CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40306

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-306 APPLICANT: Medeva Pharmaceuticals

DRUG PRODUCT: Meperidine ER Tablets, 10 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 500 mL of simulated gastric fluid without pepsin , pH 1.0 - 1.5, at 37° C using USP Apparatus (2) at 50 rpm. The test product should meet the following tentative specifications:

1 Hour	-	%
2 Hours	-	%
5 Hours	-	%
7 Hours	- NLT	%

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Study Design:

Protocol No.:	970932 A Single Dose, Fasting Bioequivalence Study Comparing Methylphenidate ER 10 mg Tablets to Ritalin-SR® 20 mg Tablets
Design Type:	crossover
Randomized:	Y
No. of Sequences:	2
No. of Periods:	2
No. of Treatments:	2
Washout Period:	7 days
Single or Multiple dose:	single

Subjects:

Normal Healthy Volunteers:	Y
IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	26 (13 males and 13 females)
Inclusion/Exclusion criteria	vol:1.2 ; pages: 94 - 95
Housing	Evening prior to each drug administration until 24 hours after dosing

Treatment Information:

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	Methylphenidate Hydrochloride ER Tablet	Ritalin-SR® Tablet
Strength:	10 mg	20 mg
Manufacturer:	MD Pharmaceuticals	CIBA Pharmaceuticals
Batch/Lot No.:	H561W01	1T193044
Batch Size:	( )tablets	N/A
Expiration Date:	N/A	July 1998
Content Uniformity	96.7% - 101.2%	97.8% - 102.2%
Assay	%	%
Dose Administered:	2 x 10 mg	1 x 20 mg
Length of Fasting:	10 hours	10 hours

Dosing:

After an overnight fast of ten hours, each subject randomly received either a test product or a reference product with 240 mL of water. Standard meals were provided at 4 and 10 hours after dosing. Water was not

permitted for 1 hour before and 2 hours after dosing in each dosing period.

Blood Sampling:

Blood sample volume	10 mL
No. of time points	14
Time points	0 and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing

The blood samples were centrifuged for 20 minutes at 2500 rpm and plasma samples were separated and stored at -20°C until analyzed.

Analytical Method

Results

Of the 26 healthy, adult subjects enrolled in the study, 25 subjects successfully completed both phases of the study. Subject 10 was dropped by the principal investigator due to an elevated pulse prior to period 2 dosing.

1. Adverse Events

Both drugs were well tolerated. During the study, a total of sixteen (Trt A = 8, Trt B = 8) adverse events such as headache, tiredness were reported as possibly or probably related to study drug. Six other events were unrelated to treatment. All events were mild to moderate in nature and resolved spontaneously.

2. Pharmacokinetics/Statistical Analysis

Mean methylphenidate hydrochloride plasma levels of 25 subjects are summarized in Table 2 and Figure 1.

Table 2: Mean Methylphenidate hydrochloride levels for test and reference products (N=25)

Time	Test (ng/mL)		Reference (ng/mL)		Ratio
(hour)	Mean	Std	Mean	Std	T/R
0	0.00	0.00	0.00	0.00	.
0.5	0.42	0.33	0.52	0.81	0.80
1	2.13	0.73	2.48	1.10	0.86
1.5	3.19	1.10	3.44	1.33	0.93
2	3.76	1.30	4.14	1.63	0.91
3	4.31	1.35	4.60	1.72	0.94
4	4.05	1.07	4.39	1.58	0.92
5	4.38	1.42	4.69	1.71	0.93
6	4.04	1.37	4.00	1.46	1.01
8	2.76	1.09	2.52	0.97	1.10
10	1.81	0.67	1.76	0.74	1.03
12	1.24	0.45	1.21	0.50	1.03
16	0.53	0.22	0.58	0.26	0.92
24	0.01	0.05	0.03	0.10	0.37

Pharmacokinetic Parameters/Statistical Analysis

Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for methylphenidate hydrochloride are shown in Table 3. The LS means of the non-transformed and log-transformed pharmacokinetic parameters,

ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 4.

Table 3: Test mean/Reference mean ratios of methylphenidate hydrochloride pharmacokinetic parameters

Parameter*	Test Mean	SD	Ref Mean	SD	Ratio
AUCI	41.13	12.89	42.64	15.27	0.96
AUCT	40.57	12.56	41.75	14.98	0.97
CMAX	4.87	1.43	5.08	1.72	0.96
KE	0.21	0.03	0.19	0.03	1.09
LAUCI	39.47	0.29	40.59	0.31	0.97
LAUCT	38.96	0.28	39.73	0.31	0.98
LCMAX	4.69	0.27	4.84	0.32	0.97
THALF	3.42	0.49	3.76	0.66	0.91
TMAX	4.04	1.15	3.92	1.15	1.03

* AUCT=ng-hr/mL, AUCI= ng-hr/mL, TMAX=hr, CMAX=ng/Ml

Table 4: LSMeans and 90% confidence intervals for methylphenidate hydrochloride

Parameter	LS Mean $_{test}$	LS Mean $_{ref}$	Low CI	Upp CI
AUCI	41.13	42.91	90.49	101.23
AUCT	40.57	41.99	91.17	102.07
CMAX	4.87	5.10	88.95	102.02
LAUCI	39.47	40.93	91.12	102.06
LAUCT	38.96	40.04	91.84	103.11
LCMAX	4.69	4.86	89.64	103.88

Comment:

The 90% confidence intervals of LAUCT, LAUCI and LCMAX for methylphenidate hydrochloride are all within the acceptable limit of 80 - 125% .

Non-fasting Study

Study Facility Information:

Clinical Facility: [redacted]ebraska
Principal Investigator: [redacted]
Clinical Study Date: January 23, 1997 - February 26, 1997
Analytical Facility: [redacted]
Analytical Study Date: February 11, 1997 - March 7, 1997
Storage Period: No more than 44 days at -20° C

Study Design:

Protocol No.:	392-04: A Single Dose, Fed, Bioequivalence Study, Comparing Methylphenidate ER 10 mg Tablets to Ritalin-SR® 20 mg Tablets
Design Type:	crossover
Randomized:	Y
No. of Sequences:	6
No. of Periods:	3
No. of Treatments:	3
Washout Period:	7 days
Single or Multiple dose:	single

Subjects:

Normal Healthy Volunteers:	Y
IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	18 (12 males, 6 females)
Inclusion/Exclusion criteria	vol: 1.5 ; pages: 1190 - 1191
Housing	Evening prior to each drug administration until 24 hours after dosing

Treatment Information:

Treatment:	A	B	C
Test or Reference:	Test	Reference	Test
Product Name:	Methylphenidate Hydrochloride ER Tablet	Ritalin-SR® Tablet	Methylphenidate Hydrochloride ER Tablet
Strength:	10 mg	20 mg	10 mg
Manufacturer:	MD Pharmaceuticals	CIBA Pharmaceuticals	MD Pharmaceuticals
Batch/Lot no.:	H561W01	1T193044	H561W01
Expiration Date:	N/A	July 1998	N/A
Content Uniformity	96.7% - 101.2%	97.8% - 102.2%	96.7% - 101.2%
Assay	99.0%	99.9%	99.0%
Dose Administered:	2 x 10 mg	1 x 20 mg	2 x 10 mg
Study Condition:	Non-Fasting	Non-Fasting	Fasting
Length of Fasting:	9.5 hours	9.5 hours	10 hours
Food-drug Interval	0.5 hours	0.5 hours	N/A
Standardized Breakfast:	Y	Y	N

Breakfast Specifics:

The subjects receiving treatments A and B received the following breakfast.

1 egg (fried)
1 serving of hash brown,
1 buttered english muffin
8 fluid oz of whole milk
1 slice of american cheese
6 fluid oz of orange juice
1 slice of canadian bacon

Dosing:

Treatments A & B :

All subjects fasted from 9 PM of the evening prior to breakfast administration. Five minutes after breakfast, each subject received either a test product or a reference product with 240 mL of water.

Treatment C:

After an overnight fast of ten hours, each subject received the test product with 240 mL of water.

During each phase of the study, standardized meals were provided to all subjects at 5 and 10 hours after dosing. Water was provided *ad libitum* until 1 hour after pre-drug and after 1 hour post drug.

Blood Sampling:

Blood sample volume	10 mL
No. of time points	14
Time points	0 and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing

The blood samples were centrifuged for 20 minutes at 2500 rpm and plasma samples were separated and stored at -20°C until analyzed.

Analytical Method

Results:

Of the 18 subjects enrolled, three subjects (# 8, 17, 18) did not complete the study due to the following reasons. Thus, fifteen subjects completed three periods of study.

Subject Dropped	Reason
8	Did not show for Period 2 check-in
17	Consumed xanthine containing food less than 48 hours prior to dosing
18	Due to an adverse experience (by Investigator)

1. Adverse Events

Both drugs were well tolerated. During the study, a total of twelve (Trt A = 3, Trt B = 4, Trt C = 5) adverse events such as drymouth, headache, tiredness were reported as possibly or probably related to study drug. Thirty one other events were unrelated to treatment. All events were mild to moderate in nature and resolved spontaneously.

2. Pharmacokinetic/Statistical Analysis

The mean plasma methylphenidate levels for the test and reference products are shown in Table 5 and Figure 2.

Table 5: Mean methylphenidate levels (ng/mL) for test and reference products (N=15)

Time (hour)	$Test_{Non\text{-}fasting}$ - A Mean	CV%	$Reference_{Non\text{-}fasting}$ - B Mean	CV%	$Test_{Fast}$ - C Mean	CV%
0	0.00	0.00	0.00	0.00	0.14	0.58
0.5	0.34	0.44	0.25	0.41	0.66	0.61
1	2.13	1.17	1.43	1.35	2.35	1.11
1.5	3.34	1.71	2.82	1.95	3.66	1.67
2	4.60	1.94	4.34	2.04	4.17	1.83
3	5.51	2.18	6.27	2.03	4.64	1.65
4	5.60	1.73	6.23	1.63	4.82	1.94
5	5.55	1.75	5.85	1.69	4.98	1.96
6	5.06	1.74	5.60	1.71	4.49	1.74
8	4.07	1.63	4.30	1.40	3.11	1.32
10	2.95	1.19	3.07	1.58	2.13	1.08
12	1.79	0.76	1.90	0.90	1.43	0.74
16	0.73	0.31	0.73	0.41	0.64	0.45
24	0.05	0.12	0.05	0.12	0.08	0.19

Pharmacokinetic Parameters

Mean reported pharmacokinetic parameters for methylphenidate are shown in Table 6.

Table 6: Mean pharmacokinetic parameters and relative ratio of test (non-fasting) vs. reference (non-fasting) for methylphenidate

Parameter*	Test (Non-fasting) A	Std	Ref (Non-fasting) B	Std	Test (Fasting) C	Std	A/B
AUCI	55.17	16.06	57.98	16.47	47.75	20.19	0.95
AUCT	52.49	15.87	55.18	16.44	44.89	19.78	0.95
CMAX	6.71	1.95	7.39	1.52	5.47	1.93	0.91
KE	0.22	0.05	0.23	0.05	0.20	0.05	0.98
LAUCI	53.22	0.27	55.82	0.29	44.65	0.37	0.95
LAUCT	50.56	0.28	52.98	0.29	41.80	0.38	0.95
LCMAX	6.45	0.29	7.24	0.21	5.18	0.34	0.89
THALF	3.25	0.77	3.19	0.72	3.62	1.08	1.02
TMAX	3.56	1.54	4.18	1.88	4.25	1.24	0.85

*AUCT=ng-hr/mL, AUCI= ng-hr/mL, TMAX=hr, CMAX=ng/mL

Comment:

Values of Cmax, AUCT and AUCI mean ratios for the test product versus the reference product administered under non-fasting conditions (Ratio A/B) are within the acceptable range of 0.8 - 1.2.

Multiple Dose Study

Study Facility Information:

Clinical Facility:
Principal Investigator:
Clinical Study Date: Phase I: August 1 - 6, 1997
Phase II: August 15 - 20, 1997

Analytical Facility:
Analytical Study Date: August 27, 1997 - September 4, 1997
Storage Period: No more than 36 days at -20° C

Study Design:

Protocol No.:	#392-06: A Multiple Dose, Bioequivalence Study, Comparing Methylphenidate ER 10 mg to Ritalin SR® 20 mg Tablets
Design Type:	crossover
Randomized:	Y
No. of Sequences:	2
No. of Periods:	2
No. of Treatments:	2
Washout Period:	7 days
Single or Multiple dose:	multiple

Subjects:

Norma; Healthy Volunteers:	Y
IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	30 (15 males and 15 females)
Inclusion/Exclusion criteria	vol: 1.8; pages 2151-2152
Housing	Evening prior to each drug administration until 24 hours after dosing

Treatment Information:

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	Methylphenidate Hydrochloride ER Tablet	Ritalin-SR® Tablet
Strength:	10 mg	20 mg
Manufacturer:	MD Pharmaceuticals	CIBA Pharmaceuticals
Batch/Lot no.:	H561W01	1T193044
Expiration Date:	N/A	July 1998
Content Uniformity	96.7% - 101.2%	97.8% - 102.2%
Assay	99.0%	99.9%
Dose Administered:	2 x 10 mg	1 x 20 mg
Dosing Interval:	8 hours	8 hours
Number of Doses:	10 doses	10 doses
Steady State Dose Time	72 hours - 80 hours	72 hours - 80 hours

Dosing:

Two 10 mg extended release methylphenidate hydrochloride tablets or one 20 mg Ritalin-SR® tablet were administered q8h for a total of 10

doses (Day 1 through 4) in each period. Each morning dose was administered after a 10 hour overnight fast. Fasting continued for 2 hours after the morning dose. The other two daily dosings were administered after a fast of at least 2 hours and the fasting continued for 2 hours post dose. Water was allowed at all times except within 1 hour of each drug administration. After the last dose (Day 4^{th}, 10^{th} dose), blood samples were collected up to 8 hours (steady state interval, 72 hours to 80 hours). The entire sequence was repeated after a one week washout utilizing the formulation not given in the first period.

Blood Sampling

Blood sample volume	10 mL
No. of time points	15
Time points	0 (prior to dosing), 24, 48, 56, 64, 72, 72.5, 73, 73.5, 74, 75, 76, 77, 78 and 80 hours

The blood samples were centrifuged for 20 minutes at 2500 rpm and plasma samples were separated and stored at -20°C until analyzed.

Analytical Method

Results:

Of the 30 subjects (15 males and 15 females) enrolled, twenty eight subjects completed both periods of study. Subject 17 experienced adverse event and was withdrawn from the study. Subject 22 withdrew from the study during period I for personal reasons.

1. Adverse Events

During the study, a total of thirty eight (Trt A = 26, Trt B = 12) adverse events such as headache, frequent urination, tiredness were reported as possibly or probably related to study drug. One other event was unrelated to treatment. Most of the events were mild in severity, however, there was one severe adverse event was reported by subject # 17 (Please see Attachment B for more details, vol 1.8, pages 2095-2096). He was withdrawn from the study. All other events were resolved without medical intervention.

2. Pharmacokinetic/Statistical Analysis

Mean plasma methylphenidate concentrations are summarized in Table 7 and mean pharmacokinetic parameters are summarized in Table 8.

Table 7: Mean methylphenidate hydrochloride levels (ng/mL) for test and reference products (N=28)

Time (hour)	Test A Mean	Std	Reference B Mean	Std	Ratio A/B
0	0.00	0.00	0.00	0.00	.
24	5.81	2.44	5.77	2.21	1.01
48	5.85	2.03	6.49	2.41	0.90
56	5.01	2.14	5.39	1.84	0.93
64	5.16	2.08	5.27	2.33	0.98
72	6.01	2.13	6.20	2.21	0.97
72.5	6.13	2.20	6.29	2.05	0.97
73	8.12	2.74	7.98	2.80	1.02
73.5	9.36	3.36	9.34	3.63	1.00
74	9.89	3.55	9.53	3.41	1.04
75	9.81	3.80	9.38	3.48	1.05
76	9.16	3.17	9.02	3.22	1.02
77	8.44	3.30	8.57	3.20	0.98
78	7.51	3.16	7.50	2.81	1.00
80	5.50	2.16	5.30	2.05	1.04

Pharmacokinetic Parameters

Table 8: Mean pharmacokinetic parameters and relative ratio of test vs. reference for methylphenidate hydrochloride (n=28)

Parameter*	Test Mean	std	Ref Mean	Std	Ratio
AUCτ	64.90	23.80	64.01	22.30	1.01
CAVG	8.11	2.97	8.00	2.79	1.01
CMAX	10.42	3.60	10.35	3.60	1.01
CMIN	5.22	2.15	5.08	2.06	1.03
% Swing	116.6	92.32	122.8	85.92	0.95
LAUCτ	61.14	0.35	60.32	0.36	1.01
LCAVG	7.64	0.35	7.54	0.36	1.01
LCMAX	9.88	0.32	9.78	0.34	1.01
LCMIN	4.77	0.45	4.60	0.50	1.04
TMAX	2.57	1.02	2.43	1.09	1.06

$AUC\tau = AUC_{72\text{-}80h}$

*AUCτ =ng-hr/mL, TMAX=hr, CMAX=ng/mL, CMIN=ng/mL

% swing = ((Cmax-Cmin)/Cmin)*100

Table 9: LSMeans and 90% confidence intervals for methylphenidate hydrochloride (N=28)

Parameter*	LS Mean $_{test}$	LS Mean $_{ref}$	Low CI	Upp CI
AUCτ	64.86	64.05	96.54	105.97
CAVG	8.11	8.01	96.54	105.97
CMAX	10.40	10.36	95.56	105.24
CMIN	5.23	5.08	96.61	109.06
LAUCτ	61.08	60.39	95.52	107.09
LCMAX	9.87	9.80	95.14	106.59
LCMIN	4.78	4.59	94.87	114.26
TMAX	2.58	2.42	89.37	123.33

*AUCτ =ng-hr/mL, CMAX=ng/mL

Comments:

1. The firm has confirmed the achievement of steady-state level by performing repeated measures analysis of variance of predose concentrations (24, 48 and 72 hours).

2. The firm has also compared the pharmacokinetic parameters in males and females separately. The mean values of AUCτ and Cmax were comparable in male and female subjects

3. The 90% confidence intervals of LAUCτ and LCMAX for methylphenidate hydrochloride are all within the acceptable limit of 80 -125%.

Dissolution Testing:

The dissolution testing was carried out according to the procedure described in the OGD guidance. General conditions were described in Table 10:

Table 10- In Vitro Dissolution Testing

Drug (Generic Name): Methylphenidate hydrochloride
Dosage Form: Extended Release Tablet
Dose Strength: 20 mg

I. Conditions for Dissolution Testing: **According to OGD Guidance**

Apparatus: Paddle
Speed: 50 rpm
No. Units 12
Medium: Aqueous media of the following pH ranges 1-1.5, 4-4.5, 6-6.5 and 7-7.5
Volume: 500 ml*
Sampling Time: 1, 2, 3.5, 5 and 7 hours and every two hours until % of the drug is released

II. Results of In Vitro Dissolution Testing:

pH: 1.0-1.5
Media: Simulated gastric fluid without pepsin

Time (hr)	Test Lot # H561W01 Mean	Range	Std	Reference Lot # 1T193044 Mean	Range	Std
1	39.7		0.8	43.4		1.5
2	54.8		0.9	59.5		1.5
3.5	69.0		1.1	75.0		1.6
5	80.3		1.1	86.1		1.8
7	91.2		0.9	95.7		1.5

pH: 4.0-4.5
Media: phthalate Buffer

Time (hr)	Test Lot # H561W01 Mean	Range	Std	Reference Lot # 1T193044 Mean	Range	Std
1	41.5		0.6	37.4		1.4
2	55.1		0.9	51.9		1.6
3.5	68.5		1.0	65.3		1.2
5	78.5		1.0	75.2		1.6
7	88.4		0.8	84.3		1.2

pH: 6.0-6.5
Media: Phosphate Buffer

Time (hr)	Test Lot # H561W01 Mean	Range	Std	Reference Lot # 1T193044 Mean	Range	Std
1	41.6		0.9	39.8		0.7
2	56.7		0.9	55.0		0.9
3.5	71.5		1.1	69.1		1.2
5	81.7		1.2	80.4		1.7
7	90.4		1.5	89.2		1.7

pH: 7.0-7.5
Media: Phosphate Buffer

No dissolution data were generated in this pH range due to instability of methylphenidate in this medium.

* Conditions deviated from the guidance to accommodate USP 23 monograph for methylphenidate ER tablets

Comment:

The firm has conducted dissolution according to the procedure described in the OGD guidance. The dissolution data are acceptable.

Composition of Methylphenidate hydrochloride 20 mg ER Tablet

(Not To Be Released Under FOI)

Components	mg/Tablet
Anhydrous Lactose	
Cetyl Alcohol	
ethylcellulose	
Magnesium Stearate	
Methylphenidate Hydrochloride, USP	

*Will be evaporated during the coating process

Comments:

1. Assay method validation: Pre-study and within-study validations are acceptable.

2. For fasting study, the 90% confidence intervals of LAUCT, LAUCI and LCMAX for methylphenidate hydrochloride are all within the acceptable limit of 80 -125%.

3. Values of Cmax, AUCT and AUCI mean ratios for the test product versus the reference product administered under non-fasting conditions (Ratio A/B) are within the acceptable range of 0.8 - 1.2.

4. For multiple dose study, the 90% confidence intervals of $LAUC_{\tau}$ and LCMAX for methylphenidate hydrochloride are all within the limit of 80 - 125%.

5. The firm has conducted dissolution according to the procedure described in the OGD guidance. The dissolution data are acceptable.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Medeva Pharmaceuticals on its methylphenidate hydrochloride Tablets, 10 mg, lot # H561W01, comparing it to Novartis' Ritalin® Tablets, 20 mg, lot # 1T193044, is acceptable.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Medeva Pharmaceuticals on its methylphenidate hydrochloride Tablets, 10 mg, lot # H561W01, comparing it to Novartis' Ritalin® Tablets, 20 mg, lot # 1T193044, is acceptable.

3. The bioequivalence study conducted at steady state conditions by Medeva Inc. on its methylphenidate hydrochloride Tablets, 10 mg, lot # H561W01, comparing it to Novartis' Ritalin® Tablets, 20 mg, lot # 1T193044, is acceptable.

4. The *in vitro* dissolution testing submitted by the firm on its methylphenidate hydrochloride Tablets, 10 mg is acceptable.

5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution method and specifications recommended by the Division of Bioequivalence are as follow:

Media: Simulated gastric fluid without pepsin, pH: 1.0-1.5 at 37°C
Apparatus: Paddle
RPM: 50
Specifications: 1Hour -])%
2 Hours - %
5 Hours - %
7 Hours - NLT(%:

6. From the bioequivalence point of view, the application has been found complete.

/S/
Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED BDAVIT BMO 9/8/98
FT INITIALED BDAVIT /S/ Date 9/10/98

Concur: /S/ Date 9/21/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA # 40-306 (original, duplicate), Kharidia, HFD-658, HFD-630, Drug File, Division File

FIGURE 1. PLASMA METHYLPHENIDATE LEVELS

METHYLPHENIDATE ER TABLETS, 10 MG, ANDA #40-306
UNDER FASTING CONDITIONS
DOSE= 1 X 10 MG

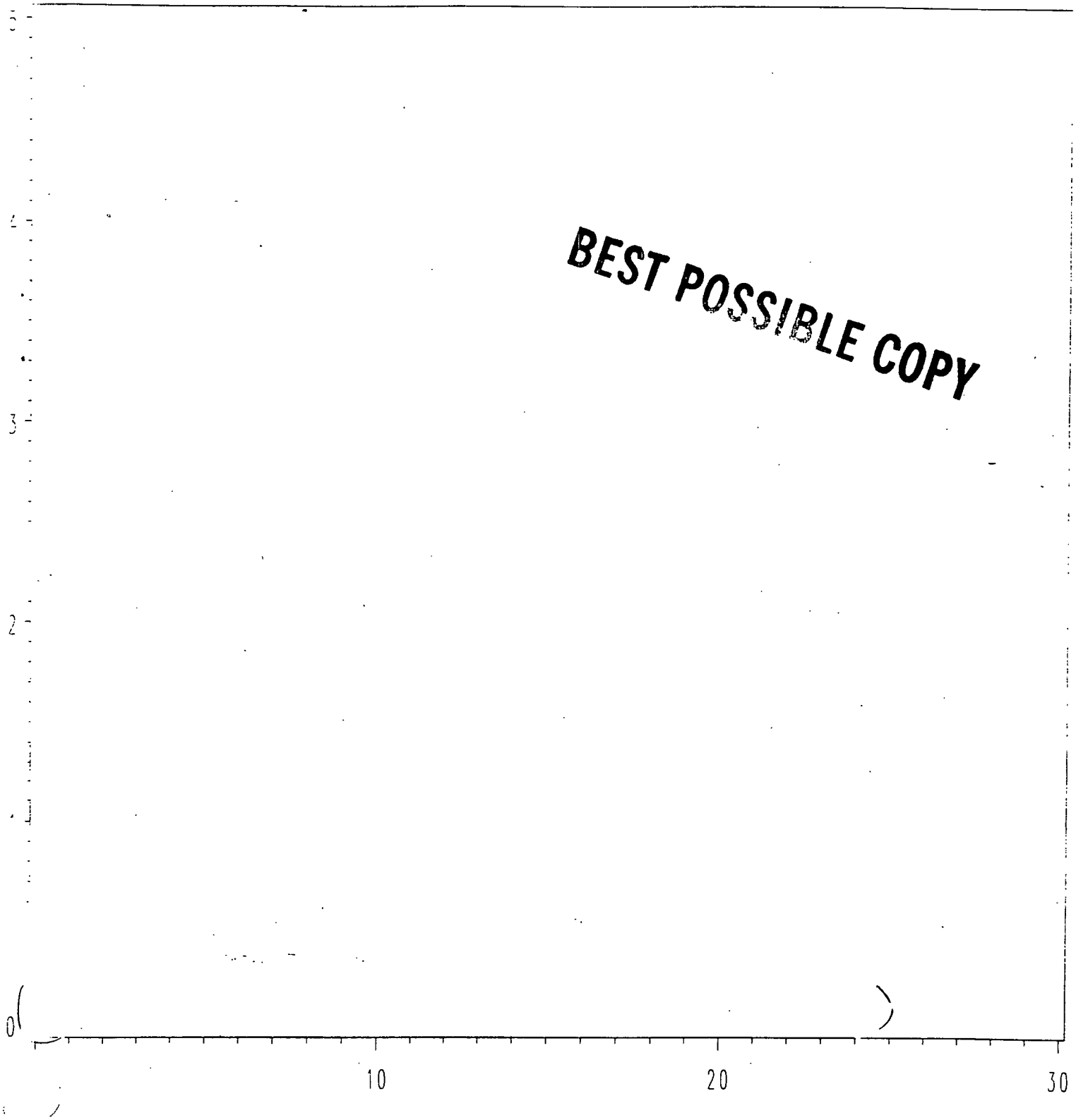


FIGURE 2. PLASMA METHYLPHENIDATE LEVELS

BUPROFEN CAPSULES, 10 MG, LOT# 40-306
UNDER FAST MG/KG FAST MG DOSE PLAS
DOSE=2 X 10 MG

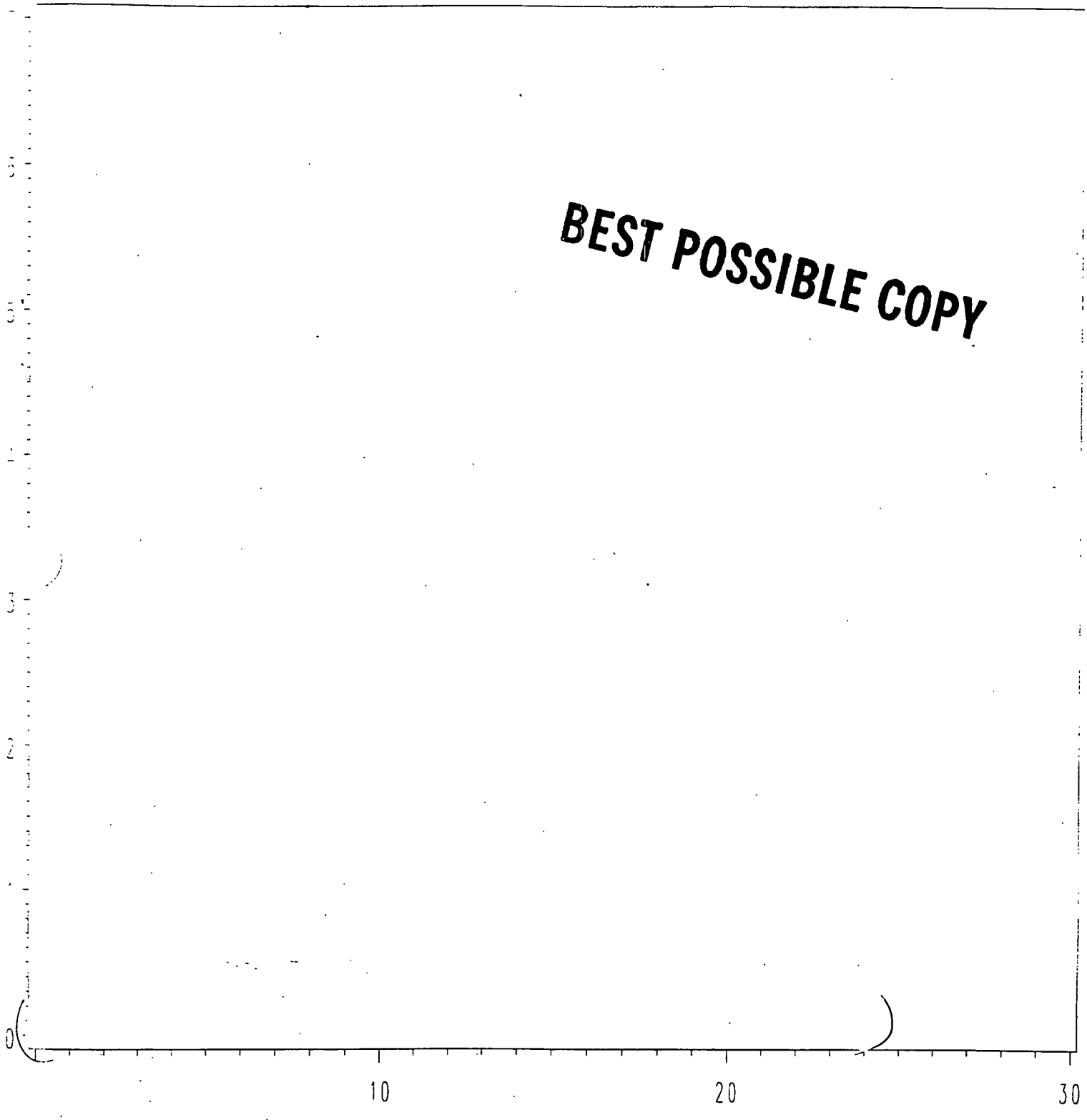
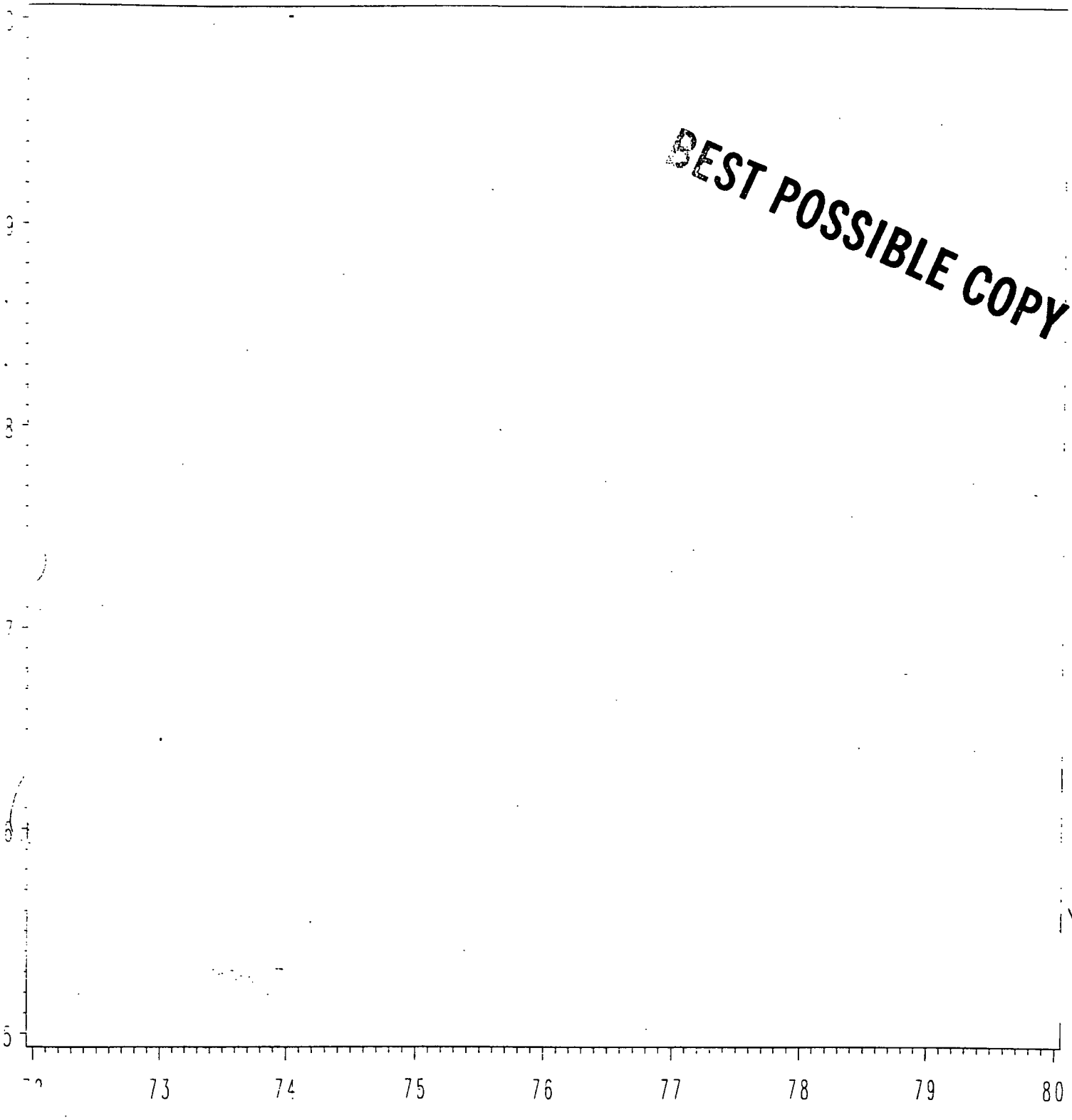


FIGURE 3. PLASMA METHYLPHENIDATE LEVELS



Methylphenidate Hydrochloride
10 mg Extended Release Tablet
ANDA # 40-306
Reviewer: Jahnavi S. Kharidia

Medeva Pharmaceuticals
755 Jefferson Road
Rochester, NY 14603-1710
Submission Date:
April 10, 1998

Amendment to Review

This is an amendment to the review for ANDA 40-306 dated September 21, 1998.

Comments:

1. As stated in the review of ANDA# 40-306, the dissolution method and specifications recommended by the Division of Bioequivalence were as follows:

Media:	Simulated gastric fluid without pepsin, pH: 1.0-1.5 at 37°C		
Apparatus:	Paddle		
RPM:	50		
Specifications:	1Hour	-	[%
	2 Hours	-	%
	5 Hours	-	%
	7 Hours	-	NLT(%:

2. There is a USP method for Methylphenidate Hydrochloride ER tablets (USP 23, supplement 5, pg. 3423). The USP method and specifications are as follows:

Media: Water, 500 mL			
Apparatus:	Paddle		
RPM:	50		
Specifications:	1 Hour	-	(%%
	2 Hours	-	%
	3.5 Hours	-	%
	5 Hours	-	%
	7 Hours	-	NLT(%%

3. The firm has submitted dissolution data (Table 1) using the USP method and would like to use the USP method for their manufacturing controls and stability program. Their proposal of using the USP method is acceptable.

Table 1- In Vitro Dissolution Testing						
Drug (Generic Name): Methylphenidate hydrochloride Dosage Form: Extended Release Tablet Dose Strength: 20 mg						
I. Conditions for Dissolution Testing: **According to OGD Guidance**						
Apparatus: Paddle Speed: 50 rpm No. Units 12 Medium: Water Volume: 500 ml Sampling Time: 1, 2, 3.5, 5 and 7 hours						
II. Results of In Vitro Dissolution Testing:						
Time (hr)	Test Lot # H561W01			Reference Lot # 1T193044		
	Mean	Range	Std Dev	Mean	Range	Std Dev
1	41.3		0.7	41.0		0.8
2	54.9		0.6	57.5		1.2
3.5	68.5		1.2	72.4		2.0
5	77.8		0.6	82.8		1.6
7	86.3		1.0	91.7		1.9

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Medeva Pharmaceuticals on its methylphenidate hydrochloride Tablets, 10 mg, lot # H561W01, comparing it to Novartis' Ritalin® Tablets, 20 mg, lot # 1T193044, is acceptable.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Medeva Pharmaceuticals on its methylphenidate hydrochloride Tablets, 10 mg, lot # H561W01, comparing it to Novartis' Ritalin® Tablets, 20 mg, lot # 1T193044, is acceptable.

3. The bioequivalence study conducted at steady state conditions by Medeva Inc. on its methylphenidate hydrochloride Tablets, 10 mg, lot # H561W01, comparing it to Novartis' Ritalin® Tablets, 20 mg, lot # 1T193044, is acceptable.

4. The *in vitro* dissolution testing submitted by the firm on its methylphenidate hydrochloride Tablets, 10 mg is acceptable.

5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution method and specifications recommended by the Division of Bioequivalence are as follow:

   Media: Water, 500 mL
   Apparatus: Paddle
   RPM: 50
   Specifications: 1 Hour -( )%

2 Hours - [%
3.5 Hours - %
5 Hours - %
7 Hours - NLT(%

From the bioequivalence point of view, the application has been found complete.

/S/
Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED BDAVIT BMD 12/4/98
FT INITIALED BDAVIT /S/ Date 12/4/98

Concur /S/ Date 12/7/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ANDA # 40-306 (original, duplicate), Kharidia, HFD-658, HFD-630, Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-306 APPLICANT: Medeva Pharmaceuticals

DRUG PRODUCT: Methylphenidate Hydrochloride ER Tablets
10 mg

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

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

Printed in final on 12/4/98

Endorsements: (Final with Dates)
HFD-658/ J. Kharidia JK 12/4/98
HFD-655/ B. Davit BAD 12/4/98
HFD-650/ D. Conner DR 12/7/98

BIOEQUIVALENCY - ACCEPTABLE submission date: April 10, 1998

4. **DISSOLUTION DATA** (DIS) Outcome: **AC**

Outcome Decisions: **AC** - Acceptable

Please enter as a US document.

AD

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-306 SPONSOR : Medeva pharmaceuticals

DRUG AND DOSAGE FORM : Methylphenidate Hydrochloride ER Tablets

STRENGTH(S) : **10 mg**

TYPES OF STUDIES : Fasting Study, Non-fasting study, and Multiple Dose Study

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S)

STUDY SUMMARY : STF –AC, STP – AC, STM - AC

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Jahnavi S. Kharidia, Ph.D. BRANCH : 3

INITIAL : /S/ DATE : 8/30/99

for TEAM LEADER : Barbara M Davis BRANCH : 3

INITIAL : /S/ DATE : 8/30/1999

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 8/30/99