 45 minutes before meals. Some patients may require 40 to 60 mg daily. In others, 10 to 15mg daily will be adequate. In children 6 years of age and older, treatment should start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dose of above 60mg is not recommended.

(2) Is the bioanalytical assay validated prior to and during the studies?

Overall, the validity of the bioanalytical assay is satisfactory. The LC/MS/MS analytical method for methylphenidate in EDTA treated human plasma was found to be specific, reproducible, sensitive and adequate to characterize the PK of methylphenidate.

However, from the initial DSI investigation, the following deficiencies were found and the sponsor was requested to further address these issues:

(a) The sponsor failed to establish the proposed bench-top stability at 6.5 hours. Specifically, the percent deviations from original theoretical values were [redacted] Seven out of nine stability samples showed greater than 15% percent deviation ([redacted] that is recommended by the Guidance.

(b) From the DSI investigation of pivotal BE study #610, the quality control (QC) samples and subject samples were handled differently (i.e. generally speaking, subject samples were exposed to room temperature 1.5- 2.5 hours longer than QC samples).

Therefore, the sponsor was requested to submit additional bench-top stability around 2.5 and 4 hours for QC samples to support the bench-top stability of subject samples.

Overall, the subsequent response from the sponsor was satisfactory to address the above issues. Specifically, the sponsor submitted additional bench-top plasma stability study at 1, 3, 4, and 6 hours. We considered these bench-top stability results acceptable to establish the bench-top stability at 4 hours. In addition, the sponsor indicated that the maximum time that samples sat at room temperature in the analytical sites for both studies (#610 and #722) was 3 hours.

(3) Is the oral solution bioequivalent to the reference tablet?

The test product of Methylin [redacted] (10mg/5ml) is bioequivalent to the reference product of Ritalin® tablet. The sponsor has conducted a fasting BE study on the higher strength of Methylin [redacted] solution (10mg/5ml). Results from the BE study are discussed below. The 90% CI of test-to-reference ratio fell within the recommended 0.80-1.25 goal-post for the log transformed PK parameters (Cmax and AUC0-inf) and the elimination half-lives and tmax were comparable for test and reference products (Table1 & 2, Fig 1)

Fig. 1

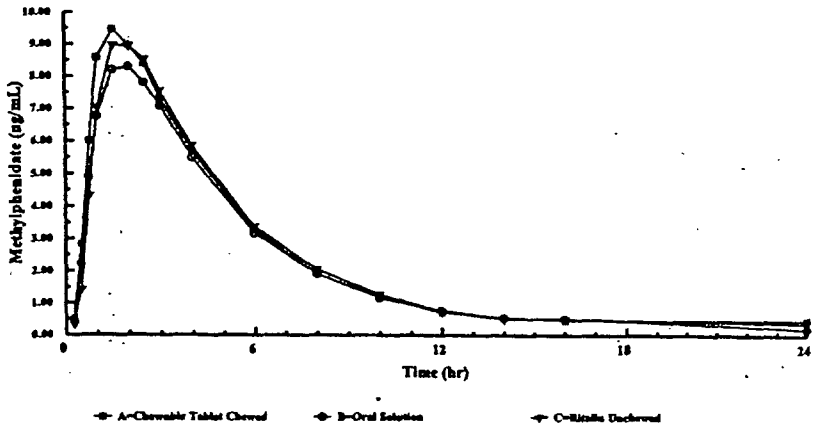


Figure 11.5-1: Mean Plasma Concentration Profile of Methylphenidate Formulations (20 mg)

Table. 1

Table 3.1.5 Summary of 90% Confidence Intervals and CV MPH HCl Oral Solution (B) versus Ritalin® Tablet (C)

	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	91.26-98.02	90.90-97.75	90.13-99.11	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	94.58	94.26	94.52	101.51	98.29	90.55
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82

*N/A = Not applicable
Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610

Table 2

Table 3.1.2 Summary of Untransformed Pharmacokinetic Data [Mean (SD)]

Parameter	Treatment Groups		
	MPH HCl Chewable Tablet (A)	MPH HCl Oral Solution (B)	Ritalin® Tablet Unchewed (C)
N	33	33	34
AUCinf (ng·hr/mL)	49.97 (16.28)	46.70 (15.58)	49.66 (14.80)
AUCt (ng·hr/mL)	48.32 (15.95)	45.10 (15.37)	48.01 (14.35)
Cmax (ng/mL)	9.982 (2.607)	9.075 (2.610)	9.804 (2.723)
Kel (1/hr)	0.2515 (0.0363)	0.2604 (0.0385)	0.2579 (0.0374)
T1/2 (hr)	2.826 (0.516)	2.725 (0.449)	2.756 (0.506)
Tmax (hr)	1.530 (0.413)	1.712 (0.597)	1.868 (0.432)

Reference: Tables 14.2.1-8 through 14.2.1-10 of MI report for Study 610

(4) Is there a food effect on bioavailability of the oral solution?

Significant food-effect on the PK of Methylin[redacted] oral solution has been demonstrated. The 90% CI of test (fed)-to-reference (fasted) ratio fell outside of the recommended 0.80-1.25 goal-post for average BE assessment for the log transformed PK parameters (Cmax and AUC0-inf) (Table 3). The elimination half-lives were comparable for test and reference products. Tmax was prolonged with food from 1.7 hours to 2.7 hours (Table 4).

Overall, these results (BE of Methylin [redacted] and Ritalin tablet in fed state), combined with the prior demonstration that these formulations are bioequivalent in the fasted state (QBR #3), indicate that although a statistically significant food effect on methylphenidate PK may exist, the magnitude of this effect appears to be comparable for the test formulation methylphenidate HCl oral solution (10 mg/5ml) and Ritalin® tablet 20 mg (Table 5).

Table 3

Table 3.2.3 Summary of 90% Confidence Intervals and CV MPH Oral Solution with Food (B) versus MPH HCl Oral Solution Fasting (A)							
	Ln (AUCinf)	Ln (AUCt)	Ln (Cmax)	Ln (AUCtmx)	Kel	T1/2	Tmax
90% CI (%)	123.41-134.45	122.94-134.47	108.43-124.46	81.44-106.71	N/A*	N/A*	N/A*
LSM Ratio B/A (%)	128.82	128.58	116.17	93.22	102.04	98.80	160.23
CV (%)[a]	8.52	8.91	13.71	26.88	9.65	11.77	24.41
P[b]	0.0001	0.0001	0.0006	0.3786	0.4765	0.7317	0.0001

*N/A = Not applicable [a]Intra-subject coefficient of variation [b] p-value from ANOVA contrast Ln (B) – Ln (A)
Reference: Tables 14.2.1-11 through 14.2.1-15 of Mallinckrodt Inc. report for Study 722

Table 4

Table 3.2.2 Summary of Untransformed Pharmacokinetic Data [Mean (SD)]			
	Treatment Groups		
Parameter	MPH HCl Oral Solution Fasting (A)	MPH HCl Oral Solution With Food (B)	Ritalin® Tablet With Food (C)
N	23	24	24
AUCinf (ng·hr/mL)	51.91 (24.73)	64.95 (25.21)	68.71 (26.52)
AUCt (ng·hr/mL)	50.27 (23.73)	62.65 (23.54)	66.24 (25.33)
AUCtmx* (ng·hr/mL)	15.65 (5.21)	14.79 (4.83)	15.71 (6.42)
Cmax (ng/mL)	9.391 (3.002)	10.693 (2.639)	12.079 (3.477)
Kel (1/hr)	0.2411 (0.0346)	0.2477 (0.0408)	0.2401 (0.0483)
T1/2 (hr)	2.955 (0.602)	2.897 (0.663)	3.038 (0.811)
Tmax (hr)	1.707 (0.444)	2.667 (0.747)	2.438 (0.812)

Reference: Tables 14.2.1-8 through 14.2.1-10 of report for Study 722 * AUCtmx = AUC_{0-1}

Table 5

Table 3.2.4 Summary of 90% Confidence Intervals and CV MPH HCl Oral Solution with Food (B) versus Ritalin® Tablet with Food (C)							
	Ln (AUCinf)	Ln (AUCt)	Ln (Cmax)	Ln (AUCtmx)	Kel	T1/2	Tmax
90% CI (%)	91.03-99.03	91.16-99.55	83.82-95.98	86.23-112.45	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	94.94	95.26	89.69	98.47	103.18	95.36	109.40
CV (%)[a]	8.52	8.91	13.71	26.88	9.65	11.77	24.41
p[b]	0.0408	0.0659	0.0087	0.8438	0.2654	0.1686	0.1606

*N/A = Not applicable [a]Intra-subject coefficient of variation [b] p-value from ANOVA contrast Ln (B) – Ln (C)
Reference: Tables 14.2.1-11 through 14.2.1-15 of Mallinckrodt Inc. report for Study 722

(5) Can we waive in vivo BE study for lower strength oral solution?

The biowaiver for lower strength oral solution can be granted based on the following:

- The in-vivo BE study performed on the higher strength (10mg/5ml) versus Ritalin tablet met the recommended criteria for BE (0.8-1.25). (QBR #1)
- The proportional similarity in composition for the two strengths and the fact that there is no excipient that is known to significantly affect the drug absorption (Table. 6)

Table 6 Methylin [redacted] 5mg/5ml and 10mg/5ml are proportionally similar in composition:

Quantitative Formula for Methylin® [redacted] 5 mg/5 mL

Formulation Component	Concentration (mg/mL)	Concentration (kg/ [redacted]	Concentration (kg/ [redacted]
Methylphenidate HCl, USP	1.00	0.60	2.75
Polyethylene Glycol 1450, NF			
Grape Flavor			
Citric Acid anhydrous, USP			
Glycerin, USP			
Purified Water, USP			

Quantitative Formula for Methylin® [redacted] 10 mg/5 mL

Formulation Component	Concentration (mg/mL)	Concentration (kg/t [redacted]	Concentration (kg/ [redacted]
Methylphenidate HCl, USP	2.00	1.20	5.50
Polyethylene Glycol 1450, NF			
Grape Flavor			
Citric Acid anhydrous, USP			
Glycerin, USP			
Purified Water, USP			

APPEARS THIS WAY
ON ORIGINAL

Appendices
Individual study review

An Open-Label, Randomized, Three-Way, Crossover Study to Evaluate the Relative Bioavailability of Two Test Formulations (10 mg Chewable Tablet and 2 mg/mL Liquid) of Methylphenidate Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects Under Fasting Conditions (MI Protocol 1137-00-610)

INVESTIGATOR: [redacted]

STUDY CENTER: [redacted]

STUDY PERIOD: Period 1 -October 28 through October 30, 2000
Period 2- November 4 through November 6, 2000
Period 3 -November 11 through November 13,2000

Analytical testing Laboratory: [redacted]

OBJECTIVE:
The objective of this study was to compare the oral bioavailability of two Mallinckrodt test formulations of methylphenidate HCl (chewable tablets and oral solution) to an equivalent oral dose of commercially available methylphenidate HCl product (Ritalin® 20 mg tablet, Ciba-Geigy Corporation) in a group of healthy subjects under fasting conditions.

Study design:
An open-label, randomized, three-period, three-treatment; six-sequence crossover study in which healthy subjects randomly received three separate drug administrations separated by a washout period of at least 7 days. Subjects fasted for 10 hours prior to dosing and an additional 4 hours after dosing. Drug administration consisted of two Mallinckrodt methylphenidate HCl chewable tablets 10 mg formulation (chewed), 10 mL (20 mg) of the Mallinckrodt 2 mg/mL methylphenidate HCl oral solution, or a single 20 mg tablet of Ritalin® swallowed whole. Subjects were excluded if they were chronic users of tranquilizers, sedatives, aspirin, antibiotics, other medications.

NUMBER OF SUBJECTS:

	Age (years)	Gender
Planned (N=36)	18-48	Males/Females
Actual (N=36)	18-46	Males

Treatment group/Dose/Route/Lot number:
(A) Methylphenidate HCl (2 x 10 mg) chewable tablets (Mallinckrodt Inc., Lot # MHSC0043).
(B) Methylphenidate HCl 10 mL (2 mg/mL) oral solution (Mallinckrodt Inc., Lot #MHSC0044, batch size [redacted] Note: proposed commercial batch size [redacted]).

(C) Reference treatment, Ritalin® 20 mg tablet, Ciba-Geigy Corporation, Lot #1T197608, expiration date 01/02.

PK measures:
Blood samples (10 mL) were obtained prior to dosing and at the 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post-dose following each dose. Blood samples were collected using potassium ethylenediaminetetraacetate (potassium EDTA) as the anticoagulant. Plasma was separated from the collected blood samples. All plasma samples were analyzed for methylphenidate using LC-MS/MS analytical method.

Safety Measures: The safety of methylphenidate oral solution and Ritalin® tablet was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.

Data Analysis
Pharmacokinetics: PK parameters were compared between the two methylphenidate HCl test formulations [2 x 10 mg chewable tablets (chewed) and 10 mL oral solution (2 mg/mL)] and the reference formulation -Ritalin® 20 mg tablet swallowed as a whole tablet. In addition, 90% confidence intervals were calculated for the log-transformed AUCt, AUCinf, and Cmax.
PK parameters, such as AUCt, AUC0-inf, Cmax, Tmax, terminal elimination half-life (Tl/2), and apparent first-order terminal elimination rate constant (Kel) were calculated using the standard non-compartmental approach.

Summary statistics, including the mean, standard deviation, coefficient of variation, and geometric mean for both untransformed and logarithmic values of all PK parameters, are presented. Parametric General Linear Model (GLM) methodology was used in the analysis of selected PK parameters. The SAS GLM procedure was used to perform analysis of variance (ANOVA) on each PK parameter with sequence, drug, period, and subjects nested within sequences as sources of variation. For each formulation, least squares means and the associated standard errors were obtained using the LSMEANS option. The ESTIMATE option of SAS GLM was used to obtain estimates of formulation mean differences.

The natural logarithm of AUCt, AUC0-inf, and Cmax were used in the analysis of bioequivalence. Sequence effects were tested using the subject-within-sequence mean square in the denominator of the F -statistic. Tests on all other effects were performed using the error mean square in the denominator. Bioequivalence was to be established if a 90% confidence interval (CI) on the ratio of formulation averages was completely contained in the interval [80%, 125%].

ANOVA results, 90% CI, and coefficient of variation are presented for AUCt, AUC0-inf, and Cmax; these results are based on log-transformed data.

RESULTS:
Pharmacokinetics: Systemic exposure of methylphenidate HCl was similar for the methylphenidate HCL test formulations, 2 x 10 mg chewable tablets (chewed) and 10 mL oral solution (2 mg/mL), as compared to the reference formulation, Ritalin® 20 mg tablet,

swallowed as a whole tablet (Fig 2, Table 7). The 90% CI requirements for average bioequivalence were met for all PK parameters(Cmax, AUC0-inf) (Table 8, 9, 10). BE was demonstrated among all three formulations.

Fig 2

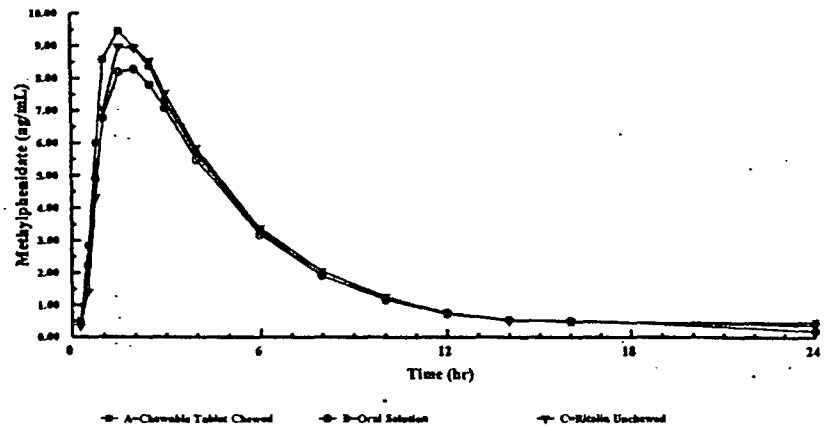


Figure 11.5-1: Mean Plasma Concentration Profile of Methylphenidate Formulations (20 mg)

Table 7

Table 3.1.2
Summary of Untransformed Pharmacokinetic Data
[Mean (SD)]

Parameter	Treatment Groups		
	MPH HCl Chewable Tablet (A)	MPH HCl Oral Solution (B)	Ritalin® Tablet Unchewed (C)
N	33	33	34
AUCinf (ng·hr/mL)	49.97 (16.28)	46.70 (15.58)	49.66 (14.80)
AUCt (ng·hr/mL)	48.32 (15.95)	45.10 (15.37)	48.01 (14.35)
Cmax (ng/mL)	9.982 (2.607)	9.075 (2.610)	9.804 (2.723)
Kel (1/hr)	0.2515 (0.0363)	0.2604 (0.0385)	0.2579 (0.0374)
T1/2 (hr)	2.826 (0.516)	2.725 (0.449)	2.756 (0.506)
Tmax (hr)	1.530 (0.413)	1.712 (0.597)	1.868 (0.432)

Reference: Tables 14.2.1-8 through 14.2.1-10 of MI report for Study 610

Table 8

Table 3.1.3 Summary of 90% Confidence Intervals and CV
MPH HCl Chewable Tablet (A) versus MPH HCl Oral Solution (B)

	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	105.34-113.28	105.64-113.73	106.73-117.53	N/A*	N/A*	N/A*
LSM Ratio A/B (%)	109.24	109.61	112.00	97.01	103.44	89.91
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82

*N/A = Not applicable
Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610

Table 9

Table 3.1.4 Summary of 90% Confidence Intervals and CV MPH HCl Chewable Tablet (A) versus Ritalin® Tablet (C)						
	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	99.69-107.08	99.63-107.15	100.95-111.01	N/A*	N/A*	N/A*
LSM Ratio A/C (%)	103.32	103.32	105.86	98.48	101.68	81.41
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82
*N/A = Not applicable Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610						

Table 10

Table 3.1.5 Summary of 90% Confidence Intervals and CV MPH HCl Oral Solution (B) versus Ritalin® Tablet (C)						
	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	91.26-98.02	90.90-97.75	90.13-99.11	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	94.58	94.26	94.52	101.51	98.29	90.55
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82
*N/A = Not applicable Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610						

Demographic and other baseline characteristics:

- Only male subjects were enrolled. Race distribution was primarily Caucasian (83.3 %, 30/36), with 5 Black subjects (13.9%) and 1 Asian subject (2.8%)(table 11)

Table 11

Table 11.2-1 Summary of Demographics	
Parameter	N = 36
Sex N (%)	
Male	36 (100)
Race N (%)	
Asian	1 (2.8)
Black	5 (13.9)
White	30 (83.3)
Age (years)	
Mean	26.6
Standard Deviation	8.2
Range	18 - 46
Weight (lb)	
Mean	187.8
Standard Deviation	22.2
Range	144 – 232
Height (in)	
Mean	70.3
Standard Deviation	2.3
Range	65 - 76
Reference: Table 14.1	

CONCLUSION: The two Mallinckrodt methylphenidate HCl formulations of chewable tablet (2 x 10 mg) and 10 mL oral solution (2 mg/mL) are well tolerated and bioequivalent to each other and to a commercially available reference formulation of 20 mg methylphenidate tablet (Ritalin®, Ciba-Geigy Corporation).

Reviewer's Comments:

Study design: We consider the design acceptable.

PK measures

- % CV for Cmax and AUC 0-inf were comparable for test products (Methylin — and methylphenidate chewable tablet) and reference listed product Ritalin®.
- Terminal t1/2 for test products (Methylin — and methylphenidate chewable tablet) were comparable to the reference listed product Ritalin®.

BE:

- We consider the test products of Methylin — oral solution and methylphenidate chewable tablet bioequivalent to the marketed products of Ritalin®. The 90% CI of test-to-reference ratio fell within the recommended 0.80-1.25 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf). The elimination half-lives and tmax were comparable for test and reference products. There was no significant sequence or period effect for AUC0-inf and Cmax.

- This reviewer has confirmed the validity of the statistical analysis (90% CI) using an in-house BE program. Following are the results from this analyses for 2 pivotal PK parameters (AUC0-inf and Cmax) (Table 12-1, 12-2 Fig 3; Table 13-1, 13-2, Fig 4):

Methylin — solution versus Ritalin tablet

Table 12-1

AUC 0-inf (BE)	POWER ANALYSIS	
ERROR MEAN SQUARE	6.96117E-03	POWER FOR .2 M(r)= > 99.9834 %
REFERENCE MEAN (LN)	3.858474	POWER FOR -.2 M(r)= > 99.9834 %
TEST MEAN (LN)	3.802749	
NUMBER OF SUBJECTS	36	DETECTABLE DIFFERENCE: 5.836904 %
DEGREES OF FREEDOM	34	
NUMBER OF TREATMENTS.	2	14 SUBJECTS NEEDED FOR A
DELTA	2	10.10214 % DETECTABLE DIFFERENCE

Table 12-2

90% CONFIDENCE INTERVAL		**P VALUES OF TWO ONE-SIDED TEST**
LOWER CI (% OF REF MEAN):	91.48666	p< 80 % REF MEAN: <0.00017
UPPER CI (% OF REF MEAN):	97.77784	p> 120 % REF MEAN: <0.00017
CONCLUSION: PASS	CONCLUSION: PASS	

Fig 3

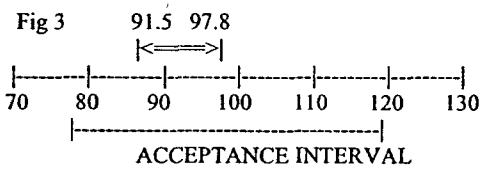


Table 13-1

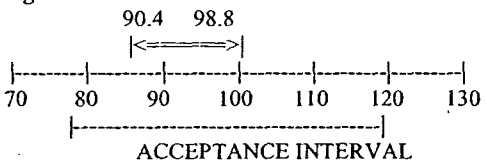
Cmax (BE)		**POWER ANALYSIS**
ERROR MEAN SQUARE	1.227221E-02	POWER FOR .2 M(r)= > 99.9834 %
REFERENCE MEAN (LN)	2.250468	POWER FOR -.2 M(r)= > 99.9834 %
TEST MEAN (LN)	2.194079	
NUMBER OF SUBJECTS	36	DETECTABLE DIFFERENCE: 7.823205 %

DEGREES OF FREEDOM	34	
NUMBER OF TREATMENTS	2	10 SUBJECTS NEEDED FOR A
DELTA	2	17.15032 % DETECTABLE DIFFERENCE

Table 13-2

90% CONFIDENCE INTERVAL		**P VALUES OF TWO ONE-SIDED TEST**
LOWER CI (% OF REF MEAN):	90.43491	p< 80 % REF MEAN: <0.00017
UPPER CI (% OF REF MEAN):	98.78372	p> 120 % REF MEAN: <0.00017
CONCLUSION:	PASS	CONCLUSION: PASS

Fig 4



APPEARS THIS WAY
ON ORIGINAL

An Open-Label, Randomized, Three-Way, Food Effect Study to Evaluate the Relative Bioavailability of Test Formulation of MPH HCl Oral Solution 10 mL (2 mg/mL)(fed and fasted) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation)(fed) in Normal Human Subjects (MIProtocol 8882-00- 722)

INVESTIGATOR: [redacted]

STUDY CENTER: [redacted]

STUDY PERIOD: Period 1 -January 6 through January 8, 2001
Period 2- January 13 through January 15, 2001
Period 3- January 20 through January 22, 2001

Analytical testing Laboratory: [redacted]

OBJECTIVE:
To compare the oral bioavailability of methylphenidate HCl oral solution (2 ng/ml) to an equivalent oral dose of a commercially available methylphenidate HCl product (Ritalin® 20 mg tablet, Ciba-Geigy Corporation) in a group of healthy subjects under fasting and fed conditions. .

Study Design:
An open-label, randomized, three-period, three-treatment, six-sequence crossover study in which healthy subjects randomly received three separate drug administrations separated by a washout period of at least 7 days. Subjects were excluded if they were chronic user of tranquilizers, sedatives, aspirin, antibiotics, other medications. Drug administration consisted of three treatment groups:

Treatment Group/Dosing/Treatment Conditions/ Lot number
(A) Mallinckrodt test formulation -Methylphenidate HCl oral solution (10 mL, 2 mg/ml) following an overnight fast and orally administered under fasting conditions without high fat breakfast. (Mallinckrodt Inc., Lot MHSC0044).
(B) Mallinckrodt test formulation-Methylphenidate HCl oral solution (10 mL, 2 mg/ml) following an overnight fast and consumption of a standardized high-fat breakfast 15 minutes prior to dosing. (Mallinckrodt Inc., Lot MHSC0044).
(C) One 20 mg Ritalin® tablet (Ciba-Geigy Corporation) following an overnight fast and consumption of a high-fat breakfast* 15 minutes prior to dosing. (Ciba-Geigy Corporation, Lot 1 T197608, expiration date 01/2002).

*High-fat breakfast consisted of one buttered English muffin, one fried egg, one slice American cheese, one slice Canadian bacon, one serving of hash brown potatoes, 6 fluid ounces of orange juice, and 8 fluid ounces of whole milk.

NUMBER OF SUBJECTS:

	Age (years)	Gender
Planned (N=24)	18 years or older	Males/Females
Actual (N=24)	18-41	19 Males/5 females

PK measures:
Blood collections (1 x 10 mL) in pre-chilled EDTA tubes were obtained via venipuncture at 0 (pre-dose), 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post-dose. Plasma was separated from the collected blood samples. All plasma samples were analyzed for

methylphenidate using a [redacted] LC-MS/MS analytical method. PK parameters (AUCt, AUCtmax*, AUC0-inf, tmax, Kel, t1/2) were calculated using non-compartmental methods. (*AUCtmax: area under the plasma concentration curve to medium tmax value of reference treatment, a measure of an early exposure)

Safety Measures: The safety of methylphenidate chewable tablet and oral solution administration was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.

Data analysis:
PK: In evaluating the food effect on MPH PK, treatment A (test-fasting) was regarded as the reference treatment. For evaluating the relative bioavailability under the fed condition, treatment C (reference with fed) was used as the reference.

Parametric General Linear Model (GLM) methodology was used in the analysis of selected PK parameters. The SAS GLM procedure was used to perform analysis of variance (ANOVA) on each PK parameter with sequence, drug, period and subjects nested within sequences as sources of variation. For each treatment, least square means and the associated standard errors were obtained using the LSMEANS option. The ESTIMATE option of SAS GLM was used to obtain estimates of treatment mean differences.

The natural logarithm of AUCt, AUC0-inf, AUCtmax and Cmax were used in the analysis of bioequivalence. Sequence effects were tested using the subject-within-sequence mean square in the denominator of the F-statistic. Tests on all other effects were performed using the error mean square in the denominator.

Ninety percent confidence intervals, LSM Ratio, and coefficient of variation were calculated for AUCt, AUC0-inf, AUCtmax and Cmax based on log-transformed data for food-effect.

Results:
- Significant food effect was observed on the oral solution (oral solution, fed versus oral solution, fasted): the LS mean ratios were approximately 129% for AUC0-inf and AUCt, 116% for Cmax, and 160% for Tmax (Fig 5, Table 14, 15)
- For the comparison of tablet, fed versus oral solution, fasted, the LS mean ratios were 135% for AUC0-inf and AUCt, 130% for Cmax, and 146% for Tmax (Table 17). All of these contrasts were statistically significant ($p < 0.001$).
- High-fat breakfast appears to have similar effect on the PK parameters of test formulation methylphenidate HCl oral solution (2 mg/ml) and the RLD Ritalin® tablet 20 mg (Ciba Geigy Corporation). 90% CI for PK parameters (Cmax, AUC0-inf) for Methylin [redacted] fed versus Ritalin fed are within the limit of 80 to 125% (Table 16)

Fig 5

MI PROTOCOL 8882-00-722

FIGURE 14.2.2-1
MEAN PLASMA CONCENTRATION-TIME PROFILE OF METHYLPHENIDATE

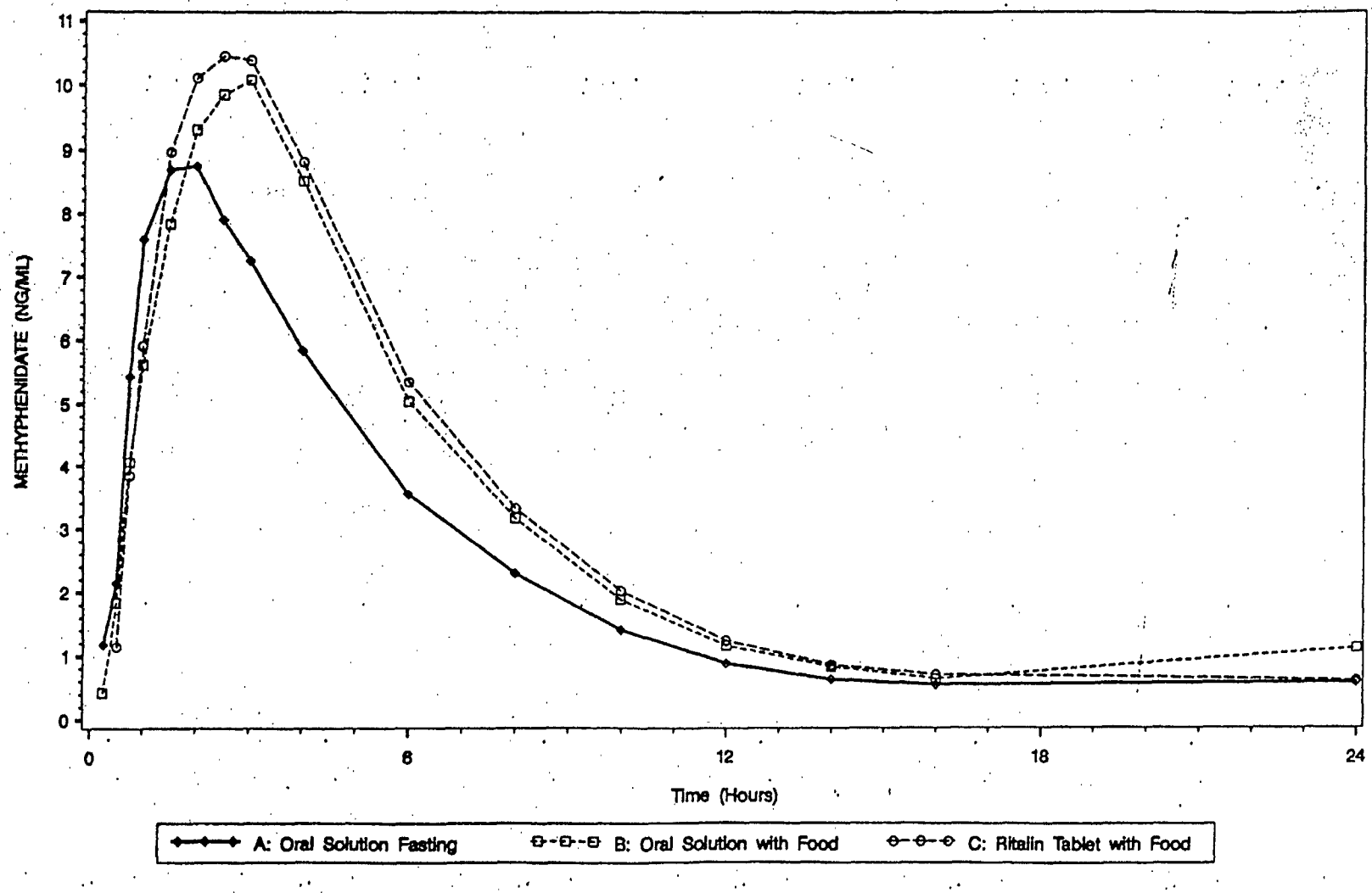


Table 14

Table 3.2.2 Summary of Untransformed Pharmacokinetic Data [Mean (SD)]			
	Treatment Groups		
Parameter	MPH HCl Oral Solution Fasting (A)	MPH HCl Oral Solution With Food (B)	Ritalin® Tablet With Food (C)
N	23	24	24
AUCinf (ng/hr/mL)	51.91 (24.73)	64.95 (25.21)	68.71 (26.52)
AUCt (ng/hr/mL)	50.27 (23.73)	62.65 (23.54)	66.24 (25.33)
AUCtmx* (ng/hr/mL)	15.65 (5.21)	14.79 (4.83)	15.71 (6.42)
Cmax (ng/mL)	9.391 (3.002)	10.693 (2.639)	12.079 (3.477)
Kel (1/hr)	0.2411 (0.0346)	0.2477 (0.0408)	0.2401 (0.0483)
T1/2 (hr)	2.955 (0.602)	2.897 (0.663)	3.038 (0.811)
Tmax (hr)	1.707 (0.444)	2.667 (0.747)	2.438 (0.812)

Reference: Tables 14.2.1-8 through 14.2.1-10 of report for Study 722 * AUCtmx = AUC_{0-1}

Table 15

Table 3.2.3 Summary of 90% Confidence Intervals and CV MPH Oral Solution with Food (B) versus MPH HCl Oral Solution Fasting (A)							
	Ln (AUCinf)	Ln (AUCt)	Ln (Cmax)	Ln (AUCtmx)	Kel	T1/2	Tmax
90% CI (%)	123.41-134.45	122.94-134.47	108.43-124.46	81.44-106.71	N/A*	N/A*	N/A*
LSM Ratio B/A (%)	128.82	128.58	116.17	93.22	102.04	98.80	160.23
CV (%)[a]	8.52	8.91	13.71	26.88	9.65	11.77	24.41
p[b]	0.0001	0.0001	0.0006	0.3786	0.4765	0.7317	0.0001

*N/A = Not applicable [a]Intra-subject coefficient of variation [b]p-value from ANOVA contrast Ln (B) – Ln (A)
Reference: Tables 14.2.1-11 through 14.2.1-15 of Mallinckrodt Inc. report for Study 722

Table 16

Table 3.2.4 Summary of 90% Confidence Intervals and CV MPH HCl Oral Solution with Food (B) versus Ritalin® Tablet with Food (C)							
	Ln (AUCinf)	Ln (AUCt)	Ln (Cmax)	Ln (AUCtmx)	Kel	T1/2	Tmax
90% CI (%)	91.03-99.03	91.16-99.55	83.82-95.98	86.23-112.45	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	94.94	95.26	89.69	98.47	103.18	95.36	109.40
CV (%)[a]	8.52	8.91	13.71	26.88	9.65	11.77	24.41
p[b]	0.0408	0.0659	0.0087	0.8438	0.2654	0.1686	0.1606

*N/A = Not applicable [a]Intra-subject coefficient of variation [b] p-value from ANOVA contrast Ln (B) – Ln (C)
Reference: Tables 14.2.1-11 through 14.2.1-15 of Mallinckrodt Inc. report for Study 722

Table 17

Table 3.2.5 Summary of 90% Confidence Intervals and CV Ritalin® Tablet with Food (C) versus MPH Oral Solution Fasting (A)							
	Ln (AUCinf)	Ln (AUCt)	Ln (Cmax)	Ln (AUCtmx)	Kel	T1/2	Tmax
90% CI (%)	129.99-141.61	129.06-141.16	120.89-138.76	82.70-108.36	N/A*	N/A*	N/A*
LSM Ratio C/A (%)	135.67	134.97	129.52	94.67	98.89	103.60	146.46
CV (%)[a]	8.52	8.91	13.71	26.88	9.65	11.77	24.41
p[b]	0.0001	0.0001	0.0001	0.4909	0.6974	0.3079	0.0001

*N/A = Not applicable [a]Intra-subject coefficient of variation [b] p-value from ANOVA contrast Ln (C) – Ln (A)
Reference: Tables 14.2.1-11 through 14.2.1-15 of Mallinckrodt Inc. report for Study 722

Demographics (Table 18): Only White subjects were enrolled.

Table 18

Table 11.2-1 Summary of Demographics	
Parameter	**N = 24**
Sex N (%)	
Male	19 (79.2)
Female	5 (20.8)
Race N (%)	
Asian	0 (0,0)
Black	0 (0.0)
White	24 (100)
Age (years)	
Mean	28.5
Standard Deviation	13.2
Range	19 – 65
Weight (lb)	
Mean	180.7
Standard Deviation	18:7
Range	153 – 218
Height (in)	
Mean	70.3
Standard Deviation	3.3
Range	63 – 75
Reference: Table 14.1	

Conclusion:

- The food (high fat meal) affects the bioavailability of methylphenidate oral solution (10mg/5ml). Cmax and AUC0-inf are increased and tmax is prolonged. No change was noted in elimination kinetics.
- Overall, these results (BE of Methylin [redacted] versus Ritalin in fed state), combined with the prior demonstration that these formulations are bioequivalent in the fasted state, indicate that although a statistically significant food effect on methylphenidate PK exists, the magnitude of this effect appears to be comparable for the test formulation methylphenidate HCl oral solution (10 mg/5ml) and Ritalin® tablet 20 mg.

Reviewer's Comments:

- **Study design**: We consider the design acceptable.

PK measures

- % CV for Cmax and AUC were comparable for test Methylin [redacted] (fasted and fed condition) and reference listed product Ritalin® (fed condition).
- Terminal t1/2 was comparable for test product Methylin [redacted] (fasted and fed condition) and reference listed product Ritalin® (fed condition).

Food-Effect:

- Significant food-effect on the PK of Methylin [redacted]) oral solution has been demonstrated. Specifically, the 90% CI of test (fed)-to-reference (fasted) ratio fell outside of the recommended 0.80-1.25 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf). The elimination half-lives were comparable for test and reference products. Tmax was prolonged with food from 1.7 hours to 2.7 hours. There was

no significant sequence effect for AUC0-inf or Cmax. However, there was significant period effect on the AUC0-inf (p=0.0001) and Cmax (p=0.045).

- Since the study design was balanced and each individual received all treatments randomly, the period effects observed in the study should not significantly affect the BE conclusion.
- This reviewer has confirmed the validity of statistical analysis (90%CI) using an in-house BE program. Following are the results from this analyses for 2 pivotal PK parameters (AUC0-inf and Cmax)(Table 19-1, 19-2, Fig 6; Table 20-1, 20-2, Fig 7):

Methylin [redacted] solution fasted versus fed

Table 19-1

AUC0-inf (Food-effect)		POWER ANALYSIS
ERROR MEAN SQUARE	7.26028E-03	POWER FOR .2 M(r)= > 99.97 %
REFERENCE MEAN (LN)	3.869729	POWER FOR -.2 M(r)= > 99.97 %
TEST MEAN (LN)	4.122941	
NUMBER OF SUBJECTS	24	DETECTABLE DIFFERENCE: 7.478071 %
DEGREES OF FREEDOM	22	
NUMBER OF TREATMENTS	2	8 SUBJECTS NEEDED FOR A
DELTA	2	15.35518 % DETECTABLE DIFFERENCE

Table 19-2

90% CONFIDENCE INTERVAL		P VALUES OF TWO ONE-SIDED TEST
LOWER CI (% OF REF MEAN): 123.4883		p< 80 % REF MEAN: <0.00030
UPPER CI (% OF REF MEAN):	134.3728	p> 120 % REF MEAN: 0.99566
CONCLUSION: FAIL	CONCLUSION: FAIL	

Fig 6

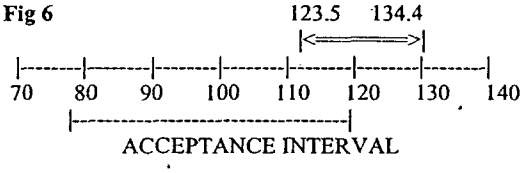


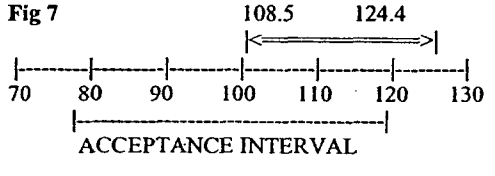
Table 20-1

Cmax (Food-effect)		POWER ANALYSIS
ERROR MEAN SQUARE	1.888079E-02	POWER FOR .2 M(r)= 99.05724 %
REFERENCE MEAN (LN)	2.192335	POWER FOR -.2 M(r)= 99.93985 %
TEST MEAN (LN)	2.342219	
NUMBER OF SUBJECTS	24	DETECTABLE DIFFERENCE: 12.33294 %
DEGREES OF FREEDOM.	22	
NUMBER OF TREATMENTS	2	12 SUBJECTS NEEDED FOR A
DELTA	2	19.04089 % DETECTABLE DIFFERENCE

Table 20-2

90% CONFIDENCE INTERVAL		P VALUES OF TWO ONE-SIDED TEST
LOWER CI (% OF REF MEAN):	108.521	p< 80 % REF MEAN: <0.00030
UPPER CI (% OF REF MEAN):	124.358	p> 120 % REF MEAN: 0.21119
CONCLUSION: FAIL	CONCLUSION: FAIL	

Fig 7



Bioanalytical Assay for Study #610 and #722

LC-MS/MS Bioanalytical Method for MPH in EDTA-treated Human Plasma:
In both clinical studies conducted to evaluate the bioequivalence of the Mallinckrodt test formulation Methylin® [redacted] PK blood samples were collected using EDTA as the anticoagulant. Plasma samples prepared from these blood samples were stored at -20°C except during plasma separation and sample preparation for MPH assay. All samples were analyzed at [redacted] using a validated [redacted] LC-MS/MS assay. The LC-MS/MS method involves extraction of methylphenidate and the internal standard (trideuterated methylphenidate) from 0.20 mL of plasma with ethyl acetate in the presence of pH 10.0 sodium bicarbonate buffer. Following further preparation of the extract, an aliquot was in [redacted] mass spectrometer. The peak area of the methylphenidate product ion (m/z 234→84) was measured against the same product ion of the internal standard (m/z 237→84). The calibration curve was established using 1/x weighted linear least square regression. Quality control (QC) samples, prepared in control human plasma were included in each analytical run.

The sponsor had briefly summarized in Table 21 &22 the pre-study and within-study validation of MPH in human plasma (directly excerpted from the sponsor):

Table 21

Table 3.3.1: Pre-study Assay Validation Summary for MPH in EDTA Human Plasma

Parameter	Quality Control Samples	Standard Curve Samples
Concentration (ng/mL)	0.750, 10.0, 20.0, 50.0	0.25, 0.500, 1.00, 2.00, 5.00, 10.0, 25.0
Intra-Day Precision (% CV)		
Intra-Day Accuracy (% Accuracy)		
Inter-Day Precision (% CV)		
Inter-Day Accuracy (% Accuracy)		
Correlation (Range of R^2 values)		
Linear Range (ng/mL)		
Sensitivity/ LLOQ		
Extraction Recovery of analyte		
Extraction Recovery of Internal Standard		
Stability in Plasma		
1) Bench-Top stability at Room Temp. (hrs.)		
2) Auto-Sampler Stability of Extract at Room Temp. (hrs.)		
3) Freeze-Thaw Stability (Cycles)		
4) Storage Stability (Temp. days)		
Specificity		
Reference: Table 8 in		

Table 22

Table 3.3.2
Within-Study Assay Performance for Methylphenidate in EDTA Human Plasma

Parameter	Study 610		Study 722	
	Quality Control Samples	Standard Curve Samples	Quality Control Samples	Standard Curve Samples
Concentration (ng/mL)	0.750, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0	0.750, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0
Intra-Day Precision (% CV)				
Intra-Day Accuracy (%Accuracy)				
Inter-Day Precision Range (% CV)				
Inter-Day Accuracy Range (% Accuracy)				
Correlation (Range of R^2 values)				
Linear Range (ng/mL)				
Sensitivity/ LLOQ (ng/mL)				
References:				

C:\WINDO

Fig 8

Fig 9

No Comment

Fig 10

Reviewer's Comments:

Bioanalytical method and assay validation:

Overall, the validity of the bioanalytical assay is satisfactory. The LC/MS/MS analytical method for methylphenidate in EDTA treated human plasma was found to be specific, reproducible, sensitive and adequate to characterize the PK of methylphenidate.

However, from the review of the initial submission and the DSI investigation (reports were briefly described below and attached in the appendix), the sponsor was requested to further address following four issues:

(a) The sponsor failed to establish the proposed bench-top stability at 6.5 hours. Specifically, the percent deviations from original theoretical value were [redacted] Seven out of nine stability samples showed greater than 15% percent deviation ([redacted]) recommended by the Guidance. (Table 23, 24, 25, 26, 27; see brief summary of DSI issues below and appendix for details)

(b) From the DSI investigation of pivotal BE study #610, the quality control (QC) samples and subject samples were handled differently (i.e. generally speaking, subject samples were exposed to room temperature 1.5- 2.5 hours longer than QC samples). Therefore, the sponsor was requested to submit additional bench-top stability around 2.5 and 4 hours for QC samples to support the bench-top stability of subject samples.

(c) The sponsor failed to adequately address the pre-specified criteria for reanalyzing the sample and how the final reported value was assigned if sample was reanalyzed. The sponsor was requested to submit the [redacted] Section 2 regarding criteria for re-analysis and decision tree to select final reported values.

(d) The sponsor indicated that commonly used over-the counter (OTC) drugs were tested and submitted to demonstrate the specificity of the bioanalytical assay. However, this section was missing from the submission. The sponsor was requested to submit the name of OTC drugs along with the chromatographs.

Overall, the subsequent response from the sponsor was satisfactory for the four issues above. Specifically, the sponsor submitted an additional bench-top plasma stability study at 1, 3, 4, and 6 hours (Table 28). We considered that these results establish the bench-top stability at 4 hours since percent deviations from the original theoretical value up to 4 hours were acceptable [redacted] except three values [redacted] (lowest QC) at 1, 3 hours respectively, [redacted] at 4 hours] and since the sponsor indicated that the maximum time that samples sat at room temperature in the analytical sites for both studies (#610 and #722) was 3 hours. Moreover, the sponsor submitted the requested information on OTCs and repeat samples. In conclusion, the stability in EDTA treated plasma (bench-top stability at room temperature) for the validated LC-MS/MS of methylphenidate could only be established at 4 hours instead of the 6.5 hours proposed initially. In the future, this should be taken into consideration in terms of sample handling.

Briefly summarized below are specific issues related to the initial DSI-investigation and reviewer's comments on the initial submission regarding individual criteria regarding bioanalytical assay:

(a) The sponsor failed to establish the proposed bench-top stability at 6.5 hours. This reviewer concurred with the observation made by Dr. Sriram Subramaniam from DSI that the sponsor failed to establish acceptable validation data to support the short-term stability (bench-top) of methylphenidate in EDTA plasma at 6.5 hours.

(b) The quality control (QC) samples and subject samples were handled differently (i.e. generally speaking, subject samples were exposed to room temperature 1.5- 2.5 hours longer than QC samples)

The Division of Scientific Investigation (DSI) audit was requested for the clinical study site and the analytical site for the pivotal BE study (#610). The following are the deficiencies described in the DSI transmittal memorandum from Dr. Sriram Subramaniam dated April 1, 2002 and the comment to the analytical site's response from Dr. C.T. Viswanathan dated April 15 2002:

- The sponsor failed to demonstrate bench-top stability of the drug in EDTA-plasma under the conditions described for the quality control samples and for the subject plasma samples.

- First, SOP PS-002, Revision 5 is deficient in failing to contain explicit acceptance limits for stability experiments. The phrase "within ranges established earlier for QC pools" does not constitute a suitable acceptance limit.

- Second, the bench-top stability experiment in validation project X7-037-01 resulted in loss of analyte, since a consistent decline in the concentrations was found at all levels. Specifically, the percent deviations from original theoretical value were [redacted] Seven out of nine stability samples showed greater than [redacted] percent deviation [redacted], recommended by the Guidance.

It should be noted that the sponsor only submitted the percent deviation from the back-calculated control mean concentration not the theoretical concentration as reference for short-term stability studies (Table 23, 24, 25). The DSI transmittal memorandum, however, indicated that the sponsor calculated absolute deviation using both theoretical and back-calculated concentrations

(Table 26, Exhibit 1 and Table 27, Exhibit 2) but only submitted the result with smaller % deviations using back-calculated concentration. All the remaining comparisons submitted in the bioanalytical assay validation section were using the theoretical concentrations as reference. This reviewer concurred with the DSI comment that theoretical value of the QC sample should be used when calculating absolute % deviation since the QC pools were prepared at 0.750, 10.0 and 20.0 ng methylphenidate free base per milliliter of human plasma.

- Third, the subject samples and quality controls (QC) were handled differently, therefore, the QC results from the analytical runs do not support bench-top stability of the subject samples. Specifically, the subject samples were at bench-top for 1 to 2.5 hours for aliquoting, 1 to 4 days prior to analysis. On the day of analysis, both subject samples and QCs were exposed for 0.5 to 1.5 hours at room temperature.

- Four, the conditions of freeze-thaw stability samples do not support the pre-aliquoting of subject samples. Specifically, the thaw cycles (45 minutes or less) of freeze- thaw samples were of shorter duration than the actual subject sample bench-top duration (1 to 2.5 hours).

Note: The additional bench-top plasma stability study at 1, 3, 4, and 6 hours the sponsor submitted on May 7, 2002 (Table 28) will support the bench-top stability at 4 hours since the percent deviations from the original theoretical value up to 4 hours were acceptable (except three values) at 1, 3 hours respectively, at 4 hours]. In addition, since the sponsor indicated that the maximum time that samples sat at room temperature in the analytical sites for both studies (#610 and #722) was 3 hours, these additional data support the bench-top stability of subject samples at 3 hours that original submission failed to address.

(c) **The sponsor failed to adequately address the pre-specified criteria for reanalyzing the sample and how the final reported value was assigned if sample was reanalyzed.** The sponsor indicated that sample runs were accepted if at least 2/3 of the QC samples were ±20% of theoretical with at least 50% of the QCs at each level meeting this criteria. This reviewer has noted that several repeat analyses of the samples were conducted for both studies for other reasons such as possible contamination, hemolysis, no or low or high internal standard, and technical error. Moreover, in study #722 (Food-effect study), in addition to the repeat analysis from the analytical lab, additional 94 samples were selected and repeated twice due to client request without providing reasons why those sample were selected for re-analysis. **We have requested the sponsor to submit the ; Section 2 regarding criteria for re-analysis and decision tree to select final reported values.**

Note: The pe-specified criteria for "Client Requested Reassay for a sample" were for pharmacokinetic reasons based on the judgement of the Pharmacokineticist that they contained one or more data points presenting an anomalous concentration vs. time profile. The practice is to analyze a sequence of data points (at least one) on either side of an anomalous point. The ; specifies that all samples were reanalyzed in duplicate and the median of the three assay values obtained for a given sample will be that reported.

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Confidential,
Commercial Information

Table 28

Table 5-0-1

Stability Data for Methylphenidate in EDTA Human Plasma versus Theoretical Concentration
Masterfile No.: X7-037-X1

[redacted] CORPORATION

Benchtop: 04/25/2002	0 Hour		1 Hour		3 Hours		4 Hours		6 Hours**	
Amount Added (ng/mL)	Stability Samples (ng/mL)	% Deviation from Amount Added	Stability Samples (ng/mL)	% Deviation from Amount Added	Stability Samples (ng/mL)	% Deviation from Amount Added	Stability Samples (ng/mL)	% Deviation from Amount Added	Stability Samples (ng/mL)	% Deviation from Amount Added

[redacted]

[redacted]

(d) The sponsor indicated that commonly used over-the counter (OTC) drugs were tested and submitted to demonstrate the specificity of the bioanalytical assay. However, this section was missing from the submission. The sponsor was requested to submit above data during the teleconference dated April 15, 2002.

> **Note**: Following are list of OTC drugs tested for specificity: acetaminophen, acetylsalicylic acid, brompheniramine, caffeine, chlorpheniramine, cimetidine, dextromethorphan, diphenhydramine, ibuprofen, ketoprofen, naproxen, phenylpropanolamine, pseudoephedrine, ranitidine, salicylic acid, and triprolidine

Following are this reviewer's additional comments specific to individual bioanalytical assay criteria:

- **Recovery of methylphenidate is within the acceptable range**: The average recovery (n=3) of methylphenidate was [redacted], at 0.25ng/ml, [redacted] at 2.00g/ml, and [redacted] at 25.0ng/ml. The average recovery (n=9) of the internal standard was [redacted].

- The **inter-day and intra-day precision** for the 0.75ng/ml QC sample were out of the acceptance criteria of ±15% (inter-day, [redacted], intra-day).

- Instead of [redacted] the LLOQ for study #722 (food effect study) should be set at [redacted], since [redacted] However, this modification should not affect the significant food effect observed in this study since the quantifiable concentrations in concentration-time curve had captured major portion of the AUC based on the observed concentration-time curve.

- In addition, it should be noted that the %CV was [redacted]) for the intra-day precision of the QC samples at the 0.75ng/ml for "pre-study assay validation" (table 21). However, this should not be of importance since the value in the within-study assay for pivotal BE study (#610) was acceptable (3.0-7.3%).

- **Concentration range of short-term stability studies**: Short –term stability studies (bench-top, freeze-thaw and auto-sampler) were only conducted at three concentrations (0.75, 10.0, and 20.0 ng/ml), but not at the concentration of 50ng/ml.

- The storage stability of methylphenidate in human plasma at –20°C has only been evaluated within the concentration ranges of 0.750-20.0ng/ml but not at the 50.0mg/ml. However, the validation of this assay for the 2 studies would not be affected since the Cmax of methylphenidate for both studies are ranging from 6.389-15.556ng/ml which is within the limit of the storage stability defined by this assay validation.

APPEARS THIS WAY
ON ORIGINAL

Partial validation of LC-MS/MS in heparinized plasma against EDTA-treated plasma:
The sponsor submitted a report on the partial validation of LC-MS/MS in heparinized plasma against EDTA-treated plasma. Briefly, this reviewer has summarized in table 28 the result from cross-validation of heparinized plasma against EDTA-treated plasma:

Table 28

Cross assay validation summary for the cross-validation of heparinized plasma against EDTA-treated plasma:				
	heparinized plasma		**EDTA-treated plasma**	
Parameters	Quality control samples	standard curve samples	Quality control samples	standard curve samples
concentration (ng/ml)	0.750, 10.0, 20.0	NA	0.750, 10.0, 20.0	0.25, 0.500, 1.00, 2.00, 5.00, 10.0, 25.0
Intra-day precision (%CV)	[redacted]			
Intra-day accuracy (% accuracy)				
Inter-day precision (%CV)				
Inter-day accuracy(% accuracy)				
correlation (range of R2 values)				
Linear range (ng/ml)				
Sensitivity/LLOQ				
Extraction Recovery of analyte				
Extraction recovery of internal standard				
Stability in Plasma				
1) Bench-top stability of extract at room temperature (hrs)				
2) Auto-sampler stability of extract at room temperature (hrs)				
3) freeze-thaw stability (cycles)				
4) storage stability (temp, days)				
Specificity				

Reviewer's Comments:

- From a brief review, this reviewer concluded that the partial validation is irrelevant to current submission since heparin was not used as anticoagulant in either of the two studies submitted in this NDA. Specifically, all the plasma samples of methylphenidate in 2 studies submitted used EDTA as anticoagulant. Therefore, this analytical report has not been fully reviewed. We will review the validity of this partial validation in future when the sponsor submits a biostudy where the plasma sample is treated with heparin.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 26, 2002

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. /S/ April 1, 02
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-419,
Methylin —— (Methylphenidate Hydrochloride Oral Solution) 5 mg/5 ml; 10 mg/5 ml,
Sponsored by Mallinckrodt Inc., St. Louis, MO.

TO: Russell Katz, M.D.
Director
Division of Neuropharmacological
Drug Products (HFD-120)

At the request of HFD-120, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Protocol: 1137-00-610, An Open-Label, Randomized, Three-Way Crossover Study to Evaluate the Relative Bioavailability of Two Test Formulations (10 mg Chewable Tablet and 2 mg/ml Liquid) of Methylphenidate Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects Under Fasting Conditions (Study #610).

The clinical and analytical portions of the study were conducted at [redacted]

Following the inspection at [redacted] (3/5-7/2002), Form FDA-483 was issued. No Form 483 was issued at [redacted] (1/16-22/2002). The Form 483 item issued at [redacted] (Attachment 1) and its evaluation follows:

Page 2 - NDA 21-419, Methylin [redacted]

1. **Bench-top stability of drug in human EDTA-plasma for 6.5 hours was not demonstrated. Also, in the study, the subject samples and quality controls (QC) were not handled identically.**

The mean back-calculated concentrations of the 0.75, 10 and 20 ng/mL stability samples were **84.4%, 80.9%** and **78.2%** of theoretical concentrations, respectively. Specifically, 8 of 9 stability samples were 85% or less than the theoretical concentrations, of which 4 were less than 80% of the theoretical concentrations (Exhibit 1). The stability results are consistently lower than the nominal concentrations and deviate significantly from the validated assay accuracy (6-9%), suggesting instability of the analyte in EDTA-human plasma following 6.5 hours at room temperature. During the inspection, the firm stated that at the time of validation, stability was routinely estimated by comparing stability sample data against validated mean concentration, not theoretical concentration. Nonetheless, this comparison also shows a trend towards instability at room temperature (Exhibit 2).

The quality control (QC) results from the analytical runs also do not support bench-top stability of the subject samples, as QCs and subject samples were not handled identically. The subject samples were at bench-top for 1 to 2.5 hours for aliquoting, 1 to 4 days prior to analysis (Exhibit 3). On the day of analysis, both subject samples and QCs were exposed for 0.5 to 1.5 hours to room temperature. Therefore, unlike the QCs, the subject samples were exposed for 1 to 2.5 hours at room temperature, frozen, and again exposed for 0.5 to 1 hour at room temperature. The stability samples in the freeze-thaw experiments also do not simulate the handling of the subject samples, as the samples were at room temperature for less than 45 minutes between freeze cycles (Exhibit 4).

Overall, no data was available to demonstrate the bench-top stability of the drug in EDTA-plasma under the conditions described above for the subject plasma samples.

[redacted] intends to respond to Item 1, however, to date they have not submitted one.

Conclusions:

The accuracy of the subject methylphenidate concentrations in Study 610 is questionable as the bench-top stability of the subject samples was not demonstrated (Item 1). We recommend that the subject concentration data not be accepted for review until demonstration of analyte stability under conditions that mimic the handling of subject plasma samples. Available data suggests instability of the analyte in EDTA-plasma following 6.5 hrs at room temperature.

In the event [redacted] submits a response, DSI will notify HFD-120 only if the response warrants a revision of our current recommendation.

The data from the clinical portion of Study 610 are acceptable for Agency review.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

/S/

Sriram Subramaniam, Ph.D.

Attachments

Final Classifications:
NAI -
VAI - [redacted]

cc:
HFD-45 RF
HFD-48 Subramaniam(2)/CF
HFD-120 Homonnay
HFD-860 Chou/Uppoor
HFR-SE1525 Martinez
Draft: SS 3/25/02
Edit: MKY 3/26/02
DSI:5400; O:\BE\EIRCOVER\21419mal.met
FACTS ID: 256558

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Confidential,
Commercial Information

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Number of Pages Redacted 12

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Draft Labeling
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Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21,419**	**Brand Name**	**Methylin [redacted]**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Methylphenidate Hydrochloride**
Medical Division	**HFD-120**	**Drug Class**	
OCPB Reviewer	**Wen-Hwei Chou, Pharm.D., Ph.D.**	**Indication(s)**	Attention Deficit Disorders and Narcolepsy
OCPB Team Leader	**Ramana, Uppoor. Ph.D.**	**Dosage Form**	Oral solution (5mg/5ml; 10mg/5ml)
		Dosing Regimen	Adult: average dosage, 20-30mg daily (10~60mg daily, 2-3 times daily , preferably 30-45 minutes before meals); Children: 5mg daily (before breakfast and lunch) with gradual increments of 5- 10mg weekly.
Date of Submission	**07/31/01**	**Route of Administration**	**P.O.**
Estimated Due Date of OCPB Review	**01/15/02**	**Sponsor**	**Mallinckrodt Inc, 650 McDonnell Boulevard P.O. Box 5840, St.Louis MO63134**
PDUFA Due Date	**05/31/02**	**Priority Classification**	**S**
Division Due Date	**02/28/02**		

Clin. Pharm. and Biopharm. Information

Background

- This is 505(b) (2) NDA submission for an oral solution (5mg/5ml, 10mg/5ml).
- The sponsor submitted 2 BE studies (1 in fasted and 1 in fed condition) using higher strength against reference listed drug, Ritalin tablet.
- The sponsor requests waiver of BE study on lower strength (5mg/5ml, The lower strength is proportionally similar (see table attached)

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary				• Literature data was summarized in the preclinical section along with animal data. • Some of the abstracts of references were submitted
Labeling	x			• The proposed text is essentially the same as the reference listed drug. • No ADME or PK data is included in the labeling.

Reference Bioanalytical and Analytical Methods	x			The Sponsor had submitted both pre-study assay validation & within-study assay performance
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				

APPEARS THIS WAY
ON ORIGINAL

traditional design; single / multi dose:	x			• 3-way, crossover BE study in the fasting state, comparing Methylin [redacted] 20mg (10mg/5ml), Methylin CT (chewable tab 10mgx2, another new dosage form being proposed by Mallinckrodt in a separate NDA) and Ritalin 20mg tab, a commercially available product as Reference Listed Drug), [SD, 3-period, six sequence, crossover in 36 healthy subjects using to-be-marketed product, lot #MHSC0044]
replicate design; single / multi dose:				
Food-drug interaction studies:	x (high-fat meal)			3-way, crossover food-effect study: 20mg (10mg/5ml, fast or fed) vs Ritalin (20mg tab, fed) SD, 3-period, six sequence, in 24 healthy subjects
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				• The labeling approved for the reference listed drug, Ritalin, and proposed labeling for this product includes the pediatric population age 6 and above. • The sponsor requests the Agency to grant a deferral of the requirement to perform pediatric studies in accordance with 21 CFR 314.55(b). The Sponsor indicated that pediatric studies (preschool age children, under age 6) are presently being conducted by the NIH which will be used to develop class labeling into the labeling proposed herein, once it is available.
Literature References	x			Clinical data (literature-based).
Total Number of Studies	2			

APPEARS THIS WAY
ON ORIGINAL

Filability and QBR comments		
	"X" if yes	*Comments*
Application filable ?	x	• The Sponsor had included statistical analysis of PK measurements in paper format. • DSI will be consulted to inspect the fasting BE study
Comments sent to firm ?	x	• The Sponsor should perform an extensive literature search for methylphenidate in humans and submit all the necessary information along with the reference articles. Information includes ADME (absorption, distribution, metabolism, elimination), special populations (gender, age, race, hepatic and renal impairment), dose proportionality, inhibitory and inductive effect of methylphenidate on the isozymes, activity of metabolites and drug interactions, etc. • Label update based on the above information. • Submit PK data in electronic format for the 2 BE studies. Consult guidance for type of format for electronic submission.
QBR questions (key issues to be considered)	• **Is the oral solution BE to the reference tablet?** • **Is there a food effect on bioavailability of the oral solution?** • **Can we waive BE of lower strength?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Wen-Hwei Chou, Pharm.D., Ph.D.**	
Secondary reviewer Signature and Date	**NA**	
Team Leader Signature and Date	**Ramana Uppoor, Ph.D.**	

CC: NDA 21-419, HFD 860 (Mehta, Sahajwalla, Uppoor, Chou), HFD-850(Lee), HFD-120(CSO), CDR (B. Murphy)

APPEARS THIS WAY ON ORIGINAL

Attachment

Each milliliter of Methylin® [redacted] (methylphenidate hydrochloride oral solution, 5 mg/5 mL and 10 mg/5 mL) contains the following:

Quantitative Formula for Methylin® [redacted] 5 mg/5 mL

Formulation Component	Concentration (mg/mL)	Concentration (kg/[redacted]	Concentration (kg/[redacted]
Methylphenidate HCl, USP	1.00	0.60	2.75
Polyethylene Glycol 1450, NF			
Grape Flavor		[redacted]	
Citric Acid anhydrous, USP			
Glycerin, USP		[redacted]	
Purified Water, USP			

Quantitative Formula for Methylin® [redacted] 10 mg/5 mL

Formulation Component	Concentration (mg/mL)	Concentration (kg/[redacted]	Concentration (kg/[redacted]
Methylphenidate HCl, USP	2.00	1.20	5.50
Polyethylene Glycol 1450, NF			
Grape Flavor			
Citric Acid anhydrous, USP		[redacted]	
Glycerin, USP			
Purified Water, USP		[redacted]	

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wen-Hwei Chou
5/21/02 04:46:15 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/21/02 04:57:51 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

Indication:	Attention Deficit Disorders and narcolepsy
Sponsor:	Mallinckrodt Inc.
Type of submission:	New submission [505(b)(2)]
Clinical Division:	HFD-120/Neuropharmacological Drug Products
OCPB Division:	HFD-860/DPEI
Priority:	Standard
Submission date:	07/31/01; 10/16/01 (electronic submission of 2 BE studies);
OCPB Consult date:	08/14/01
Reviewer:	Wen-Hwei Chou, Pharm.D., Ph.D.
Team leader:	Ramana Uppoor, Ph.D.

Executive summary

This is a 505 (b)(2) NDA submission for Methylin ─ oral solution (5mg/5ml, and 10mg/5ml). The sponsor submitted two BE studies (one pivotal in fasted condition and another in fed condition) using higher strength against reference listed drug, Ritalin® tablet. The sponsor requested waiver of BE study on lower strength (5mg/5ml). The approvability of this NDA is entirely determined by the two BE studies submitted. Overall, [pending the submission of bench-top stability of QC samples at 2.5 and 4 hours that mimics the conditions that subject samples were exposed to,] the sponsor has submitted sufficient information to support the approval. This approval is based on the bioequivalence of the 10mg/5ml and granting of biowaiver for the lower strength (5mg/5ml) based on the proportional similarity in composition of two oral solution strengths and the fact that there is no excipient that is known to significantly affect the drug absorption.

The proposed label text is essentially the same as the reference listed drug product Ritalin® tablet except the text that reflects change from reference listed product Ritalin® to an oral solution dosage form. However, relevant clinical pharmacology information is lacking in current Ritalin® label. In the forty-five days filing meeting, we have requested the sponsor to update label from available sources. Unfortunately, during a teleconference dated April 15, 2002, the sponsor indicated that the firm) ─────────── . From the Office of Clinical Pharmacology and Biopharmaceutics perspective, it is important to modify and incorporate current knowledge of methylphenidate in the Methylin ─ labeling. The sponsor will be requested to update labeling. Based on information from current submission and literature, we have suggested some relevant PK information to be included in the label.

Recommendation:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed this NDA and finds it (acceptable). Please forward "comments to the sponsor" (1)-(2) to the sponsor.

Comments to the sponsor:

1. The partial validation of LC-MS/MS in heparinized plasma against EDTA-treated plasma is irrelevant to current submission and its validity can not be established at this point due the incomplete data submitted. We will review the validity of this partial validation on LC-MS/MS when the sponsor submits the complete report and when the plasma sample is treated with heparin.

Labeling:

2. We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the pharmacokinetics of methylphenidate is lacking in current label for reference list drug Ritalin®. You are requested to update labeling to incorporate the above information from literature and/or other available resources. Based on information from current submission and literature, following are some of suggestions on the relevant PK information which should be added to the "Clinical Pharmacology" section of the label:

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Special Population:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT Initialed by Ramana Uppoor, Ph.D. _____

cc: NDA21-419 Methylin®; [redacted] HFD-120, HFD-860 (Mehta, Marroum, Uppoor, Chou), Central Documents Room (Biopharm-CDR)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults	
From: Wen-Hwei Chou, Pharm.D., Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 11/25/02	IND No: NA	NDA No. 21,419	DATE OF DOCUMENT	10/31/02
NAME OF DRUG/ Formulation & strength /Route of Administration/Indication Methylin Oral solution (methylphenidate HCl) 5mg/ml, 10mg/ml ADHD	PRIORITY CONSIDERATION Standard		Date of informal/Formal Consult:	11/13/02
NAME OF THE SPONSOR: Mallinckrodt Inc				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

___PRE-IND ___ANIMAL to HUMAN SCALING ___IN-VITRO METABOLISM ___PROTOCOL (New IND) ___PHASE II PROTOCOL ___PHASE III PROTOCOL ___DOSING REGIMEN CONSULT ___PK/PD- POPPK ISSUES ___ PHASE IV RELATED	___DISSOLUTION/IN-VITRO RELEASE ___BIOAVAILABILITY STUDIES ___IN-VIVO WAIVER REQUEST ___SUPAC RELATED ___CMC RELATED ___PROGRESS REPORT ___SCIENTIFIC INVESTIGATIONS ___MEETING PACKAGE (PRE-ADVISORY MEETING)	___FINAL PRINTED LABELING ___LABELING REVISION ___CORRESPONDENCE ___DRUG ADVERTISING ___ADVERSE REACTION REPORT ___ANNUAL REPORTS ___FAX SUBMISSION **X OTHER (SPECIFY BELOW):** Response to Agency's approvable letter (dated May 31, 2002)

REVIEW ACTION

X NAI (No action indicated) ___E-mail comments to: ___Medical___Chemist___Pharm-Tox ___ Micro___Pharmacometrics___Others (Check as appropriate and attach e-mail)	___Oral communication with Name: [ ] ___Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	___Formal Review/Memo (attached) **___See comments below** ___See submission cover letter ___OTHER *(SPECIFY BELOW)*:

REVIEW COMMENT(S)

___NEED TO BE COMMUNICATED TO THE SPONSOR **___ HAVE BEEN COMMUNICATED TO THE SPONSOR**

(6)

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/s/

Wen-Hwei Chou
11/26/02 06:13:06 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
11/26/02 06:34:58 PM
BIOPHARMACEUTICS

(E)

Number of Pages Redacted 19

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OCT 23 2000

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 8/29/2000

Pre-NDA

Name of Drug:	Methylphenidate HCl Chewable 2.5, 5 and 10-mg tablets, Oral 5mg/5ml and 10mg/5ml Solution
Indication of Drug:	ADHD
Type of Document:	Request for FDA Comment
Sponsor:	Mallinckrodt Inc.
Reviewer:	Hong Zhao, Ph.D

Introduction

The sponsor faxed abbreviated PK Study plan for Methylphenidate HCL Chewable Tablets and Methylphenidate oral solution and requested comments on acceptability of the plan for approval of 505(b)(2) application for these products. The sponsor also intends to request a waiver for the requirement to establish bioequivalence on the lower strengths of these dosage forms.

Sponsor's Planned PK Studies

Three pharmacokinetic studies that the sponsor has planned (See Attachment I) are:

1) dose equivalency study evaluates the relative bioavailability of two test formulations (10 mg Chewable and 2mg/ml liquid) of methylphenidate compared to an equivalent dose of Ritalin (20mg) under single-dose, fasting condition;
2) food study evaluates the highest strength chewable tablets (10-mg x 2) after FDA high fat breakfast compared to the same tablets under fasting condition and to Ritalin 20 mg tablet under fed condition
3) food study evaluates the highest strength oral solution (10ml of 10mg/5ml) after FDA high fat breakfast compared to the same solution under fasting condition and to Ritalin 20 mg tablet under fed condition.

Comments

1. The dosage strengths of the methylphenidate chewable tablets are compositionally proportional (Attachment II), the sponsor can request biowaiver for lower strengths of the tablet, provided that the drug follows linear kinetics, and dissolution data shows that the 2.5mg and 5mg chewable tablets have comparable dissolution performance as the 10mg chewable tablet that is used in the bioequivalence study.
2. For oral solution, two dose strengths are constant in composition (Attachment III), therefore sponsor can request biowaiver for lower strengths of the solution.
3. The sponsor should conduct dissolution test with application/compendium dissolution method and specification for all strengths of methylphenidate Chewable Tablets.
4. OCPB has no special concern regarding the sponsor's proposed pharmacokinetics studies.

Please convey the above Comments to the sponsor.

Hong Zhao, Ph.D. /S/ 10/23/00

RD/FT Initialed by Raman Baweja, Ph.D. /S/ 10/23/00.

cc: Pre-NDA (Methylphenidate HCl Chewable tablets and Oral Solution), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (Biopharm-CDR)

APPEARS THIS WAY
ON ORIGINAL

METHYLPHENIDATE CHEWABLE/LIQUID
CLINICAL SUMMARY

Planned Clinical Studies

STUDY #1

Three-Period, Crossover Study to Evaluate the Relative Bioavailability of Two Test Formulations (10 mg Chewable and 2 mg/mL Liquid) of Methylphenidate Compared to an Equivalent Dose of Ritalin (20 mg) under fasting conditions

Three Periods: 2x Methylin 10 mg Chewable Tablets (chewed)
10 mL Methylin (2 mg/mL) Liquid
1x Ritalin 20 mg Tablets

36 Healthy Subjects at one clinical site.

STUDY #2

Three-Period, Crossover, Food Effect Study to Evaluate the Relative Bioavailability of a Test Formulation Methylphenidate (10 mg Chewable Tablets) Compared to an Equivalent Dose of Ritalin (20 mg).

Three Periods: 2x Methylin 10 mg Chewable Tablets (chewed) (under fasting conditions)
2x Methylin 10 mg Chewable Tablets (chewed) (after FDA High fat breakfast)
1x Ritalin 20 mg tablet (after FDA High fat breakfast)

24 Healthy Subjects at one clinical site.

STUDY #3

Three-Period, Crossover, Food Effect Study to Evaluate the Relative Bioavailability of a Test Formulation Methylphenidate (2 mg/mL Liquid) Compared to an Equivalent dose of Ritalin (20 mg).

Three Periods: 10 mL Methylin [redacted] (liquid) (under fasting conditions)
10 mL Methylin [redacted] (liquid) (following FDA high fat breakfast)
1x Ritalin 20 mg tablet (following FDA high fat breakfast)

24 healthy subjects at one clinical site.

APPEARS THIS WAY
ON ORIGINAL

Attachment 3
1 of 1

Formulation

Project: Methylin® - Methylphenidate Hydrochloride Oral Liquid
Dosage Strength: 5 mg/5 mL and 10 mg/5 mL

Proposed Formulation Official USP/NF Material Name	5 mg/5 mL Product	10 mg/5 mL Product
Methylphenidate HCl, USP	1 mg/mL	2 mg/mL
Glycerin, USP	[redacted]	
PEG 1450, NF		
N&A Grape Flavor		
Citric acid anhydrous, USP		
Purified water, USP		

APPEARS THIS WAY
ON ORIGINAL