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RESEARCH**

APPLICATION NUMBER:

40-300

BIOEQUIVALENCE

JUN 30 1998

Methylphenidate HCl Tablets, USP
5 mg, 10 mg, 20 mg
ANDA #40-300
Reviewer: Kuldeep R. Dhariwal
File name: 403Q0SDW.298

Mallinckrodt Inc.,
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134
Submission Date:
February 27, 1998
June 8, 1998

Review of Fasting and Non-Fasting Bioequivalence Studies, Dissolution Data, and Waiver Request

The firm has submitted fasting and non-fasting bioequivalence studies and dissolution data comparing its methylphenidate hydrochloride tablet, 20 mg with Ciba Geigy's Ritalin[®] hydrochloride tablet, 20 mg. The firm has also requested waivers of *in vivo* bioequivalence study requirements for its 5 and 10 mg tablets. To support the request, the firm has submitted comparative dissolution profiles on 5 and 10 mg strengths of its product and reference listed drug Ritalin[®] hydrochloride, 5 and 10 mg tablets.

The firm was asked on June 1, 1998 to submit the chromatograms of at least 20% of the subjects who completed the study. The firm submitted the chromatograms as amendment on June 8, 1998.

Introduction:

Methylphenidate hydrochloride is a mild central nervous system stimulant. It is available in three strengths: 5, 10, and 20 mg. This is also available as 20 mg sustained-release tablets. Ritalin in the SR tablets is more slowly but as extensively absorbed as in the regular tablets. The time to peak rate in children was 4.7 hours for the SR tablets and 1.9 hours for the regular tablets. An average of 67% of SR tablet dose was excreted in children as compared to 86% in adults.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol #: 97204

IRB approval: Yes
Consent Form Signed: Yes
Clinical Site: Gateway Medical Research
Principal Investigator: Earl J. Wipfler Jr., M.D.
Clinic Director: Daniel R. Shipley
Analytical Facility:
Analytical Director:
Study Dates: Period I November 8-9, 1997
Period II November 15-16, 1997
Analysis Dates: November 19-26, 1997
Storage Period: 19 days
Study Design: Randomized, two-way crossover design
with a washout period of 7 days
Randomization Scheme: AB: 3,5,8,11,12,14,15,16,17,18,20,21,
24,25,27,32
BA: 1,2,4,6,7,9,10,13,19,22,23,26,28,29,
30,31

Treatments:

A: Methylphenidate hydrochloride tablets, 1x20 mg;
Mallinckrodt, Lot #MHSC9721; Lot size: Theoretical yield:
tablets, Actual yield: :tablets; Manufacture
date: 10/8/97; Assay: 97.5%; Content Uniformity: 96.6%

B: Ritalin[®] hydrochloride tablets, 1x20 mg; Ciba-Geigy; Lot
#1T197606; Expiry Date: 12/2001; Assay: 99.5%; Content
Uniformity: 100.4%

Formulation of test product: Table 1

Subjects: 32 subjects in the age range 18-43 years were
enrolled in the study according to
inclusion/exclusion criteria specified in the
protocol.

Housing: From the evening before dosing until after 24
hour blood draw.

Dosing: After 10 hour fast, with 240 mL of water.
Water was not allowed one hour before dosing
and for two hours after dosing. No food for 4
hours post-dose.

Sample Collection: Blood samples were collected at predose (0 h) and at following times post-dose: 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16 and 24 hours. Plasma was separated and stored at -20°C or lower.

B. Study Results:

1. Clinical:

Drop-outs: Of the 32 male subjects enrolled in the study, 30 completed the study. Subject #24 and 25 withdrew for personal reasons.

Adverse events: Some subjects experienced headache, nausea, dizziness, cephalgia, lightheadedness, elevated heart rate and fatigue. The events were comparable on test and reference products.

Protocol Deviations: There was one sampling deviation of more than 2 minutes.

2. Analytical:

Method:

Internal Standard:

Linearity: Standard curve range 0.250 ng/mL to 25 ng/mL. Peak areas of m/z 234.0-83.9 product ion of methylphenidate were measured against the peak areas of the m/z 237.0-83.9 product ion of the internal standard, ion coefficients were greater than 0.9991.

Regression: 1/Concentration (Linear)

QC Samples: 0.75 ng/mL, 10.0 ng/mL, 20.0 ng/mL

Accuracy: Standards: 98% to 101%

QC samples: 93.8% to 98%

Precision: Standards: 1.9% to 9.7%

QC samples: 3.1% to 11.5%

Reassays: 1 for poor chromatography

1 for low internal std.

1 for no internal std.
1 for no peak

The firm has provided following pre-study method validation results:

Linearity: Standard curve range 0.25 to 25 ng/mL
Correlation coefficients were greater than 0.9983

Accuracy:

Inter-day	Standards	97.9% to 101.6%
	QC samples	90.6% to 93.9%
Intra-day	Standards	95.2% to 110.8%
	QC samples	86.13% to 91.1%

Precision:

Inter-day	Standards	2.6% to 11.3%
	QC samples	3.9% to 17.6%
Intra-day	Standards	0.29% to 17.2%
	QC samples	1.5% to 21.9%

Recovery:

0.250 ng/mL	119%
2.000 ng/mL	106%
25.00 ng/mL	102%
Internal Standard	108%

Stability:

- a) Bench-top: Methylphenidate was stable in plasma left at room temperature for 6½ hours before extraction.
- b) Stability after extraction: Methylphenidate was stable in samples stored at room temperature for 24 hours after extraction.
- c) Freeze-thaw: Stable over 3 cycles.
- d) Long-term stability: Stability demonstrated for 2 months. Study samples were stored for no more than 19 days.

3. Pharmacokinetics/Statistics:

Mean plasma concentrations: Table 2 and Figure 1

Pharmacokinetic parameters: Table 2

90% Confidence Intervals:

LAUC _{0-t}	95.11-102.37%
LAUC _{0-inf}	95.21-102.35%
LC _{max}	92.26-103.95%

The test/reference ratios for AUC_{0-t} ranged from 0.83-1.52 (mean 0.99), AUC_{0-inf} ranged from 0.84-1.48 (mean 0.99), and for C_{max} ranged from 0.69 to 1.90 with a mean of 1.00.

The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.93 to 0.98 for test and from 0.92 to 0.98 for reference product.

Comments:

1. The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.
2. The elimination constant and therefore AUC_{0-inf} could not be calculated for subject #3 on test and for subject #4 and 22 on reference product.
3. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as T_{max} , and no subjects with first measurable drug concentration as C_{max} .
4. The 90% confidence intervals for log transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} are within acceptable limits of 80-125%. There was no statistically significant period, sequence or treatment effect for any of these parameters.
5. The fasting study is acceptable.

Bioequivalence Study Under Non-Fasting Conditions:

A. Study Information:

Protocol #:	97247
IRB approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	Gateway Medical Research
Principal Investigator:	Thomas Christopher, M.D.
Clinic Director:	Daniel R. Shipley
Analytical Facility:	---
Analytical Director:	---
Study Dates:	Period I December 7-8, 1997 Period II December 14-15, 1997

Period III December 21-22, 1997
Analysis Dates: December 29, 1997 to January 19, 1998
Storage Period: 43 days
Study Design: Randomized, three-way crossover design
with a washout period of 7 days

Randomization Scheme: ABC: 1,10,16,19
ACB: 2,12,17,24
CAB: 3,9,13,20
BAC: 4,7,15,23
CBA: 5,11,14,22
BCA: 6,8,18,21

Treatments:

A: Methylphenidate hydrochloride tablets, 1x20 mg;
Mallinckrodt, Lot #MHSC9721; administered after a 10 hour
fast

B: Methylphenidate hydrochloride tablets, 1x20 mg;
Mallinckrodt, Lot #MHSC9721; administered after a standard
breakfast

C: Ritalin[®] hydrochloride tablets, 1x20 mg; Ciba-Geigy;
Lot #1T197606; administered after a standard breakfast

Lot numbers of drug products administered in this study are the
same as those for the fasting study.

Subjects: 24 male subjects in the age range 18-42 years
were enrolled in the study according to
inclusion/exclusion criteria specified in the
protocol.

Housing: From the evening before dosing until after 24
hour blood draw.

Dosing: Treatment A: Subjects were given a single
oral dose of the assigned formulation with
240 mL of water after a 10 hour fast
Treatments B and C: Subjects were given OGD
approved standardized breakfast 15 minutes
before dosing after a fast lasting at least

10 hours. All subjects completed their entire meal. The dose was given with 240 mL of water.

Water was not allowed one hour before dosing and for two hours after dosing. No food for 4 hours post-dose.

Sample Collection: Blood samples were collected at predose (0 h) and at following times post-dose: 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16 and 24 hours. Plasma was separated and stored at -20°C or lower.

B. Study Results:

1. Clinical:

Drop-outs: Of the 24 male subjects enrolled in the study, 22 completed the study. Subject #23 left after the 6 h blood draw in Period III. Subject #14 left during period II due to gastroenteritis.

Adverse events: Some subjects experienced headache, nausea, dizziness, diaphoresis, pallor, and gastroenteritis. All events except gastroenteritis occurred on test drug.

Protocol Deviations: There were three sampling deviations of more than 2 minutes.

2. Analytical:

Method:

Internal Standard:

Linearity: Standard curve range 0.250 ng/mL to 25 ng/mL. Peak areas of m/z 234.0-83.9 product ion of methylphenidate were measured against the peak areas of the m/z 237.0-83.9 product ion of the internal standard, Correlation coefficients were greater than 0.9996.

Regression: .1/Concentration (Linear)
QC Samples: 0.75 ng/mL, 10.0 ng/mL, 20.0 ng/mL
Accuracy: Standards: 97.2% to 101.6%
 QC samples: 97.5% to 103.3%
Precision: Standards: 1.9% to 12.2%
 QC samples: 4.0% to 11.5%
Reassays: 3 for poor chromatography
 1 for no internal standard
Long-term Stability: The firm has demonstrated stability of methylphenidate in frozen plasma samples for 2 months. Samples in the present study were stored for less than 43 days.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations: Table 3, Figure 2

Pharmacokinetic Parameters: Table 4

Comparison of test and reference products after a meal: The LS means for AUC_{0-t} and AUC_{0-inf} of the test product were 4% and 3% lower than the respective means of the reference product. The LS means for C_{max} of the test product was 3% lower than that of the reference product and occurred 4 minutes later (Table 4).

Comparison of test product given after a meal vs. given under fasting conditions: The LS means for AUC_{0-t} and AUC_{0-inf} given after a meal were 20% higher compared to that of the same product given under fasting conditions. The LS means for C_{max} given after a meal was 19% higher and occurred 30 minutes later when compared to that of the same product given under fasting conditions (Table 4).

The individual subject test non-fasting/reference non-fasting ratios for AUC_{0-t} ranged from 0.83 to 1.26, AUC_{0-inf} ranged from 0.83 to 1.22, and for C_{max} ranged from 0.74 to 1.38.

The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.93 to 0.98 for test fasting, from 0.95 to 0.99 for test non-fasting, and from 0.94 to 0.99 for reference non-fasting.

Comments:

1. The pharmacokinetic parameters and ratios of means were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.
2. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as T_{max} , and no subjects with first measurable drug concentration as C_{max} .
3. Subject #14 dropped during period II and subject #23 dropped after 6 h blood draw in period III. The reviewer dropped the data of these two subjects for analyses. Ratios of means for AUC_{0-t} , AUC_{0-inf} , and C_{max} between test non-fasting and reference non-fasting are within acceptable limits. The non-fasting study is acceptable.

In Vitro Dissolution Testing:

The dissolution testing was done by USP method: apparatus 1 (basket) at 100 rpm in 900 mL of water. The dissolution data are acceptable (Table 5).

Waiver Request:

The firm is requesting a waiver of *in vivo* bioequivalence studies for its 5 and 10 mg tablets. The 5 and 10 mg tablets are proportionally similar in their active and inactive ingredients to 20 mg tablets and all three strengths have a common master blend (Table 1). The dissolution profiles are acceptable (Table 5). The waivers can be granted.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Mallinckrodt on its methylphenidate hydrochloride 20 mg tablet, lot #MHSC9721 comparing it to Ritalin® tablet, 20 mg, lot #1T197606 manufactured by Ciba Geigy is acceptable to the Division of Bioequivalence. The study demonstrates that Mallinckrodt's methylphenidate hydrochloride tablet, 20 mg is bioequivalent to the reference product, Ritalin®, 20 mg tablet manufactured by Ciba Geigy.

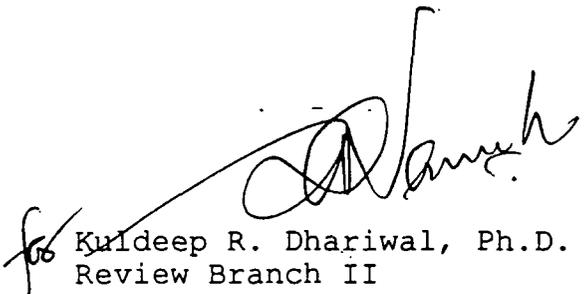
2. The bioequivalence study conducted under non-fasting conditions by Mallinckrodt on its methylphenidate hydrochloride 20 mg tablet, lot #MHSC9721 comparing it to Ritalin® 20 mg tablet, lot #1T197606 manufactured by Ciba Geigy is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Mallinckrodt's methylphenidate hydrochloride 20 mg tablet is similar to that of the reference product Ritalin® 20 mg tablet manufactured by Ciba Geigy.

3. The dissolution testing conducted by the firm on its methylphenidate hydrochloride tablets 5 mg, 10 mg and 20 mg is acceptable. The formulation for 5 and 10 mg test tablets is proportionally similar to the 20 mg strength of the test product which underwent bioequivalency testing. The waiver of the *in vivo* bioequivalence study requirements for 5 and 10 mg tablets of the test product is granted. The 5 and 10 mg test tablets are therefore deemed bioequivalent to Ritalin® 5 and 10 mg tablets, manufactured by Ciba Geigy.

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37°C using apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

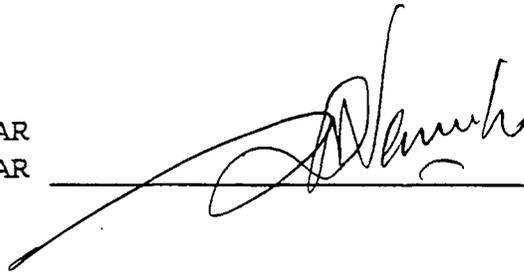
Not less than _____ of the labeled amount of methylphenidate in the dosage form is dissolved in 45 minutes.

5. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.


for Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

6/10/1998

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

A large, stylized handwritten signature in black ink, appearing to be 'S. Nerurkar', written over a horizontal line.

Date 6/10/98

Concur:

A handwritten signature in black ink that reads 'Dale P. Conner', written over a horizontal line.

Date

6/30/98

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

TABLE 1

Comparative Quantitative Composition of Methylphenidate
Hydrochloride Tablets

Ingredient	5 mg	10 mg mg/tablet	20 mg
Methylphenidate HCl	5.0	10.0	20.0
Lactose			
Magnesium Stearate			
Microcrystalline Cellulose			
Talc			
----- Total			

TABLE 2
 MEAN PLASMA METHYLPHENIDATE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2)
 PRODUCTS IN FASTING STUDY (N=30)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME-HR:					
0	0.00	0.00	0.00	0.00	
0.33	0.43	1.05	0.32	0.61	1.36
0.67	4.65	4.28	3.82	3.69	1.22
1	8.21	3.50	7.42	4.13	1.11
1.5	9.51	3.18	9.63	3.49	0.99
2	8.99	2.47	9.36	2.90	0.96
2.5	8.04	2.07	8.46	2.45	0.95
3	7.23	2.06	7.55	2.12	0.96
3.5	6.35	1.87	6.59	1.87	0.96
4	5.63	1.65	5.88	1.79	0.96
6	3.17	1.02	3.25	1.06	0.98
8	1.93	0.58	2.03	0.69	0.95
10	1.08	0.36	1.15	0.43	0.93
12	0.66	0.28	0.67	0.32	0.98
14	0.37	0.23	0.36	0.28	1.05
16	0.12	0.18	0.11	0.20	1.08
24	0.00	0.00	0.00	0.00	

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
 ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	48.24	14.53	49.38	16.32	0.98
AUCT	46.48*	14.28	47.32**	15.64	0.98
CMAx	9.92	3.19	10.12	3.28	0.98
KE	0.27*	0.03	0.26**	0.03	1.01
LAUCI	46.41	0.28	47.20	0.30	0.98
LAUCT	44.66	0.29	45.24	0.30	0.99
LCMAx	9.51	0.29	9.73	0.28	0.98
THALF	2.64	0.30	2.66	0.30	0.99
TMAx	1.59	0.48	1.73	0.49	0.92

*N=29, **N=28

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	47.90	48.83	0.98	94.47	101.76
AUCT	46.66	47.52	0.98	94.59	101.78
CMAx	9.96	10.16	0.98	92.15	104.01
LAUCI	46.06	46.65	0.99	95.22	102.34
LAUCT	44.79	45.39	0.99	95.10	102.38
LCMAx	9.54	9.75	0.98	92.25	103.95

TABLE 3
 MEAN PLASMA METHYLPHENIDATE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS
 IN NON-FASTING STUDY (N=22)

TIME HR.	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.33	0.23	0.36	0.21	0.32	0.38	0.47	1.10
0.67	4.06	2.79	3.46	3.23	4.09	2.70	1.18
1	8.39	3.94	7.27	4.80	7.49	4.30	1.15
1.5	10.31	4.03	10.21	4.85	10.93	4.87	1.01
2	10.00	3.71	11.02	3.63	12.23	4.29	0.91
2.5	9.08	3.18	11.35	3.23	12.19	3.46	0.80
3	8.29	2.94	10.75	2.79	11.32	3.24	0.77
3.5	7.39	2.72	9.85	2.83	9.97	2.72	0.75
4	6.56	2.39	8.86	2.84	8.78	2.34	0.74
6	3.80	1.58	4.76	1.60	4.96	1.57	0.80
8	2.33	1.13	3.03	1.10	3.11	1.19	0.77
10	1.27	0.61	1.79	0.81	1.80	0.81	0.71
12	0.86	0.46	1.14	0.53	1.16	0.60	0.76
14	0.55	0.38	0.70	0.40	0.69	0.39	0.78
16	0.31	0.29	0.41	0.35	0.41	0.32	0.76
24	0.03	0.08	0.04	0.10	0.04	0.12	0.68

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
 MEAN PLASMA METHYLPHENIDATE LEVELS FOR TEST AND REFERENCE PRODUCTS

TIME HR	RMEAN13	RMEAN23
0	.	.
0.33	0.61	0.55
0.67	0.99	0.84
1	1.12	0.97
1.5	0.94	0.93
2	0.82	0.90
2.5	0.74	0.93
3	0.73	0.95
3.5	0.74	0.99
4	0.75	1.01
6	0.77	0.96
8	0.75	0.97
10	0.71	1.00
12	0.74	0.98
14	0.80	1.02
16	0.75	0.98
24	0.57	0.84

1= TEST FASTING
 2= TEST NON-FASTING
 3= REFERENCE NON-FASTING

TABLE 4

METHYLPHENIDATE ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY (N=22)

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	55.54	22.61	67.57	20.13	70.05	21.69	0.82
AUCT	53.84	22.22	65.63	19.80	68.38	21.55	0.82
CMAx	10.69	3.97	12.86	3.65	13.36	3.99	0.83
KE	0.24	0.04	0.24	0.04	0.25	0.04	0.99
LAUCI	51.55	0.39	65.00	0.28	67.04	0.30	0.79
LAUCT	49.86	0.40	63.06	0.28	65.33	0.31	0.79
LCMAx	10.04	0.36	12.41	0.27	12.80	0.30	0.81
THALF	2.97	0.52	2.97	0.64	2.90	0.53	1.00
TMAx	1.77	0.40	2.27	0.70	2.20	0.48	0.78

(CONTINUED)

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 ARITHMETIC MEANS AND RATIOS

PARAMETER	RMEAN13	RMEAN23
AUCI	0.79	0.96
AUCT	0.79	0.96
CMAx	0.80	0.96
KE	0.98	0.99
LAUCI	0.77	0.97
LAUCT	0.76	0.97
LCMAx	0.78	0.97
THALF	1.02	1.02
TMAx	0.80	1.03

UNIT: AUC=NG HR/ML CMAx=NG/ML TMAx=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
 LSMEANS AND RATIOS

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	55.62	67.52	70.02	0.82	0.79	0.96
AUCT	53.92	65.57	68.36	0.82	0.79	0.96
CMAx	10.70	12.87	13.34	0.83	0.80	0.96
LAUCI	51.63	64.91	67.02	0.80	0.77	0.97
LAUCT	49.95	62.96	65.31	0.79	0.76	0.96
LCMAx	10.05	12.42	12.78	0.81	0.79	0.97

1= TEST FASTING
 2= TEST NON-FASTING
 3= REFERENCE NON-FASTING

Table 5. In Vitro Dissolution Testing

Drug (Generic Name): Methylphenidate Hydrochloride Tablets
 Dose Strength: 5, 10, 20 mg
 ANDA No.: 40-300
 Firm: Mallinckrodt
 Submission Date: February 27, 1998
 File Name: 40300SDW.298

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: X Paddle: RPM: 100
 No. Units Tested: 12
 Medium: Water Volume: 900 mL
 Specifications: NLT in 45 minutes
 Reference Drug: Ritalin® (Ciba Geigy)
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #MHSC 9719 Strength(mg) 5			Reference Product Lot #1T188802 Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	100.6		2.07	67.7		7.59
30	100.9		1.30	98.9		2.52
45	100.0		1.45	98.9		2.82
60	100.5		1.81	98.6		2.51

Sampling Times (Minutes)	Test Product Lot #MHSC 9720 Strength(mg) 10			Reference Product Lot #1T191633 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
15	100.8		1.90	64.2		2.87
30	100.7		1.46	96.7		1.49
45	101.9		1.68	97.1		2.03
60	101.6		2.43	96.5		1.94

Continued.

Table 5. In Vitro Dissolution Testing

Drug (Generic Name): Methylphenidate Hydrochloride Tablets
 Dose Strength: 5, 10, and 20 mg
 ANDA No.: 40-300
 Firm: Mallinckrodt
 Submission Date: February 27, 1998
 File Name: 40300SDW.298

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: x Paddle: RPM: 100
 No. Units Tested: 12
 Medium: Water Volume: 900 mL
 Specifications: NLT in 45 minutes
 Reference Drug: Ritalin* (Ciba Geigy)
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #MHSC9721 Strength(mg) 20			Reference Product Lot #1T197606 Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
15	103.3		1.15	73.6		3.26
30	104.5		1.40	101.4		1.99
45	102.7		1.69	96.9		1.95
60	103.0		1.96	101.1		0.99
Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

FIG 1. PLASMA METHYLPHENIDATE LEVELS

METHYLPHENIDATE HYDROCHLORIDE TABLETS, 20 MG, ANDA #40-300
UNDER FASTING CONDITIONS
DOSE=1 X 20 MG

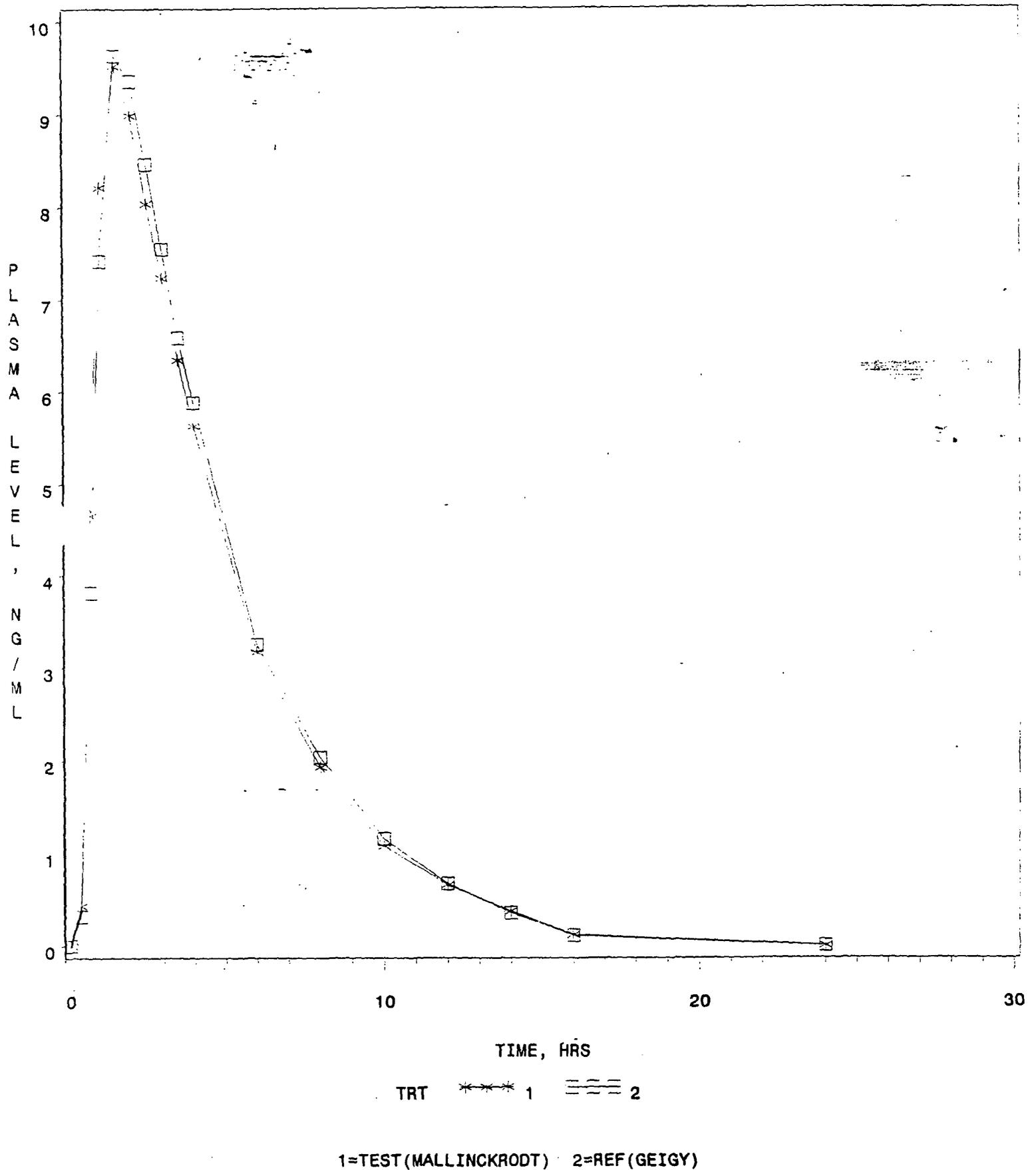


FIG 2. PLASMA METHYLPHENIDATE LEVELS

METHYLPHENIDATE HYDROCHLORIDE TABLETS, 20 MG, ANDA #40-300
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 20 MG

