Medeva Development
Methylphenidate Protocol MAI 1001-05

PK MEASURES AND METHODS:

The pharmacokinetics of methylphenidate were assessed by measuring serial plasma methylphenidate concentrations after the administration of a single dose of modified-release methylphenidate to fed and fasted subjects. The effect of food was assessed by comparison of the pharmacokinetic parameters after administration of 2 x 20 mg modified-release capsules of methylphenidate to fed and fasted subjects. The effect of food was considered significant if the 90% confidence intervals of the ratios of product means for the log-transformed C_{max}, $LN[AUC_{0-t}]$ and $LN[AUC_{0-inf}]$ were not within the range of ——— %. A nonparametric analysis was used to assess the effect of food on T_{max}.

RESULTS:

The arithmetic means of plasma methylphenidate pharmacokinetic parameters for Treatment A (fed) vs. Treatment B (fasted), and the statistical comparisons are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Plasma Methylphenidate for Treatments A and B

	Plasma Methylphenidate Treatment A		Plasma Methylphenidate Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	11.723	4.603	8.863	3.025	119.6-144.9	132.3
Tmax(hr)	5.66	1.68	4.79	1.23	101.1-135.2	118.1
AUC(0-t)(ng*hr/ml)	110.3	45.86	92.78	40.00	113.0-124.7	118.8
AUC(0-inf)(ng*hr/ml)	116.5	47.98	99.72	41.32	111.1-122.5	116.8
T 1/2el(hr)	5.00	0.914	5.90	1.14	77.0- 92.6	84.8
Kel(1/hr)	0.143	0.0271	0.122	0.0266	107.4-126.8	117.1
LN(Cmax)	2.394	0.3745	2.131	0.3235	116.9-144.6	130.0
LN[AUC(0-T)]	4.636	0.3609	4.464	0.3567	113.1-124.9	118.9
LN[AUC(0-INF)]	4.694	0.3542	4.539	0.3509	111.3-122.4	116.8

Treatment A = 2 x 20 mg Methylphenidate MR Capsules, Fed: test
Treatment B = 2 x 20 mg Methylphenidate MR Capsules, Fasted: reference

The nonparametric analysis of T_{max} for fed vs. fasted is summarized in the following table.

Nonparametric Statistical Comparisons of Methylphenidate Tmax Fed Vs Fasted

	Difference A-B		
Parameter	90% C.I		Median
Tmax	-0.0134	- 1.5039	0.4848

The Confidence Interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks Test Statistic
C.I = Confidence Interval
Treatment A = 2 x 20 mg Methylphenidate MR Capsules, Fed
Treatment B = 2 x 20 mg Methylphenidate MR Capsules, Fasted

The plasma concentration curve for the fasted group demonstrated a secondary elevation at approximately 2 hours and a T_{max} at approximately 5 hours (precisely 4.79 hours according to the above table). In the fed group the initial rapid rise in methylphenidate plasma concentration occurred approximately one-half hour later than that observed in the fasted group. This delay in rapid rise resulted in the early initial peak being combined with the extended-release portion and a biphasic plasma concentration curve was not observed in 12 out of 18 subjects.

SAFETY:

Methylphenidate HCl MR, 40 mg was well tolerated in the Fasted and Fed condition. No unexpected adverse events were observed. There were no detectable effects on vital signs during the fasted or fed condition.

Overall, the adverse events associated with *Methylphenidate HCl* MR, 40 mg in the Fasted Condition did not differ from those experienced in the Fed Condition.

Twelve adverse events were reported during the trial. The AEs with the highest prevalence according to COSTART classification, were: Body as a Whole (42%), Neurological (42%), and Digestive (17%). Eleven of the 12 AEs were classified as mild; all AEs resolved without interfering with study treatment.

CONCLUSION:

The pharmacokinetic and statistical analyses of methylphenidate suggested that food delayed the absorption from the immediate-release portion of the formulation. This resulted in an increased C_{max} from 8.9 to 11.7 ng/ml, likely due to combined absorption from the immediate and extended-release portions of the formulation. The 90% confidence interval for LN(C_{max}) was 116.9 to 144.6%, with a mean ratio of 130.0%. The ratios for AUC were within the desired range for LN[AUC_{0-t}] (113.1 to 124.9%) and LN[AUC_{0-inf}] (111.3 to 122.4%).

Study #2 cont.

Table 1.1. Demographic Summary for All Subjects

Trait		Female	Male	Overall
Gender	Female	7		7
	Male		11	11
Race	Asian	.	1	1
	Black	1	.	1
	Caucasian	6	9	15
	Hispanic	.	1	1
Frame Size	Small	2	1	3
	Medium	4	6	10
	Large	1	4	5
Age	Mean	29	32	31
	S.D.	10	10	10
	Minimum	20	20	20
	Maximum	47	50	50
	N	7	11	18
Weight (lb)	Mean	138.6	177.4	162.3
	S.D.	16.6	27.6	30.4
	Minimum	119.0	122.0	119.0
	Maximum	164.0	217.0	217.0
	N	7.0	11.0	18.0
Height (in)	Mean	66.1	71.3	69.3
	S.D.	1.3	4.0	4.1
	Minimum	64.0	65.0	64.0
	Maximum	68.0	76.0	76.0
	N	7.0	11.0	18.0

5.2.2.5 Meal Schedule and Procedures

All subjects will be required to fast overnight prior to dosing or the high fat breakfast. Water will be allowed ad lib during the study, except for 1 hour prior through 4 hour post dose.

The subjects receiving Treatment A will receive the following high fat breakfast approximately 20 minutes prior to drug administration. The meals should be completed 5 minutes prior to drug administration, but no more than 30 minutes prior to drug administration.

- Two slices of toasted bread with 20 g of butter
- Two eggs fried in butter
- Two slices of bacon
- 60 g hash brown potatoes
- 250 mL of whole milk

The subjects receiving Treatment B will not receive breakfast, but will continue to fast prior to dosing.

All subjects will continue to fast through at least four hours following drug administration, at which time a standard clinic menu and meal schedule will be followed. The meal schedule listed below is approximate in relation to the time of dosing.

STUDY #3. (REPORT ———: DOSE PROPORTIONALITY

(NDA volume 1.40-1.42)

Title of study:	*dl-threo*-methylphenidate hydrochloride and *d-threo*-methylphenidate hydrochloride - A Phase I, single-blind, crossover, single oral dose, safety, tolerability and pharmacokinetic study in healthy male volunteers
Investigator:	———
Study centre:	[redacted]
Publication (Reference):	Not applicable
Study Period: 4 September 1996 to 14 October 1996	Clinical Phase: I
Objectives:	To determine the single oral dose pharmacokinetics of the d-enantiomer of *threo*-methylphenidate hydrochloride when administered as a racemic mixture (*dl-threo*-MPH) and as a single enantiomer (*d-threo*-MPH) in healthy male volunteers. To determine the single oral dose pharmacokinetics of the l-enantiomer of *threo*-methylphenidate hydrochloride when administered as a racemic mixture (*dl-threo*-MPH). To determine whether there is *in vivo* interconversion of *d-threo*-MPH to *l-threo*-MPH. To determine the safety and tolerability of single oral doses of *d-threo*-MPH in healthy male volunteers at five dose levels.
Methodology:	Statistical design: 1 group of 12 volunteers, crossover Type of blinding: Single-blind
Number of Subjects: (Total and for each treatment)	5 mg *d-threo*-MPH 11 10 mg *d-threo*-MPH 12 15 mg *d-threo*-MPH 11 20 mg *d-threo*-MPH 11 30 mg *d-threo*-MPH 11 10 mg *dl-threo*-MPH 10 20 mg *dl-threo*-MPH 11 30 mg *dl-threo*-MPH 11 40 mg *dl-threo*-MPH 11 60 mg *dl-threo*-MPH 10 Total: 12
Ten volunteers participated in Treatment Periods 1 to 10, one volunteer withdrew himself after Treatment Period 1 and one volunteer was withdrawn due to adverse events after Treatment Period 8	
Diagnosis and criteria for inclusion:	Healthy male volunteers aged 18 to 45 years
Test product:	*d-threo*-methylphenidate HCl, *dl-threo*-methylphenidate HCl
Batch numbers:	1231, G810P03
Volunteers were dosed whilst standing and were not allowed to lie supine, except for study procedures, for 2 h post-dose.	

Study #3 cont.

Duration of treatment:	Single oral doses separated by a washout period of at least 3 days
Criteria for evaluation:	
For evaluation of tolerability:	
Adverse events:	Pre-dose and at approximately 3, 12 and 24 h post-dose in each treatment period and at the post-study visit. Also, spontaneous reporting by volunteers throughout the study.
For evaluation of safety:	
Clinical pathology:	Serum biochemistry, haematology and urinalysis were assessed: Pre-dose for Treatment Periods 1, 3, 5, 7 and 9 and at the post-study visit
Vital signs:	Supine blood pressure and pulse rate were measured: Pre-dose and at 2, 4, 8 and 24 h post-dose in each treatment period and at the post-study visit Body temperature was measured : Pre-dose and at 2 and 4 h post-dose in each treatment period and at the post-study visit
Electrocardiography:	12-lead resting ECG was recorded: Screening and post-study visit
Physical examination:	Screening and post-study visit
For evaluation of pharmacokinetics:	
Blood samples were taken pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post-dose in each treatment period.	
The following pharmacokinetic parameters were determined for the *d*-enantiomer: AUC(0-t), AUC(0-∞), C_{max}, t_{max}, $t_{½}$, λ_z, MRT and Frel.	
Statistical methods:	
AUC and C_{max} were log-transformed prior to analysis. The pharmacokinetic parameters were analysed using ANOVA, except for t_{max} which was analysed using the Friedman test for comparisons among doses and the Wilcoxon signed rank test for comparisons among formulations.	
Summary:	
Twelve volunteers entered and 10 volunteers completed the study. Volunteer 3 withdrew himself after Treatment Period 1 and Volunteer 7 was withdrawn after Treatment Period 8 due to adverse events.	
Tolerability	
d- and dl-threo-MPH were relatively well tolerated. No serious adverse events were reported during the study. The number of treatment-emergent adverse events recorded (with the number of volunteers reporting these events in parentheses) for 5 mg *d-threo*-MPH, 10 mg *dl-threo*-MPH, 10 mg *d-threo*-MPH, 20 mg *dl-threo*-MPH, 15 mg *d-threo*-MPH, 30 mg *dl-threo*-MPH, 20 mg *d-threo*-MPH, 40 mg *dl-threo*-MPH, 30 mg *d-threo*-MPH and 60 mg *dl-threo*-MPH was 8 (4), 0 (0), 8 (4), 14 (6), 12 (7), 10 (5), 15 (6), 18 (5), 27 (6) and 10 (5), respectively.	

Study #3 cont.

Tolerability, cont.

There appeared to be a dose-related increase in the incidence of adverse events for *d-threo*-MPH which was not apparent for *dl-threo*-MPH. The incidence of treatment-emergent adverse events was similar for equivalent doses of *d*-enantiomer when Volunteer 7 was excluded from the comparison .

The majority of adverse events were mild in severity and most adverse events were considered to be possibly or probably related to treatment. There was variability between volunteers in their susceptibility to *d*- and *dl-threo*-MPH.

Most adverse events for *d*- and *dl-threo*-MPH were grouped under the nervous system body system. Dizziness, agitation, headache and nausea were the most frequently reported adverse events.

In Treatment Period 4, 30 mg *d-threo*-MPH, Volunteer 7 experienced 16 adverse events which were considered to be possibly or probably related to treatment and 15 incidences were considered to be moderate in severity. In Treatment Period 8, 40 mg *dl-threo*-MPH, Volunteer 7 experienced 8 adverse events which were considered to be possibly or probably related to treatment. Adverse events included moderate episodes of amblyopia, dizziness and paresthesia and mild episodes of nausea, chills, twitching, headache and pallor. Volunteer 7 was withdrawn after Treatment Period 8, before progression to 60 mg *dl-threo*-MPH, due to adverse events.

Pharmacokinetics:

The table below summarises the plasma pharmacokinetic parameters of the d-enantiomer: geometric mean and 95% confidence intervals for AUC(0-t), AUC(0-∞) and C_{max}; median and range for t_{max} and arithmetic mean and SD for $t_{½}$ and MRT:

Treatment	t_{max} (h)	C_{max} (ng/mL)	AUC(0-t) (ng.h/mL)	AUC(0-∞) (ng.h/mL)	$t_{½}$ (h)	MRT (h)
5 mg *d-threo*-MPH	1.5 (1.0-3.0)	5.04 (4.24-5.98)	21.8 (18.1-26.3)	27.5 (22.9-33.1)	2.95 (0.527)	5.18 (0.732)
10 mg *dl-threo*-MPH	1.5 (1.0-2.0)	6.00 (5.06-7.12)	21.5 (17.9-25.7)	29.1 (24.1-35.0)	3.22 (0.959)	5.35 (1.044)
10 mg *d-threo*-MPH	1.5 (1.0-2.0)	11.14 (9.40-13.19)	46.8 (41.0-53.5)	55.0 (48.6-62.4)	3.05 (0.495)	5.13 (0.713)
20 mg *dl-threo*-MPH	1.5 (1.0-2.0)	10.67 (8.68-13.11)	46.2 (37.8-56.4)	53.6 (44.9-64.0)	2.87 (0.634)	5.04 (0.662)
15 mg *d-threo*-MPH	1.5 (1.5-4.0)	14.88 (13.13-16.88)	72.6 (62.7-84.0)	81.3 (71.2-92.9)	2.90 (0.467)	5.36 (0.636)
30 mg *dl-threo*-MPH	1.5 (1.0-4.0)	16.03 (12.72-20.20)	74.5 (59.6-93.1)	81.4 (66.4-99.7)	2.67 (0.497)	4.82 (0.681)
20 mg *d-threo*-MPH	1.5 (1.0-4.0)	20.00 (17.13-23.36)	96.4 (86.2-107.8)	103.4 (92.5-115.6)	2.84 (0.419)	5.07 (0.677)
40 mg *dl-threo*-MPH	1.5 (1.5-4.0)	18.69 (15.98-21.87)	88.2 (75.0-103.6)	95.9 (82.0-112.2)	2.59 (0.532)	4.93 (1.021)
30 mg *d-threo*-MPH	1.5 (1.0-4.0)	30.42 (25.05-36.93)	146.1 (126.2-169.0)	155.6 (134.5-179.9)	2.71 (0.302)	4.84 (0.585)
60 mg *dl-threo*-MPH	1.5 (1.0-2.0)	31.81 (24.74-40.90)	150.5 (129.6-174.7)	160.9 (137.9-187.7)	2.77 (0.489)	4.93 (0.612)

l-enantiomer

l-enantiomer was not detected in the plasma of any volunteer at any dose level of *d-threo*-MPH, except for Volunteer 7 at 30 mg *d-threo*-MPH (1.11 ng/mL at 1 h post-dose). At the higher dose levels (30, 40 and 60 mg) of *dl-threo*-MPH, l-enantiomer could be detected in the plasma of some volunteers at low levels, less than 2.5 ng/mL. The pharmacokinetics of l-enantiomer could not be determined, since plasma concentrations were below the limit of the assay after 3 h. There did not appear to be any *in vivo* interconversion of *d-threo*-MPH to *l-threo*-MPH.

STUDY #4. (REPORT MAI 1001-02): A DOUBLE BLIND, CROSSOVER PHARMACOKINETIC AND PHARMACODYNAMIC COMPARISON OF TWO MODIFIED RELEASE FORMULATIONS OF METHYLPHENIDATE IN CHILDREN WITH ADHD

(NDA volume 1.27-1.35)

Objective

The primary aim of the study was to compare the efficacy and safety of two modified release (MR) formulations in children with ADHD. One formulation contained a —— ratio of IR:ER beads (Lot no. EA 543), and the second contained a ratio of 30:70 IR:ER beads (Lot no. EA 542). The study evaluated:

1. Efficacy, safety and pharmacokinetics of the two MR formulations
2. Efficacy, safety and tolerability of the two MR formulations compared to placebo

Study Design and methods

This was a double-blind, randomized, placebo controlled, balanced, 4-week, crossover study in 40 children aged 7-12 years, diagnosed with ADHD (1 of 3 DSM-IV criteria, and need of MPH). Twenty-seven subjects were randomized and 25 subjects (21M/4F) completed the full trial.

After two screening visits during the first week to determine eligibility, qualified subjects entered into the trial that consisted of two stages. In Stage I, one-week regimens of 10 mg of MPH IR b.i.d. and placebo (dose intake after breakfast and lunch) were compared in a randomized, balanced crossover design. Patients who completed the 2-week period of Stage I and responded to MPH treatment were entered into the 2-week period of Stage II. In Stage II, the patients were randomly assigned, on an equal basis, to either 20 mg/day or 40 mg/day MPH MR treatment. Both the 20 mg/day and the 40 mg/day parallel groups received, in a randomized, balanced crossover design, one week of treatment with each methylphenidate MR formulation, —— and 30:70 IR:ER ratios. The active treatment was given as a morning dose (2x20 mg or 1x 20 mg + 1 x placebo after breakfast) and 1 placebo capsule after lunch. A 1-week study hiatus was allowed between Stage I and II if a holiday would interrupt the 2-week period of Stage II. Any subject that went on hiatus received 10 mg MPH IR b.i.d. (after breakfast and lunch) during that week.

The subjects attended a laboratory classroom on four consecutive Saturdays (Day 7 of each study period) for evaluations and collection of plasma samples for pharmacokinetic evaluation. Subjects were evaluated by their regular classroom teacher and by a parent during the week.

The efficacy measurements were:

1. The SKAMP (Swanson, Kotkin, Atkins, M/Flynn, Pelham) Scale ratings of Deportment (increased compliance and effort) and Attention were completed by the regular teacher and laboratory classroom teacher. During the laboratory classroom sessions measurements were to be performed at 0 (pre-dose), 1.5, 3, 4.5, 6, 7.5 and 9 h post-dose (Day 7).
   The SKAMP has nine items describing classroom behavior, and each item is rated on a seven-point impairment scale (none, slight, mild, moderate, severe, very severe, or maximal). Ratings of subsets of items are averaged to provide two scores: Deportment and Attention.
2. The PERMP (permanent products of a math test) was completed by the subject which were to be performed at 0 (pre-dose), 1.5, 3, 4.5, 6, 7.5 and 9 h post-dose at the laboratory classroom sessions (Day 7). This is an objective performance-based measure of academic productivity, a 10-min test with 100 math problems arranged on 4 pages in ascending order of difficulty.
3. The CLAM (Conners, Loney and Milich) Scale was completed by the regular teacher and a parent on 3 days (Monday, Wednesday, Friday; 1 time/day, time of day not specified) of each week of Stages I and II.
   The CLAM has 16 items, and each item is rated on a four-point scale (not at all, just a little,

pretty much, and very much). Ratings of subsets of items are averaged to provide three scores: the Conners Global Index, the Loney/Milich Inattention/Overactivity Index (I/O) and the Aggression/Defiance Index (A/D).

Blood samples for plasma analysis of MPH were collected on Day 7, the last day of each 1-week study period, at 0, 0.5, 1.5, 2, 3, 4.5, 6, 7.5 and 9 h after the morning dose.

Safety assessments (physical examination, laboratory safety monitoring) were performed at screening and at the end of the trial. Adverse events were monitored during the investigational periods, where the regular teacher, parent and study staff filled in side effect rating forms. The parent and regular teacher filled in the forms on the same days as the CLAM ratings were recorded (Monday, Wednesday, and Friday).

Pharmacodynamic and Pharmacokinetic Analysis

The short time interval between Stages I and II did not allow an evaluation of responders and non-responders according to the protocol. All patients, who completed Stage I, continued to the Stage II treatments. The pre-dose measurements (0 h) of SKAMP and PERMP on Day 7 were not performed until 30-45 min post-dose, therefore, all efficacy evaluations were performed in a modified-intent-to-treat (MITT) population, as described below.

The MITT population included all randomized patients who received ≥ 1 dose and completed SKAMP scores for ≥ 1 laboratory school session (n=25). The safety population included all patients who received ≥ 1 dose (n=25). The MITT population for the efficacy analyses included a subset of MITT patients who had SKAMP scores beyond 0 h for all four laboratory school sessions (n=22; 1 patient withdrew consent, 1 patient was unable to tolerate placebo, 1 patient did not attend one laboratory classroom session). The per protocol (PP) population (n=16), included the subset of MITT patients who had SKAMP scores beyond 0 h for all four laboratory school sessions and who were not identified as placebo responders in Stage I. Placebo response was defined as an average of the 1.5 and 6 h of the SKAMP attention score <15% after 10 mg IR b.i.d. compared to placebo during the Stage I laboratory classroom sessions. All subjects included in the subset of MITT and PP populations, who also had MPH plasma concentration data, were included in the pharmacokinetic analysis.

Pharmacokinetic parameters (C_{max1}, a.m. 0-3 h; t_{max1}, a.m. 0-3 h; C_{max2}, p.m. 4.5-9 h; t_{max2}, p.m. 4.5-9 h; AUC_{0-9h}) for MPH were calculated by non-compartmental methods. C_{max} and AUC were log transformed.

Comparisons were made between and among formulations, where 95% confidence intervals were constructed for the mean differences for the efficacy and the pharmacokinetic variables (log transformed C_{max} and AUC). A split-plot analysis of variance (ANOVA) was used for the SKAMP and PERMP assessments on the laboratory school days. A simpler ANOVA model was used for the SKAMP and CLAM assessments performed by the regular teacher and parent. Analyses of variance were used for inter-group comparisons and, where appropriate, for same-subject comparisons across treatment conditions. Comparisons between means by t-test were done when analyses of variance results showed significant F-ratios.

Results

The demographics of the children that completed the study are shown in Table 1.

TABLE 1 Demographics of the MITT population

Continuous Variables	Mean	SD	Range
Age (years)	10	1.4	7 - 12
Weight (kg)	36.9	7.6	26.3 - 53.1
Height (cm)	142	8.4	120.7 - 165
Nominal Variables	**N**	**%**	
Gender: Male/Female	21/4	84/16	
Race: Caucasian	22	88	
Black	2	8	
Asian	1	4	

N = 25 for these variables. 2 subjects who were randomized but failed to return after the first visit are not included here.

Pharmacodynamics

SKAMP

All MPH formulations were more efficacious than placebo treatment. The SKAMP ratings of Deportment (increased compliance and effort) and Attention performed by the laboratory schoolteacher are shown in Figure 1. Figure 1 depicts the ratings for the 30:70 IR:ER formulation (20 and 40 mg), placebo and the IR formulation administered in the morning and at lunch time. A lower SKAMP score indicates improvement.

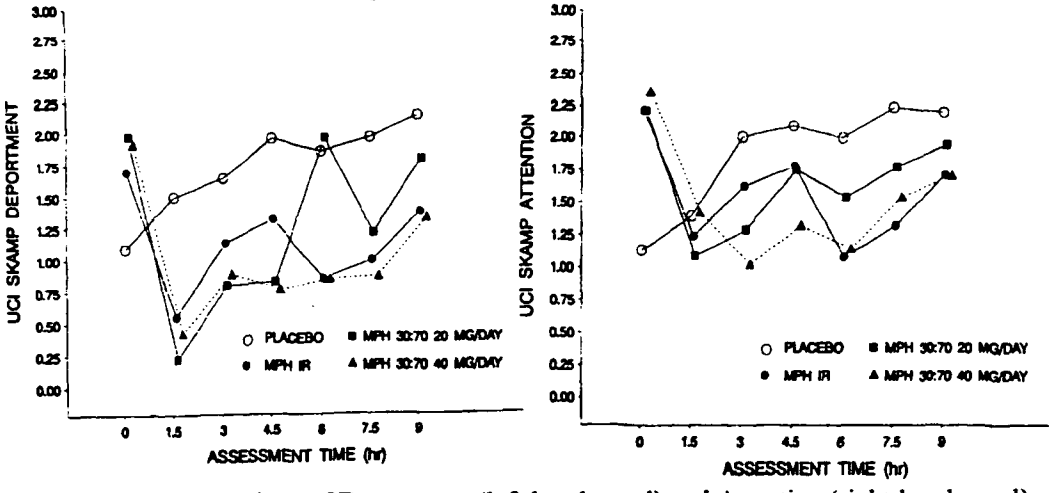

FIGURE 1. SKAMP ratings of Deportment (left-hand panel) and Attention (right-hand panel) on Day 7 after once daily (MR capsules, 20 or 40 mg q.d.) or twice daily (10 mg IR tablets or placebo at 0 and 4 h) repeated doses of MPH in children with ADHD. Doses are administered after meal intake.

Both MR formulations gave a statistically significant improvement compared to placebo treatment for the SKAMP ratings, and gave a response comparable to the 10 mg b.i.d. dose of IR tablets, as shown in Table 2.

TABLE 2 Comparisons between the different treatments of laboratory school SKAMP ratings of Deportment and Attention on Day 7 after repeated doses of MPH in children with ADHD.

UCI-CDC SKAMP OVERALL MEAN DEPORTMENT SCORES				
		Methylphenidate		
	Placebo	IR 10 mg bid	MR 30:70	MR
			20 mg/day	
LS Means	2.00	0.92	1.11	1.20
P Value versus IR	---	---	0.24	0.09
P Value versus Placebo	---	---	< 0.01	< 0.01
			40 mg/day	
LS Means*	1.63	1.06	0.81	1.05
P Value versus IR	---	---	0.26	0.98
P Value versus Placebo	---	---	<0.01	< 0.01
UCI-CDC SKAMP OVERALL MEAN ATTENTION SCORES				
		Methylphenidate		
	Placebo	IR 10 mg bid	MR 30:70	MR
			20 mg/day	
LS Means*	1.98	1.52	1.54	1.53
P Value versus IR	---	---	0.83	0.89
P Value versus Placebo	---	---	< 0.01	< 0.01
			40 mg/day	
LS Means*	2.00	1.40	1.37	1.49
P Value versus IR	---	---	0.82	0.50
P Value versus Placebo	---	---	<0.01	< 0.01

*LS Means = least squares mean calculated from the regression analysis.

Since the base-line recordings on Day 7 were not performed until 30-45 min after dose intake, the duration of effect was not determined during the study days at the laboratory school sessions.

PERMP (permanent products of a math test)

The PERMP, an objective performance-based measure of academic productivity, was evaluated over time post-dose on the study days at the laboratory school sessions. Results of ANOVAs comparing the corresponding scores by MR, IR and placebo treatments are shown in Table 3. There were no statistically significant differences between the two MR formulations in either the number attempted or number of correct scores. Both MR formulations at both dosages produced statistically significantly more number attempted and number of correct scores than placebo and, at the 40 mg/day dosage, statistically significantly more number attempted and number correct than the IR treatment.

TABLE 3: Comparisons of the overall PERMP scores by MR, IR and placebo treatments on Day 7 at the laboratory school sessions.

Dosage Group	Treatment	LS Means	p Value versus IR	p Value versus Placebo
Number Attempted				
20 mg/day	IR 10 mg *bid*	139	--	--
	Placebo	104	--	--
	MR [redacted]	141	0.89	<0.01
	MR 30:70	145	0.60	<0.01
40 mg/day	IR 10 mg *bid*	163	--	--
	Placebo	143	--	--
	MR [redacted]	222	<0.01	<0.01
	MR 30:70	203	<0.01	<0.01
Number Correct				
20 mg/day	IR 10 mg *bid*	135	--	--
	Placebo	101	--	--
	MR [redacted]	136	0.93	<0.01
	MR 30:70	141	0.59	<0.01
40 mg/day	IR 10 mg *bid*	157	--	--
	Placebo	137	--	--
	MR [redacted]	197	<0.01	<0.01
	MR 30:70	191	<0.01	<0.01

The PREMP was evaluated as an overall performance during the day (see Table 2). The differences between the MR formulations and placebo or the IR tablet were calculated at each time point. The corresponding differences between a.m. and p.m. dosing were also calculated. Statistical significance was not evaluated for the latter differences. There was a consistent positive effect for both attempted and correctly solved math problems in both a.m. and p.m. for the MR capsules *vs.* placebo. A 20 mg dose of the 30:70 IR:ER MR capsule was comparable to the IR b.i.d. doses (20 mg/day). However, the 40 mg dose of the 30:70 IR:ER MR capsule showed better effects than the IR b.i.d. doses (20 mg/day) both in the morning and in the afternoon sessions.

CLAM

One parent and the regular teacher performed CLAM ratings on three days of each dosing regimen (Monday, Wednesday, and Friday). The parents full ratings are shown in Table 3.1, and the Conners Gobal Index, performed by the regular teacher, are shown in Table 4.

TABLE 3.1: Comparisons of the parent CLAM scores [mean (SD)] evaluated by the by MR, IR and placebo treatments on three days. A lower score indicates improvement.

		CLAM[a]			
Treatment	N[b]	I/O	A/D	Mixed	Conners Global
Placebo	22	6.9 (3.9)	4.7 (4.1)	5.0 (3.4)	11.5 (7.0)
IR (10 mg *bid*)	22	4.4 (3.2)	3.0 (3.3)	3.1 (3.2)	7.3 (5.9)
20 mg (30:70)	12	7.2 (3.8)	5.1 (4.7)	5.0 (3.6)	12.4 (7.3)
20 mg [illegible]	12	4.3 (2.1)	3.6 (3.1)	3.1 (2.2)	7.3 (4.1)
20 mg overall	12	5.7 (2.4)	4.3 (3.7)	4.1 (2.6)	9.8 (4.9)
40 mg (30:70)	10	3.8 (4.2)	2.3 (3.4)	2.3 (2.6)	6.0 (5.7)
40 mg [illegible]	10	2.8 (2.9)	2.3 (2.2)	2.2 (2.5)	5.1 (4.5)
40 mg overall	10	3.2 (2.7)	2.2 (2.5)	2.3 (2.2)	5.6 (4.3)
30:70 overall	22	5.6 (4.2)	3.8 (4.3)	3.8 (3.4)	9.5 (7.2)
[illegible] verall	22	3.6 (2.5)	3.0 (2.8)	2.7 (2.3)	6.3 (4.3)

[a]CLAM scores: I/O = Inattention/Overactive; A/D = Aggression/Defiance; Mixed = I/O + A/D; Conners Global = Conners Global Index.
[b]The MITT population was used in these calculations.

TABLE 4: Comparisons of the regular teacher's CLAM scores (Global Conners Index) evaluated by the by MR, IR and placebo treatments on three weekdays.

Dosage Group	Treatment	LS Means	p Value versus IR	p Value versus Placebo
20 mg/day	IR 10 mg *bid*	7.11	--	--
	Placebo	11.67	--	--
	MR [illegible]	6.44	0.70	< 0.01
	MR 30:70	6.42	0.69	< 0.01
40 mg/day	IR 10 mg *bid*	5.95	--	--
	Placebo	11.70	--	--
	MR [illegible]	3.15	0.21	< 0.01
	MR 30:70	7.25	0.56	0.05

Both the higher and lower doses (20 and 40 mg) of the MR formulations were comparable to the IR tablets (10 mg b.i.d., 20 mg/day). Since the placebo and IR treatments were used during the first part of the study (Stage I), and the MR treatments were performed during the second part of the study (Stage II), this may be a confounding factor. Also, since the children (n=22) participating in Stage I, were subsequently divided into two treatment groups during Stage II, the sample size was reduced in half for each MR treatment.

Pharmacokinetics

The mean plasma concentration-time curves of MPH after the different treatments are shown in Figure 2.

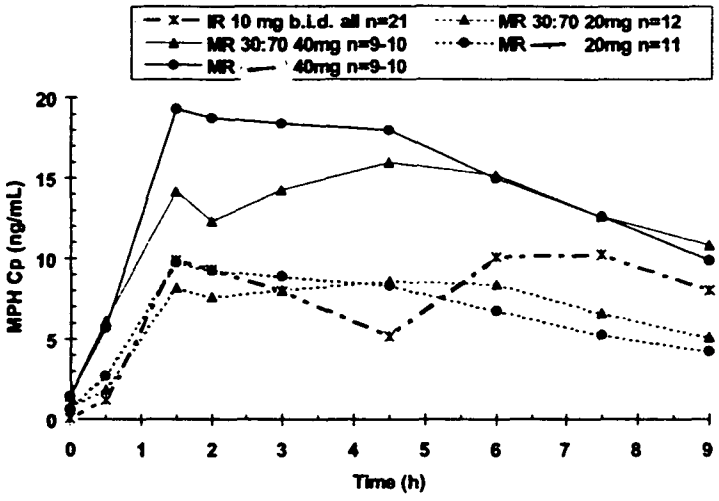

FIGURE 2. Mean MPH plasma concentration-time curves Day 7 after once daily (MR capsules, 20 or 40 mg q.d.) or twice daily (10 mg IR tablets at 0 and 4 h) repeated doses of MPH in children with ADHD. Doses are administered after meal intake.

The pharmacokinetic parameters after repeated doses of 20 and 40 mg doses of the 30:70 IR:ER capsules, the 20 and 40 mg doses of the —— IR:ER capsules and the 10 mg IR tablets (administered at 0 and 4 h) on Day 7 are shown in Table 5.

TABLE 5 Pharmacokinetics (arithmetic mean ±SD) of MPH after 1 week of repeated doses administered as 30:70 IR:ER capsules q.d., —— IR:ER capsules q.d., and 10 mg IR tablets b.i.d. (0 and 4 h) in children with ADHD. The first number for each parameter indicates the MITT population and the second number in *italics* indicates the PP population.

Parameter	IR tablet 10 mg b.i.d.	30:70 IR:ER capsules 20 mg	30:70 IR:ER capsules 40 mg	IR:ER capsules 20 mg	IR:ER capsules 40 mg
No. Patients:					
MITT pop.	19-20	**12**	**9**	12	9
PP pop.	*13-14*	***10***	***5***	*10*	*6*
C_{trough}[#] (ng/mL)	0.10 ± 0.15	**0.76 ± 0.45**	**1.41 ± 1.03**	0.65 ± 0.41	1.41 ± 0.62
	0.08 ± 0.13	***0.68 ± 0.40***	***1.22 ± 1.15***	*0.65 ± 0.31*	*1.62 ± 0.63*
C_{max1}* (ng/mL)	10.0 ± 3.3	**8.6 ± 2.6**	**15.4 ± 8.1**	9.7 ± 3.6	20.6 ± 6.4
	10.2 ± 2.9	***8.3 ± 2.1***	***17.2 ± 10.3***	*9.3 ± 3.1*	*23.0 ± 6.7*
t_{max1}* (h)	1.9 ± 0.5	**2.2 ± 0.7**	**1.9 ± 1.0**	1.6 ± 0.8	2.1 ± 0.7
	1.9 ± 0.5	***2.2 ± 0.7***	***1.7 ± 1.1***	*1.6 ± 0.6*	*2.3 ± 0.8*
C_{max2}** (ng/mL)	11.4 ± 3.4	**9.6 ± 3.8**	**17.0 ± 4.4**	8.3 ± 3.2	17.8 ± 5.3
	11.9 ± 3.3	***9.5 ± 3.4***	***18.7 ± 3.3***	*8.0 ± 2.9*	*19.3 ± 6.0*
t_{max2}** (h)	7.2 ± 1.1	**5.1 ± 1.0**	**5.2 ± 0.8**	4.5 ± 0.0	5.0 ± 0.8
	6.8 ± 0.8	***5.0 ± 0.7***	***5.1 ± 0.8***	*4.5 ± 0.0*	*5.0 ± 0.8*
AUC_{0-9h} (ng.h/mL)	65.7 ± 21.5	**63.0 ± 16.8**	**119.7 ± 39.6**	60.0 ± 20.9	131.5 ± 40.1
	65.8 ± 21.5	***61.5 ± 12.4***	***138.4 ± 37.8***	*57.4 ± 18.0*	*146.3 ± 41.4*

*C_{max} and t_{max} to first peak (0 - 3 h after first dose intake)
**C_{max} and t_{max} to second peak (4.5 - 9 h after first dose intake)
C_{trough} = MPH plasma concentrations pre-dose (0 h) before dose-intake on Day 7

As shown in Table 5, the AUC was similar between the 20 mg MPH given as an IR tablet (10 mg at 0 and 4 h) and as the 30:70 IR:ER capsule (intended for commercial use), indicating comparable performance of the two dosage forms. The time to peak MPH plasma concentrations after the morning dose intake was also comparable, indicating that the immediate release portion of the 30:70 IR:ER capsule is comparable to the IR tablet. The second peak of the 30:70 IR:ER capsule, which is related to the extended release portion of the formulation, occurred almost 2 h earlier than after the 2nd dose intake of the IR tablet.
There was a dose-proportional increase in C_{max1}, C_{max2} and AUC between the 20 mg and 40 mg doses of the MR formulation that is intended for commercial use.

Pharmacokinetic-pharmacodynamic relationships
The relationships between the mean values for SKAMP (Attention and Deportment) *vs.* mean MPH plasma concentrations are shown in Figure 3. The reviewer created these graphs.

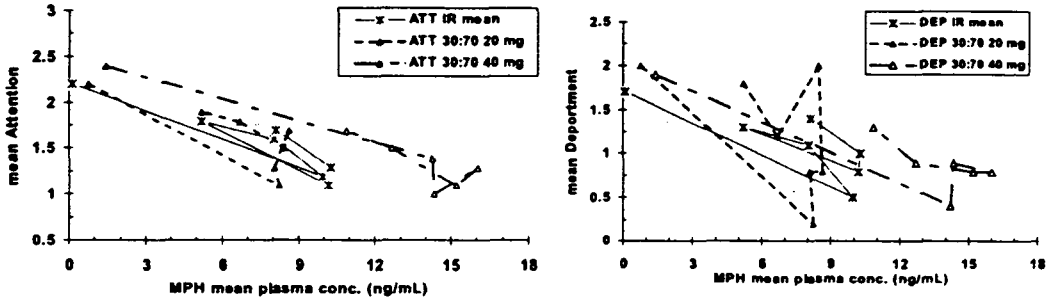

FIGURE 3. SKAMP ratings *vs.* mean MPH plasma concentrations on Day 7 after IR tablets (10 mg b.i.d.; n=22) and 30:70 IR:ER capsules q.d., at the laboratory school sessions (n=12 for 20 mg; n=12 for 40 mg). Left panel: SKAMP Attention. Right panel: SKAMP Deportment (increased compliance and effort).

There was a tendency of an increase in attention/deportment (lower scores) with an increase in blood levels. However, it should be noted that the coefficients of variation for the mean values of attention at different time points were about 50%, and over 100% for the corresponding ratings for deportment.

Adverse events
According to the sponsor, there were no serious adverse events (SAEs), deaths or treatment discontinuations due to adverse events (AEs). No unexpected AEs were observed. Most AEs were mild. The number of patients reporting any AE is shown in Table 6.

TABLE 6. The number (%) of patients reporting any AE, by treatment.

	Placebo (N = 25)	10 mg IR *bid* (N = 25)	20 mg/day MR 30:70 (N = 12)	20 mg/day MR —— (N = 13)	40 mg/day MR 30:70 (N = 11)	40 mg/day MR —— (N = 11)
Any Event	11 (44%)	14 (56%)	4 (33%)	5 (39%)	5 (46%)	1 (9%)

The following adverse events (by treatment) were the most commonly recorded by the parents in their Side Effects Rating Form:

- Appetite loss (Placebo 29%; IR 52%; MR 50 - 73%)
- Dull, tired, listless (Placebo 42%; IR 48%; MR,25 - 42%)
- Crabby, irritable (Placebo 71%; IR 56%; MR 27 - 75%)

- Tearful, sad, depressed (Placebo 38%; IR 20%; MR 8 - 55%)
- Worried, anxious (Placebo 38%; IR 8%; MR 25 - 58%)

The following adverse events (by treatment) were the most commonly recorded by the teachers in their Side Effects Rating Form:

- Dull, tired, listless (Placebo 40%; IR 60%; MR, 42 - 70%)
- Crabby, irritable (Placebo 48%; IR 28%; MR 0 - 33%)
- Worried, anxious (Placebo 52%; IR 32%; MR 17 - 40%)
- Motor tics (Placebo 28%; IR 16%; MR 8 - 33%)
- Picking at skin or fingers, nail biting, lip or cheek-chewing (Placebo 28%; IR 24%; MR 10- 25%)

Sitting systolic and diastolic blood pressure, pulse and body temperature were comparable for all treatments.

Comments:
The various efficacy ratings showed that all MPH treatments gave a statistically significant improvement compared to placebo treatment. SKAMP and CLAM ratings after daily doses of both 20 mg and 40 mg of the formulation intended for commercial use (30:70 IR:ER capsule) were comparable to that of 10 mg IR tablets administered b.i.d. (20 mg/day).

The pharmacokinetics was linear between 20 and 40 mg for the 30:70 IR:ER MR formulation.. Most patients had residual MPH concentrations in the through sample after repeated dose intake of the MR formulations. However, the trough plasma concentrations were low, about 0.8 ng/mL after the 20 mg doses, and 1.4 ng/mL after 40 mg doses of the 30:70 IR:ER capsule.

The observed PK/PD relationship is based on mean values, evaluations of the potential relationships for the individual patients were not performed. There was a tendency of an increase in attention/deportment (lower scores) with an increase in blood levels, but since the plots are based on mean pharmacodynamic values, further conclusions should not be drawn.

STUDY #5. REPORT NO 1193/63-1006 MPH: *IN VITRO* METABOLISM OF THE RACEMATE AND OF THE *D*- AND *L*-ENANTIOMERS IN HUMAN LIVER MICROSOMES

(Submission June 26, 2000)

SUMMARY

1.1 The present study was designed to compare the *in vitro* metabolism of d,l-threomethylphenidate and its d- and l-enantiomers and to investigate the role of various cytochrome P450 isozymes, in particular CYP2D6, in the metabolism of the test compounds.

1.2 Microsomal suspensions were obtained from three human donors aged between 24 and 45 years, pooled and incubated with bufurolol (0.001, 0.01 and 0.1 μmol/mL) for 10 or 30 minutes in order to determine the activity of CYP2D6.

1.3 Following optimisation of the bufurolol assay, quinidine was added to the incubates at concentrations of 0.001, 0.01, 0.1 and 1 μmol/mL to inhibit the reaction. Quinidine inhibited the activity of bufurolol hydroxylase at all concentrations studied with complete inhibition achieved at 1 μmol/mL.

1.4 Microsomal suspensions were incubated with d-threomethylphenidate at nominal concentrations of 0.0001, 0.001, 0.01, 0.1 and 1 μmol/mL for 5, 10, 30 and 60 minutes. Extracts were analysed by LC-MS to estimate d-threomethylphenidate concentrations. Following incubation of d-threomethylphenidate with human liver microsomes, no metabolism was observed with any test article concentration at any incubation time.

1.5 Due to the low levels of metabolism of methylphenidate observed in pilot studies, no definitive studies on the metabolism of the test articles in human liver microsomes were carried out. The metabolism of the racemate and of d- and l-threomethylphenidate in human liver microsomes and inhibition of metabolism by quinidine were therefore not investigated.

1.6 In conclusion, d-threomethyl phenidate was resistant to *in vitro* metabolism in human liver microsomes that demonstrated intrinsic CYP2D6 activity. Therefore, it is unlikely that this enzyme is important in the phase 1 metabolism of d-threomethylphenidate.

STUDY #6. [redacted] REPORT NO 1193/64-1006 **MPH: EFFECTS OF THE RACEMATE AND OF THE *D*- AND *L*-ENANTIOMERS ON SELECTED P450 ACTIVITIES IN HUMAN LIVER MICROSOMES**

(Submission June 26, 2000)

Methods:

The cytochrome P450 isoenzymes that were investigated were CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4.

Human microsomal suspensions were obtained from a commercial source (IIAM, Leicester, England).

Test articles (*d,l, d-*, and *l-threo*-MPH)and inhibitors were dissolved in DMSO at concentrations 100-fold the final concentration required in the incubation mixture. The amount of test article or inhibitor solution added to the incubation mixture was such that the volume of solvent did not exceed 1% of the total incubation volume.

Preliminary studies were conducted in order to establish the optimum incubation conditions and inhibitor concentrations for use in the main study. For some isozymes (1A2, 2D6, 2E1 and 3A4), assays were also conducted using test article concentrations between 0.2 nM and 10 µM. Results obtained at these concentrations were not presented as no effects on enzyme activities were observed.

After optimization of the conditions required to demonstrate inhibitory activity, assays were performed for all P450 isozymes investigated at a test article concentration of 100 µM and for known inhibitors at concentrations found to effectively inhibit target enzyme activities in the preliminary studies. All methods used for marker enzyme activity have been published.

Test article concentration: 100 µM (*d,l, d-*, and *l-threo*-MPH as hydrochloride salt)

CYP1A2	Marker enzyme activity: Methoxyresorufin O-dealkylase Standard inhibitor: Furafylline (10 µM)
CYP2C9	Marker enzyme activity: Tolbutamide hydroxylase Standard inhibitor: Sulfaphenazole (100 µM)
CYP2C19	Marker enzyme activity: S-mephenytoin hydroxylase Standard inhibitor: Tranylcypromine (50 µM)
CYP2D6	Marker enzyme activity: Bufurolol hydroxylase Standard inhibitor: Quinidine (10 µM)
CYP2E1	Marker enzyme activity: Lauric acid 11-hydroxylase Standard inhibitor: Disulfiram (10 µM)
CYP3A4	Marker enzyme activity: Testosterone 6β-hydroxylase Standard inhibitor: Troleandomycin (100 µM)

Triplicate determinations were used for controls, and duplicate determinations were used for test articles.

Study #6 cont.

Results:

Mean enzyme activities of selected P450 isozymes in the presence and absence of test articles and known inhibitors

P450 Isozyme	Enzyme activity (pmol/min/mg microsomal protein)* (% inhibition of control)				
	Control	Standard inhibitor	d,l-MPH[1]	*d*-MPH[1]	l-MPH[1]
1A2[2]	24.3 (NA)	ND (>90)	21.7 (<15)	32.3 (<15)	27.1 (<15)
2C9[3]	50.8 (NA)	ND (>90)	41.3 (19)	38.3 (25)	33.4 (34)
2C19[4]	20.3[5] (NA)	3.38[6] (83)	11.40 (44)	14.01 (31)	13.69 (32)
2D6[5]	1.03 (NA)	ND (>90)	0.37 (65)	0.38 (64)	0.61 (41)
2E1[6]	368 (NA)	196 (47)	346[6] (<15)	316 (<15)	382 (<15)
3A4[7]	373 (NA)	276 (26)	362 (<15)	338 (<15)	364 (<15)

[1] Test article concentration = 100μM (hydrochloride salt)

[2] Marker enzyme activity - Methoxyresorufin O-dealkylase. Standard inhibitor - Furafylline (10 μM)

[3] Marker enzyme activity - Tolbutamide hydroxylase. Standard inhibitor - Sulfaphenazole (100 μM)

[4] Marker enzyme activity - S-Mephenytoin hydroxylase. Standard inhibitor - Tranylcypromine (50 μM)

[5] Marker enzyme activity - Bufurolol hydroxylase. Standard inhibitor - Quinidine (10 μM)

[6] Marker enzyme activity - Lauric acid 11-hydroxylase. Standard inhibitor - Disulfuram (10 μM)

[7] Marker enzyme activity - Testosterone 6β-hydroxylase. Standard inhibitor - Troleandomycin (100 μM)

*Control values are the means of triplicate determinations except that annotated with [6] which is the result of a duplicate determination: Values for inhibitors and test articles are the means of two determinations except for those annotated with [6] which are the result of a single determination.

ND = not detected, NA = not applicable

STUDY #7 PHARMACEUTICAL FORMULATION

Final Drug Product

The 20 mg 30:70 IR:ER MR (modified release) Capsules contain two types of beads, Immediate-Release and Extended-Release beads. The capsules are filled in a ratio of immediate-release beads and extended-release beads, such that 30% of the dose (6 mg) is from the immediate release beads and 70% of the dose (14 mg) is from the extended-release beads. The composition of the MR capsule is given in Table 1 below. The target weight of the capsule fill is 141.9 mg.

TABLE 1. Final formulation of the 30:70 IR:ER MR (modified release) capsules (20 mg MPH)

Ingredient Name	mg per capsule	% per capsule (w/w)
Methylphenidate Hydrochloride, USP	20.0	
Sugar Spheres, NF		
Povidone, USP		
Ethylcellulose Aqueous Dispersion, NF		
Dibutyl Sebacate, NF		
Hard Gelatin Capsules (Size [2])		

[1] proprietary mixture of hydroxypropylmethylcellulose and polyethylene glycol
[2] composed of gelatin, titanium dioxide, FD&C blue #2
[3] theoretical capsule shell weight is

The beads will be manufactured and tested by Eurand America, Inc., Vandalia, Ohio. The final drug product will be packaged in 30 count blister cards.

Method of manufacture

Study #7 cont.

TABLE 2. Batch information on the pharmaceutical formulations used in the clinical trials.

	Finished Capsules				Immediate Release Beads		Intermediate Release Beads		Extended Release Beads		
Study No. (Report Location)	Dosage Form	Str. (mg)	Lot #	Batch Size	Lot #	Size (kg)	Lot #	Size (kg)	Lot #	Size (kg)	Formulation or Manufacturing; Changes/ Effect of Change
MAI 1001-01 (Section 6.8)	30:70 Caps	25	EA 458	—	EA 456	—	EA 454	—	EA 455	—	Laboratory scale. Clinical prototypes.
	—	25	EA 459	—	EA 456	—	EA 454	—	EA 455	—	
	—	25	EA 460	—	EA 456	—	EA 454	—	EA 455	—	
MAI 1001-02 (Sections 6.8 and 8.11)	30:70 Caps	20	EA 542	—	EA 540	—	EA 541	—	EA 544	—	Batch size increased to pilot scale. Strength change for commercial purposes. Dissolution profile matched to prototype.
	—	20	EA 543	—	EA 540	—	EA 541	—	EA 544	—	
MAI 1001-04 (Section 8.11)	30:70 Caps	20	EA 604	—	EA 612	—	EA 629	—	EA 630	—	Batch size increased to production scale. No significant changes due to scale-up.
MAI 1001-05 (Section 6.8)	30:70 Caps	20	EA 604	—	EA 612	—	EA 629	—	EA 630	—	Same as MAI 1001-04.

Capsules, 20 mg, contain two types of beads, Immediate-Release (IR) and Extended-Release (ER). The capsules are filled in a ratio of 30% IR beads and 70% ER beads, corresponding to 6 mg and 14 mg of methylphenidate hydrochloride, respectively. —

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STUDY #8 DISSOLUTION

(NDA volume 1.15; Eurand reports PF114-V2 & -V3 submissions Jun 26, Dec 15, 2000)

During the pharmaceutical formulation development, the influence of pH on the *in vitro*

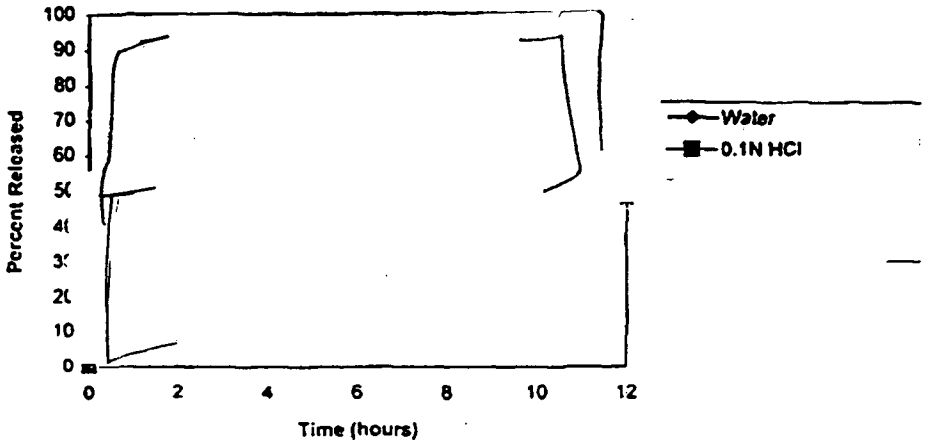

Figure 8.1. MPH HCl modified release capsule (25 mg; batch CPh-8436; n=6) release rate profiles in media of different pHs. The formulation is single bead formulation, used during product development.

As shown in the Figure 8.1, the *in vitro* dissolution of methylphenidate HCl is

The influence of pH on the release rate was further investigated using 20 mg MPH capsules (30:70 IR:ER) from one batch used in the clinical trials (lot EA 604, Study #2 & the pivotal clinical trial MAI-1001-04). Twelve capsules was tested using different pH media (water, 0.1 N HCl, pH 4.5, pH 5.8) in a USP Paddle Apparatus II (50 rpm, 500 mL). The paddle speed and volume is according to the USP monograph for methylphenidate HCl extended-release tablets.

The results were similar to the first experiment, and are depicted in Figure 8.2 and Table 8.1.

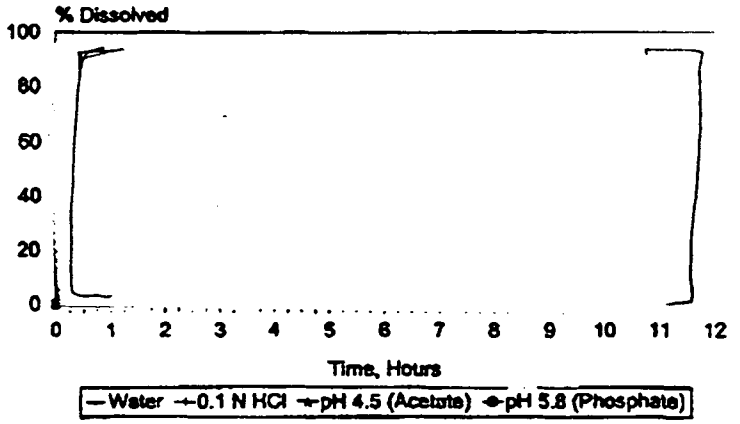

Figure 8.2. MPH HCl modified release capsule (20 mg; batch lot EA 604; n=12) release rate profiles in media of different pHs. The batch of the formulation was used in clinical trials.

Table 8.1. Mean dissolution profiles in various pH buffers of MPH HCl modified release capsule (20 mg; batch lot EA 604; n=12). Tabulated data is also depicted in Fig. 8.2.

	% Dissolved			
Time (Hours)	Water	0.1 N HCl	pH 4.5	pH 5.8
0.25				
0.50				
1				
2				
4				
6				
8				
10				
12				

The performance of proposed dissolution method with water as medium (6 capsules), was also compared to multimedia, where the influence of pH on a 25 mg formulation of the 30:70 IR:ER beads was investigated. The formulation was also used in an animal dosing study (Study TSRL-001/D; volume 1.15). The experiment with different pHs was intended to simulate the different pHs along the GI tract. The capsules (n=3) were first placed into pH 1.2 medium and samples taken at 5 minutes and 120 minutes. The vessels were emptied and replaced with pH 4.5 medium and samples taken 60 and 120 minutes later (the 180 and 240 minute time points). The vessels were emptied and the medium was replaced with pH 5.8 medium and run for an additional 60 and 120 minutes, total time 300 and 360 minutes. The vessels were emptied and replaced with pH 7.5 medium and run for an additional 60 and 120 minutes for a total of 420 and 480 minutes. Due to the emptying of vessels, a USP Basket Apparatus I (100 rpm) was used in the multimedia experiment. The results are shown in Figure 8.3.

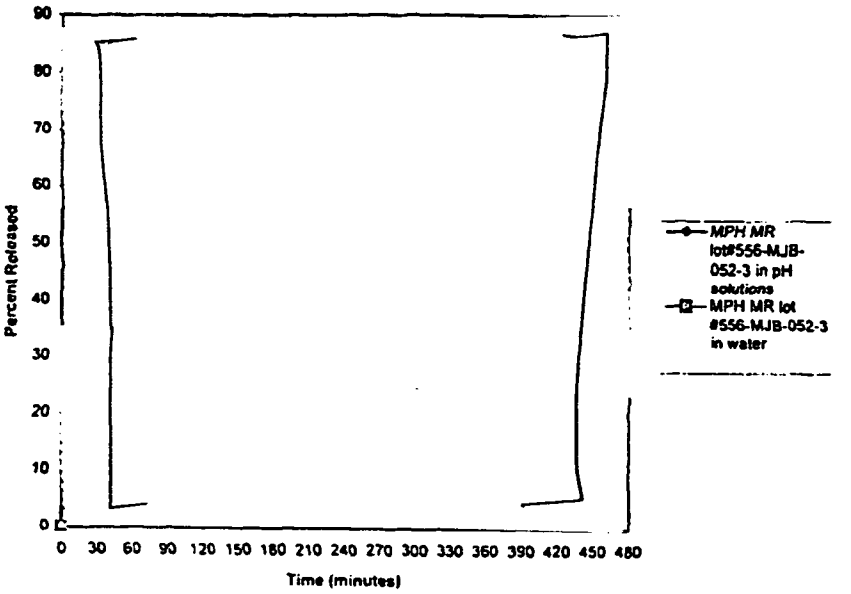

FIGURE 8.3. Methylphenidate HCl 30:70 IR:ER capsule (25 mg) *in vitro* dissolution profiles in water (n=6 USP Paddle Apparatus II; 50 rpm) *vs.* a series solutions at different pHs (n=3; USP Basket Apparatus I; 100 rpm).

The analysis of MPH HCl was performed by a validated
). The method was tested with regard to MPH and known degradants (
and was acceptable, regarding specificity, linearity, accuracy, and ruggedness (tested at two difference analytical facilities).

The influence of different paddle speeds on the *in vitro* dissolution profiles using USP apparatus II were not investigated.

For further information regarding *in vitro* dissolution data, refer to Study #9 (*in vitro – in vivo* correlation).

Comments

The investigations of influence of pH show that water is an acceptable medium for the *in vitro* dissolution testing. A conclusive study was performed on the final formulation (30:70 IR:ER capsule, 20 mg MPH HCl). The multimedia study showed a discrepancy after 180 min testing, where a lower quantity MPH HCl was released from this point in time and forward. However, since the vessels were emptied and media of different pH were substituted at the various time points, the comparison is somewhat confounded by the influence of the latter, higher pHs (>7) used in this study, which would decrease the rate of dissolution.

Water is an acceptable dissolution medium.

STUDY #9 *IN VITRO-IN VIVO* CORRELATION

(NDA volume 1.19, submission December 27, 2000)

The Sponsor has developed an *in vitro–in vivo* correlation (IVIVC) for the methylphenidate (MPH) HCl Immediate Release:Extended Release (IR:ER) formulation. The IVIVC was developed by a contract organization, [redacted]
A numerical deconvolution (Wagner-Nelson) method was used for calculation of fraction absorbed for the submitted *in vitro–in vivo* correlation (IVIVC).

The IVIVC correlation was developed by use of data from five different batches used in two pharmacokinetic studies, in healthy adults (Study #1) and children with ADHD (Study #4), respectively. Two different IVIVC reports, one for each pharmacokinetic study, were submitted. The *in vitro* dissolution data from each lot (n=6 capsules) used in the respective studies contained time points corresponding to the plasma sampling schedules for MPH determinations. A numerical deconvolution method (Wagner-Nelson) was used for calculation of the cumulative *in vivo* absorption of MPH, and directly compared with the *in vitro* release profiles.

The IVIVC report from Study #4 was not reviewed (Document No. [redacted] since plasma concentration-time profiles were only followed for 9 h post-dose, after repeated doses. As the 30:70 IR:ER formulation is intended for once-daily dosing, the collected data is considered to not fully reflect the *in vivo* process up to 24 h post-dose, to serve as a basis for acceptance of an IVIVC.

***In vitro* dissolution**

Figure 9.1 and Table 9.1-9.3 contain the *in vitro* dissolution data of the formulations with slow ([redacted] IR:ER), medium (30:70 IR:ER) and fast ([redacted] IR:ER) release rates. All formulations contained 25 mg methylphenidate (MPH) HCl. The formulation intended for commercial use, contains 20 mg MPH HCl, but since the 20 mg and 25 mg formulations consist of equal ratios of IR:ER beads, the performance is not expected to differ between the formulations.

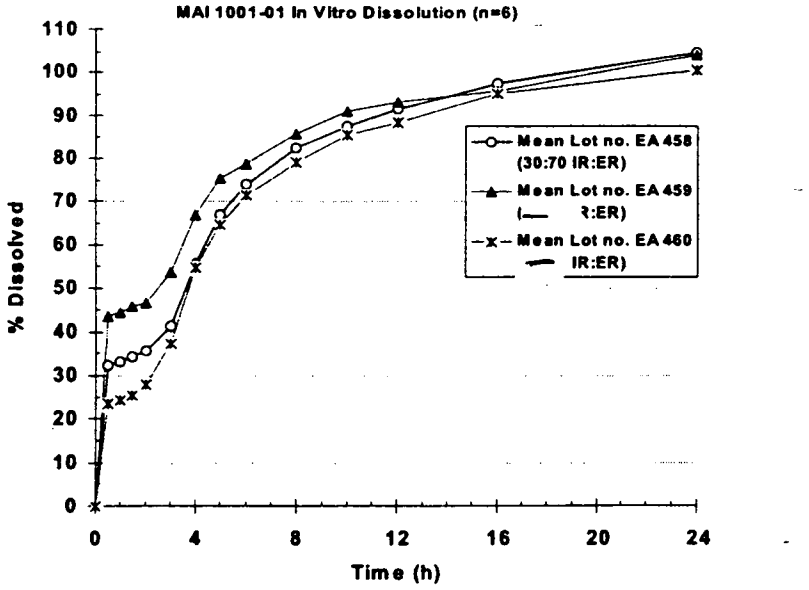

FIGURE 9.1 *In vitro* dissolution profiles of the capsules (n=6) used in the IVIVC.

TABLE 9.1 *In Vitro* Dissolution (IVIVC data), Study #1 (slow release rate)

Lot No. EA 460 (20:80 IR:ER)	Time (h)	%Dissolved: Sample No. 1	2	3	4	5	6	Mean	SD	CV%
	0.5							23.4	0.2	0.7
	1							24.3	0.1	0.5
	1.5							25.5	0.2	0.6
	2							27.9	0.6	2.2
	3							37.4	1.1	3.1
	4							54.8	1.1	2.1
	5							64.7	0.9	1.5
	6							71.6	1.0	1.3
	8							79.3	0.9	1.1
	10							85.6	1.1	1.3
	12							88.6	0.8	0.9
	16							95.3	1.1	1.2
	24							100.6	1.7	1.7

TABLE 9.2 *In Vitro* Dissolution (IVIVC data), Study #1 (medium release rate)

Lot No. EA 458 (30:70 IR:ER)	Time (h)	%Dissolved: Sample No. 1	2	3	4	5	6	Mean	SD	CV%
	0.5							32.3	0.9	2.8
	1							33.2	0.4	1.3
	1.5							34.2	0.8	2.2
	2							35.7	0.4	1.2
	3							41.2	1.2	2.9
	4							55.8	0.8	1.4
	5							66.9	0.7	1.1
	6							74.2	0.9	1.3
	8							82.7	1.1	1.4
	10							87.8	1.1	1.3
	12							91.7	1.6	1.8
	16							97.5	3.6	3.7
	24							105.0	4.3	4.1

TABLE 9.3 *In Vitro* Dissolution (IVIVC data), Study #1 (fast release rate)

Lot No. EA 459 (40:60 IR:ER)	Time (h)	%Dissolved: Sample No. 1	2	3	4	5	6	Mean	SD	CV%
	0.5							43.6	1.0	2.3
	1							44.4	0.7	1.6
	1.5							45.7	0.8	1.8
	2							46.7	1.1	2.3
	3							53.8	1.3	2.5
	4							67.0	1.5	2.3
	5							75.6	0.8	1.0
	6							78.9	0.9	1.2
	8							85.8	0.7	0.8
	10							91.1	0.9	1.0
	12							93.4	1.1	1.2
	16							96.0	1.7	1.8
	24							94.5	1.6	1.5

The data in the IVIVC report from Study #1 contained the following discrepancies from the recommendations in *Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997.*

1. The *in vitro* dissolution tests were only performed with 6 capsules (12 are recommended). Since the maximal coefficient of variation for the tested capsules was 4.1%, this was considered as acceptable.
2. The capsules with slow and intermediate release rates were not sufficiently different in release rates (*in vitro/in vivo*). The C_{max} and AUC values differed 7.6% and –1.8% between the slow and medium release rates, respectively. However, the corresponding values for C_{max} and AUC values for the medium and fast formulations were 31% and 10%, which is acceptable.

The sponsor states that an adequate level 'A' IVIVC has been established, as shown in Figure 9.2. Figure 9.2 depicts the IVIVC where the data points from the first hour (immediate release portion) were excluded from the IVIVC. The IVIVC was also performed with all data points (including the immediate release portion) of the drug release from the capsules (data not shown; equation for regression including all data points: y=1.01x-6.94; r^2=0.93).

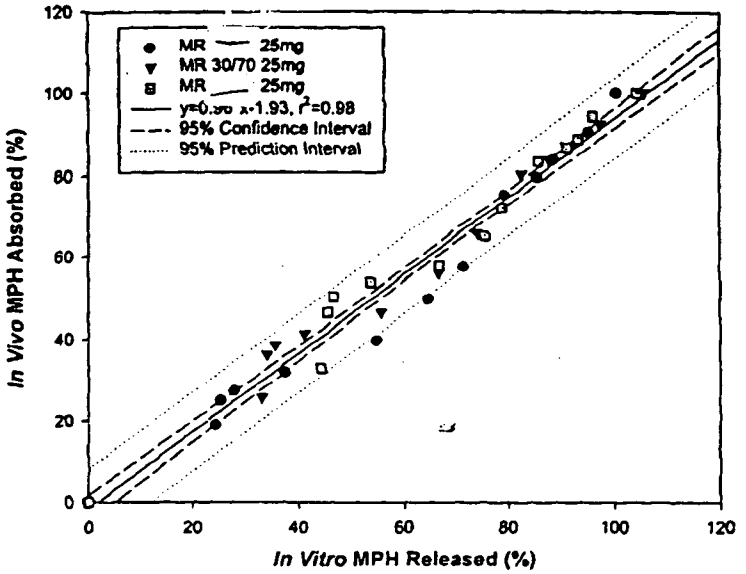

Figure 9.2 *In vitro-in vivo* correlation (IVIVC) of methylphenidate released *in vitro* (%) and absorbed *in vivo* corrected for bioavailability (%) for the MR formulations. Data points from the first hour (immediate release portion) are excluded in the IVIVC.

However, plasma concentration-time profiles were not predicted, using the IVIVC and *in vitro* dissolution data. Therefore, the following information was requested and received from the sponsor (12/27/00):

1. Recalculations of the IVIVC (deconvolution) without correcting for bioavailability (in the original submission the bioavailability for all formulations is set to be 100%)
2. Convolution of data to get predicted plasma concentration-time data and calculations of C_{max} and AUC from the predicted plasma MPH concentration-time data and calculation of prediction errors (%) from the observed and predicted C_{max} and AUC values (internal predictability)

3. External predictability of the IVIVC by use of the data from the fasting arm of the food effect study (MAI-1001-05; Study #2)
4. Calculation of the range of predicted C_{max} and AUC values based on the upper and lower limits for the *in vitro* dissolution specifications, from target (observed) C_{max} and AUC.

Internal Predictability

The internal predictability of the IVIVC, where the predicted parameters were compared to the observed C_{max} and AUC, are depicted in Table 9.4. The predictions were performed by use of the IVIVC depicted in Figure 9.2.

Table 9.4 Internal predictability of C_{max} and AUC for the MR formulations (25 mg MPH HCl)

Parameter	Formulation	Observed	Predicted	% Prediction Error †
C_{max} (ng/mL)	— IR:ER (slow release rate)	3.49	3.64	**4.30**
	30:70 IR:ER (medium release rate)	3.43	3.59	**4.66**
	— IR:ER (fast release rate)	4.88	3.98	**18.44**
mean				**9.14**
AUC (ng.h/mL)	— IR:ER (slow release rate)	43.24	42.38	**1.99**
	30:70 IR:ER (medium release rate)	43.93	44.59	**1.51**
	— IR:ER (fast release rate)	49.09	44.92	**8.50**
mean				**4.0**

† % Prediction error = [(observed value-predicted value)/ observed value] x 100

As shown in Table 9.4, the average prediction errors (PE) of C_{max} and AUC were <10%, which is within the range of acceptance of a level A IVIVC (*Guidance for Industry: Extended Release Oral Dosage forms: Development, Evaluation and Application of In Vivo/In Vitro Correlations, FDA, CDER, September 1997).* Also according to the 1997 Guidance, the %PE for each formulation should not exceed 15%. However, the PE for C_{max} of the — IR:ER capsule was 18%.

The prediction errors in Table 9.4 are based on a bioavailability of 100% for the IR:ER capsules. The sponsor's recalculations estimated the percent of dose of MPH absorbed to 60-70% *vs.* the *in vitro* release for the different IR:ER formulations when no assumptions about bioavailability were made. The resulting IVIVC was somewhat different ($y=0.63x-2.46$, $r^2=0.94$, 1st hour data omitted). The sponsor did not evaluate the predictability (%PE) of the recalculated IVIVC.

External Predictability

The sponsor performed an external predictability evaluation of the IVIVC, by use of data from Study #2 (MAI-1001-05), data from the fasting arm of the food effect study. The plasma concentration-time profiles after the 40 mg dose (2x20 mg 30:70 IR:ER capsule) were scaled to correspond to a 25 mg dose. The resulting prediction of the mean plasma concentration-time curve by use of the IVIVC is depicted in Figure 9.3.

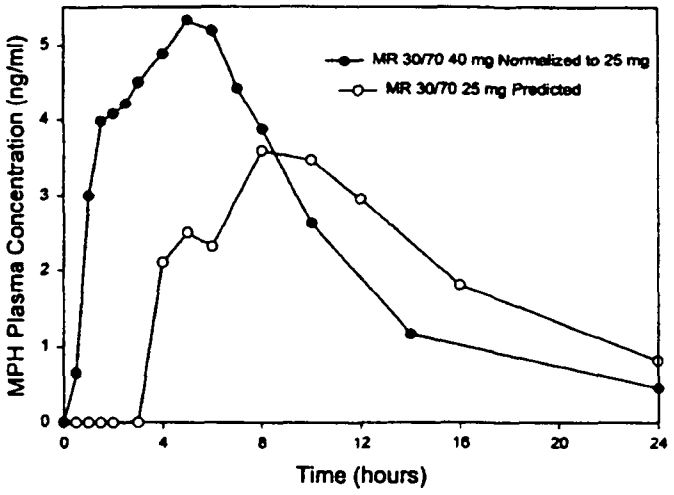

Figure 9.3. Observed (filled circles) and predicted (open circles) MPH plasma concentration – time profiles by use of the proposed IVIVC (Study # 2, fasting arm, 2x20 mg, scaled to a dose of 25 mg MPH HCl).

The external predictability (%PE) is shown in Table 9.5.

Table 9.5 External predictability (%PE = % prediction error) of C_{max} and AUC for the MR formulation intended for commercial use (Cp-time data from Study #2, fasting arm, scaled to a dose of 25 mg MPH HCl).

C_{max} Observed	C_{max} Predicted	% PE	AUC Observed	AUC Predicted	% PE
5.32	3.59	32.52	54.29	44.59	17.87

AUC and C_{max} were underestimated by 20% and 30%, respectively, when the IVIVC was used in the predictions of the pharmacokinetic parameters.

Estimations by use of *In Vitro* Dissolution Specifications
The upper and lower limits of the *in vitro* dissolution specifications (see Study #8, Appendix 2) were also used to predict C_{max} and AUC, as shown in Table 9.6.

Table 9.6 Pharmacokinetic parameters from simulated plasma profiles based on *in vitro* dissolution specifications of the 30:70 IR:ER dosage form. The upper part of the table denotes the parameters after a 25 mg dose, and the lower part of the table after a 20 mg dose.

Study	C_{max} (ng/ml)	AUC_{0-n} (hr*ng/ml)
Minimum Specs-25	7.31	69.884
Maximum Specs-25	10.20	94.053
Average Specs-25	8.13	81.990
30/70 Dissolution-25	8.49	82.464
Minimum Specs-20	11.85	110.145
Maximum Specs-20	15.70	148.913
Average Specs-20	12.89	129.547
30/70 Dissolution-20	14.32	105.645

The range between the average specifications and the lower and upper boundaries were –8% and +22% for the predicted C_{max} and ±15% for the predicted AUC (20 mg 30:70 IR:ER capsule). For the specifications to be acceptable, these upper and lower boundaries of the *in vitro* dissolution specifications should yield values for C_{max} and AUC that are within ±10% of the target. The numerical values of the average C_{max} and AUC (25 mg) are 2.37 and 1.87 times higher, respectively, compared to the observed values used to construct the IVIVC (Study #1). This may indicate a calculation error of these pharmacokinetic parameters, based on the limits of the *in vitro* dissolution specifications. Disregarding this discrepancy, the predictions based on the limits of the *in vitro* dissolution specifications are too wide to accept, based on the suggested IVIVC.

Comments

The results of the internal and external predictability evaluations indicate that an IVIVC has not been established.

1. Internal predictability:
   Although the average % prediction error was within the limits (PE<10%) described in the 1997 Guidance for IVIVC, the prediction error of C_{max} for one formulation was PE% >15% (18.44% for the ___ IR:ER capsule). While the slow and medium release rate formulations had acceptable %PEs, their *in vitro* and *in vivo* (PK parameters) profiles are not sufficiently different. That is, the IVIVC is not acceptable without external predictability. Further, the proposed IVIVC was performed without accounting for immediate release portion. If any future changes of pharmaceutical formulations would involve an alteration of the ratio between the immediate release and extended release beads, or a change in formulation of the IR or ER beads, predictions would not be feasible.
2. External predictability:
   The prediction errors were greater than 10% for both C_{max} (PE 33%) and AUC (PE 18%) of the to-be-marketed 30:70 IR:ER formulation. The predictions of the pharmacokinetic parameters indicate that the C_{max} and AUC are underestimated when the IVIVC is used for the predictions. This may in part reflect the omission of the data from the first hour of absorption/dissolution (immediate release portion) of the formulations.
3. The predictions of C_{max} and AUC from the upper and lower limits of the *in vitro* dissolution specifications by use of IVIVC yields parameter estimates that are outside the ±10% recommended in the 1997 Guidance for IVIVC. In addition, the C_{max} and AUC values in those estimations were about 2-fold higher than the observed values *in vivo*.

/s/

Maria Sunzel
1/12/01 02:38:19 PM
BIOPHARMACEUTICS

Venkata Ramana Uppoor
1/12/01 02:44:40 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	21-259	**Sponsor:**	Medeva Pharmaceuticals Inc.
IND:	[redacted]		
Brand Name:	Metadate™ MR Capsule	**Priority Classification:**	S 505(b)(2)
Generic Name:	*d,l-threo*-methylphenidate hydrochloride	**Indication(s):**	Attention deficit/ hyperactivity disorder (ADHD), Narcolepsy
Drug Class:	Centrally acting sympathomimetic	**Date of Submission:**	March 31, 2000
Dosage Form:	Modified release capsules, 20 mg	**Route of Admin.:**	Oral
Dosing Regimen:	Once daily (qd) max. 60 mg/day	**Due Date of Review:**	2/3/01 (10 month)
Division:	HFD-860	**Medical Division:**	HFD-120
Reviewer:	Maria Sunzel, Ph.D.	**Team Leader:**	Ray Baweja, Ph.D.

Items included in NDA	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies			
Mass Balance Study		X	
BA Studies			
Absolute BA		X	
Relative BA (clinical prototype formulation)	X		
BE Studies			
Average BE		X	
Population BE		X	
Individual BE		X	
Food-Drug Interaction	X		
Dissolution Tests (In Vitro-In Vivo Comparison Studies)	X		
Studies Using Human Biomaterials			
Plasma Protein Binding Studies		X	
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc	X*		**See page 3**
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies			
PK, and Initial Safety and Tolerability in Healthy Volunteers			
Single Dose	X		
Multiple Dose		X	

*2 studies in Section 5 (Nonclinical pharmacology and toxicology)

Items included in NDA (continued)	*Yes*	*No*	*Request*
PK, and Initial Safety and Tolerability in Patient Volunteers			
Single Dose			
Multiple Dose	X		
Dose Proportionality			
Single Dose (oral solution, NOT final MR capsule)	X		
Multiple Dose		X	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors			
Ethnicity		X	
Gender		X	
Pediatrics (PK ages 7-12 yrs)	X		
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors			
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies		X	
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers		X	
PK/PD studies in patients (no relationship according to Sponsor)	X		
Individual data-sets for all PK and PK/PD studies in electronic format		X	
Other			
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	

This application is filable.

A request for individual data sets for all clinical pharmacology studies and the IVIVC data on diskette will be communicated to the firm (see next page).

QBR question: (Key Issue to be Considered)

Is the IVIVC correlation of the dosage form acceptable?

/S/ 5/24/00

Signature _____
Maria Sunzel, Ph.D., Primary Reviewer

CC: NDA 21-259, HFD-850 (electronic entry + paper copy to Lee), HFD-120, HFD-860 (Mehta, Baweja, Sunzel), Central Document Room (B Murphy)

Although the Sponsor has provided study reports electronically, the data in these Word-documents are not easily convertable to Excel or ASCII-files.
Please ask Sponsor to provide the following data electronically, and if possible, as Excel files (or ASCII files);

Study MAI-1001-01 – demographics (age, weight, height), plasma concentration – time data, pharmacokinetic parameters (files corresponding to Tables 1-14 in the study report).

Study MAI-1001-02 – individual demographics (age, weight, height), individual plasma concentration – time data, individual pharmacokinetic parameters, individual effect (SKAMP deportment, attention; CLAMP Conners global index) – time data

Study MAI-1001-05 – demographics (age, weight, height), plasma concentration – time data, pharmacokinetic parameters (files corresponding to Tables 1.2-14 in the study report)

Study ———— demographics (age, weight, height), plasma concentration – time data, pharmacokinetic parameters

In vitro dissolution data used for the IVIVC (both individual and mean dissolution for all units used in the correlations)

The CPB reviewer would also like to have desk copies of two studies located in NDA volumes 15 (non-clinical section 5), and a desk copy of a dissolution report:

1. Study 1193/63 (Methylphenidate: *In vitro* metabolism of the racemate and of the *d*- and *l*-enantiomers in human liver microsomes), Vol.15, p 5-2258
2. Study 1193/64 (Methylphenidate: *Effects of the* of the racemate and of the *d*- and *l*-enantiomers on selected cytochrome P450 activities in human liver microsomes), Vol.15, p 5-2258
3. Eurand America, Inc., Document number PF114-V2: 'The validation of assay, content uniformity, dissolution, and related substance methods for methylphenidate hydrochloride modified-release capsules, 20 mg.' Reference 3, in Pharmacokinetic Summary, Section 6.7, page 6-0185

Original New Drug Application

Capsules, 20mg
(methylphenidate hydrochloride modified-release capsules)

Table 1: Summary of Studies

Study Number Study Design	Route	Study Drug(s)	Dose	Batch No.	No. of Subjects	IND Ref./ Date	Conclusions
MAI 1001-01 6-way, co, r	Oral	MPH MR —— 25 mg MPH MR (30:70) 25 mg MPH MR —— 25 mg Ritalin® 10 mg Tablets Ritalin 10 mg Tablets Ritalin-SR 20 mg Tablets	single single single single *bid* x 1 day single	EA-460 EA-458 EA-459	20 19 20 21 20 19	— —	Each of the treatments administered resulted in a unique mean methylphenidate concentration profile. The —— formulation delivered approximately 27% of the total MPH dose in the 4-8 hour interval, which is comparable to the amount of MPH released from the Ritalin-SR product in the same time period. The 30:70 and —— formulations delivered 35-37% of the total dose during that time period. The MPH MR formulations appeared to have elimination processes that were slower than the other formulations. However, any residual plasma concentrations are likely to be negligible.
MAI 1001-02 db, pa, co, r	Oral	Stage 1: Ritalin 10 mg Encap. Tabs Placebo Capsules Stage 2: MPH MR (30:70) 20 mg MPH MR (30:70) 20 mg MPH MR —— 20 mg MPH MR —— 20 mg	 *bid* x 1 week *bid* x 1 week *qd* x 1 week 2 *qd* x 1 week *qd* x 1 week 2 *qd* x 1 week	 EA-542 EA-542 EA-543 EA-543	 25 25 12 11 13 11	— —	The MR formulations, given once daily in the morning, produced a plasma concentrations profile with an initial rapid absorption phase followed by a second rising portion, and exerted a therapeutic response comparable to that of the immediate-release formulation of methylphenidate given twice-daily. Therefore, the MR formulations eliminated the need for a midday dose.

co = crossover; r =randomized; db = double-blind; pa = parallel arm; MPH = methylphenidate HCl; MR = modified-release capsules

Table 1: Summary of Studies (Cont'd)

Study Number Study Design	Route	Study Drug(s)	Dose	Batch No.	No. of Subjects	IND Ref./ Date	Conclusions
MAI 1001-05 ol, 2-way, r, co	Oral	MPH MR (30:70) 20 mg MPH MR (30:70) 20 mg	40 mg single (fast) 40 single (fed)	EA-604 EA-604	18 18	[redacted]	Pharmacokinetic and statistical analyses suggest that food delayed the absorption from the immediate-release portion of the formulation. This resulted in an increased C_{max} of approximately 32% (p=0.0004), from 8.9 to 11.7 ng/ml, likely due to combined absorption from the immediate and extended release portions of the formulation. The 90% confidence interval for LN (C_{max}) was 116.9 to 144.6%, with a mean ratio of 130.0%. The ratios for AUC were within the desired range for LN[AUC_{0-t}], 113.1 to 124.9%, and LN[$AUC_{0-\infty}$], 111.3 to 122.4%.
[redacted] sb, co	Oral	*d-threo*-MPH 5 mg sol. *d-threo*-MPH 10 mg sol. *d-threo*-MPH 15 mg sol. *d-threo*-MPH 20 mg sol. *d-threo*-MPH 30 mg sol. MPH 10 mg sol. MPH 20 mg sol. MPH 30 mg sol. MPH 40 mg sol MPH 60 mg sol.	single single single single single single single single single single		11 12 11 11 11 10 11 11 11 10	N/A conducted in the UK	There was a linear relationship with dose in terms of both C_{max} and AUC. The median T_{max} was 1.5 hours post-dose for all treatments.

ol = open-label; r = randomized; co = crossover; sb = single-blind; MPH = methylphenidate HCl; MR = modified-release capsules

6.0 Human Pharmacokinetics and Bioavailability

The overall purpose of the program was to develop a formulation of methylphenidate that would produce a therapeutic benefit of sufficient duration to eliminate the need for a midday dose. Modified-release (MR) formulations of methylphenidate (MPH) in capsule form were designed with different proportions of immediate-release (IR) beads to extended-release (ER) beads. ER beads, from which MPH is released at a slower rate, are intended to provide a second uptake phase in order to sustain a clinically meaningful treatment response. Several MR formulation prototypes, described in terms of their ratio of IR to ER dose (IR:ER), were designed and tested. MR formulations with IR:ER ratios of —— , 30:70 and —— were studied initially in a bioavailability study in healthy adult volunteers. This was followed by a safety, efficacy and pharmacokinetics study in children with ADHD comparing the 30:70 and —— ratios. Additionally, a study with the 30:70 ratio formulation, comparing the pharmacokinetics of fasting doses to doses taken with a high fat standard meal, was conducted.

At the Pre-NDA meeting held on December 9, 1999, specific requests for information regarding the biopharmaceutic studies were made by the Division for Medeva to address in the NDA. The requests are listed below in **bold** followed by Medeva's response.

- **Clarify the subject population used in the biopharmaceutics studies.**
  Patient populations are summarized below. Please refer to the individual study reports for additional information regarding the subject population.

Study I.D.	No. of Subjects	Age (years)	Gender (N)	Race (N)
MAI 1001-01	Healthy adult volunteers: 22 (enrolled) 18 (completed)	Range: 18-50 Mean: 32	Males: 14 Females: 8	Caucasian: 17 Hispanic: 3 Black: 2
MAI 1001-02	Children diagnosed with ADHD: 25 (rec'd study drug) 23 (completed)	Range: 7-12 Mean: 10	Males: 21 Females: 4	Caucasian: 22 Black: 2 Asian: 1
MAI 1001-05	Healthy adult volunteers: 18 (enrolled) 18 (completed)	Range: 20-50 Mean: 31	Males: 11 Females: 7	Caucasian: 15 Hispanic: 1 Black: 1 Asian: 1

- **Include the 90% confidence intervals for study MAI 1001-01.**
  The 90% confidence intervals the MAI 1001-01 study are presented in Appendix 3.2 of the study report.

6.1 Summary of Studies

Brief descriptions of the studies are provided in this section, followed by a tabular summary of the studies (Table 1).

Study MAI 1001-01

A Single-Dose, Bioavailability Study, Comparing Five Different Formulations of Methylphenidate (Existing IR and SR Formulations, and New Modified Release Formulations) (n=18).

Study MAI 1001-01 had a randomized, open-label, six-period crossover design. Projected enrollment was 24 subjects. Twenty-two (22) healthy adult male and female subjects were enrolled and 18 completed the study. The objective of the study was to evaluate the bioavailability of three modified-release capsule formulations of MPH, compared to the marketed immediate-release (IR) and sustained-release (SR) MPH products. The following single daily doses were administered:

- Ritalin® Tablets (IR Formulation): 10mg
- Ritalin Tablets (IR Formulation) at 0 and 4 hours: 10mg *bid*
- Ritalin-SR® Tablets (SR Formulation): 20mg
- Methylphenidate MR —— Capsules : 25mg
- Methylphenidate MR 30:70 Capsules : 25mg
- Methylphenidate MR —— Capsules : 25mg

Study MAI 1001-02

A Double Blind, Crossover Pharmacokinetic and Pharmacodynamic Comparison of Two Modified Release Formulations of Methylphenidate in Children with ADHD (n = 23).

The objectives of this study were: (1) to evaluate the efficacy, safety and pharmacokinetics of the 30:70 and —— MR formulations of MPH administered to children with ADHD; and (2) to compare the efficacy, safety and tolerability of the MPH MR formulations to placebo. The following four treatments were each administered for one week:

Stage 1 (to confirm that subjects responded to methylphenidate):

- Ritalin Tablet 10 mg *bid* (twice daily), a morning dose and a midday dose,
- Placebo,

Stage 2 (to compare the 2 MR formulations at 2 dosages):

- Methylphenidate MR 30:70 (approximately half the subjects received 20 mg/day, the other half 40 mg/day)
- Methylphenidate MR—— (approximately half the subjects received 20 mg/day, the other half 40 mg/day).

Twenty-seven subjects qualified and entered the 4-week double-blind, crossover trial consisting of the two stages. Subjects completing Stage I entered Stage II, and were randomly assigned to either 20 or 40mg/day MPH MR treatment. Both 20 mg/day and 40 mg/day parallel groups received, in a randomized, balanced crossover design, one week of treatment with each MPH MR formulation, —— and 30:70 IR:ER ratios.

Blood samples were collected for pharmacokinetic assays at planned intervals up to 9 hours post-dose on Saturdays, the last day of each treatment, when subjects attended a laboratory classroom specially designed for pharmacokinetic-pharmacodynamic studies in children with ADHD.

Study MAI 1001-05

Open-Label, Randomized, Crossover, Comparative Bioavailability Study of Methylphenidate Modified Release (MR) Capsules Given as a Single Dose After a High Fat Meal or Under Fasting Conditions (n = 18).

The objective of this study was to compare the oral bioavailability of MPH MR capsules after a single 40 mg (2x20mg) dose following a high fat meal or under fasting conditions in 18 healthy adult subjects. Subjects randomized to Treatment A received a single oral dose of two 20 mg MPH MR capsules approximately five minutes after a high-fat breakfast. Subjects randomized to Treatment B received a single oral dose of two 20 mg MPH MR capsules in a fasting condition. The effect of food was assessed by comparison of pharmacokinetic parameters derived from serial plasma concentrations of MPH in the fed and fasted conditions.

———————

d,l-threo-Methylphenidate Hydrochloride and *d-threo*-Methylphenidate Hydrochloride - A Phase I, Single-Blind, Crossover, Single Oral Dose, Safety, Tolerability and Pharmacokinetic Study in healthy Male Volunteers.

This study was conducted as part of the *d-threo*-methylphenidate development program. The doses administered were 5, 10, 15, 20 or 30 mg *d-threo*-methylphenidate and 10, 20, 30, 40, or 60 mg of the racemate as the free base in an aqueous solution. The pharmacokinetic findings of the racemate group will be summarized in support of dosing of up to 60 mg/day.

Capsules, 20mg
(methylphenidate hydrochloride modified-release capsules)

Investigational Formulations

	Finished Capsules				Immediate Release Beads		Intermediate Release Beads		Extended Release Beads		
Study No. (Report Location)	Dosage Form	Str. (mg)	Lot #	Batch Size	Lot #	Size (kg)	Lot #	Size (kg)	Lot #	Size (kg)	Formulation or Manufacturing; Changes/ Effect of Change
MAI 1001-01 (Section 6.8)	30:70 Caps	25	EA 458		EA 456		EA 454		EA 455		Laboratory scale. Clinical prototypes.
	Caps	25	EA 459		EA 456		EA 454		EA 455		
	Caps	25	EA 460		EA 456		EA 454		EA 455		
MAI 1001-02 (Sections 6.8 and 8.11)	30:70 Caps	20	EA 542		EA 540		EA 541		EA 544		Batch size increased to pilot scale. Strength change for commercial purposes. Dissolution profile matched to prototype.
	Caps	20	EA 543		EA 540		EA 541		EA 544		
MAI 1001-04 (Section 8.11)	30:70 Caps	20	EA 604		EA 612		EA 629		EA 630		Batch size increased to production scale. No significant changes due to scale-up.
MAI 1001-05 (Section 6.8)	30:70 Caps	20	EA 604		EA 612		EA 629		EA 630		Same as MAI 1001-04.
Capsules, 20 mg, contain two types of beads, Immediate-Release (IR) and Extended-Release (ER). The capsules are filled in a ratio of 30% IR beads and 70% ER beads, corresponding to 6 mg and 14 mg of methylphenidate hydrochloride, respectively.											

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **June 22, 2000**

NDA NUMBER: **21-259**

NAME OF DRUG: **(Methylphenidate Modified-release Capsules) 20 mg**

NDA HOLDER: **Medeva Pharmaceuticals, Inc.**

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the tradename '

"Metadate" is an approved proprietary name for Methylphenidate Hydrochloride Extended-release Tablets marketed under ANDAs 89-601 (20 mg) and 40-306 (10 mg), manufactured by Medeva. The firm utilizes the modifier "ER" for these ANDAs and for this reason our review focused primarily on the modifier ' A draft copy of the package insert for was the only labeling provided for review and comment.

PRODUCT INFORMATION

s a mild central nervous system (CNS) stimulant. is indicated for the treatment of Attention Deficit Hyperactivity Disorders, Narcolepsy and Special Diagnostic Considerations. The initial daily dose is 20 mg daily. The dosage can be increased weekly in increments of 20 mg, up to a maximum of 60 mg/day, depending upon tolerability and degree of efficacy observed. The product will be available as 20 mg capsules. The capsules are comprised of both immediate-release and extended-release beads such that 30% of the dose is provided by the immediate-release component and 70% of the dose is provided by the ER component.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process. Lastly, an AERS search was conducted and did not uncover any post-marketing problems associated with the use of the proprietary name "Metadate ER".

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name . Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel did not find ' .o be an acceptable modifier because it is too similar to the currently marketed Metadate product utilizing the modifier "ER". Metadate ER and .re both extended-release formulations of methylphenidate and will have an overlapping strength of 20 mg.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A separate study was conducted within FDA for each proposed proprietary name to determine the degree of confusion of with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 92 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
METADATE MR	
Inpatient: . QAM #60	*Outpatient:* ii po qam
Outpatient: ii po qam #60	

[v] WWW location http://www.uspto.gov/tmdb/index.html.

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	response	Other response
Written: Inpatient	30	15 (50%)	13 (87%)	2 (13%)
Outpatient	31	20 (65%)	16 (80%)	4 (20%)
Verbal: Outpatient	31	16 (52%)	3 (19%)	13 (81%)
Total:	92	51 (55%)	32 (63%)	19 (37%)

Among participants in the written prescription studies, 6 of 35 respondents (17%) interpreted the name incorrectly. Most of the incorrect name interpretations did not include the modifier '

Among verbal prescription study participants, 13 of 16 (81%) of the study participants interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of in addition to not including the modifier ' in their responses.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. In reviewing the proprietary name , the primary concern was the possibility of confusion between the currently marketed extended-release tablet formulation of methylphenidate "Metadate ER", and the proposed '
There are two commonalties associated with these products. First, the products have the same proprietary name and secondly, each markets a 20 mg strength. There are two major differences between Metadate ER and are the different pharmacokinetics with regards to the rate of elimination and the dosing interval (TID and QD). Because these products have similar strengths and names, there is a greater potential for confusion, particularly in the first months after product launch when a new product is not widely recognized. Diltiazem, Diltiazem CD, Diltiazem SR are good examples of this type of confusion. Each having overlapping strengths, same name, and different pharmacokinetics. To help alleviate the confusion each product includes an additional modifier on the container label to differentiate the different dosing recommendations.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confusion between and "ER" as anticipated, however there were several responses that did not include any modifier. Although the studies did not detect confusion between ' and "ER" at this time, OPDRA still believes the potential still exists given the modifiers are ff from each other. In a busy pharmacy setting with increased noise levels the two names could easily be misinterpreted on a verbal order.

2. The proposed established name (Methylphenidate Hydrochloride modified-release capsule) is not an approved pharmaceutical dosage form according to the United States Pharmacopeia (USP). OPDRA contacted Dan Boring, Chair of CDER Labeling and Nomenclature Committee, to discuss the recommended established name of this product. It was recommended the firm adopt "extended release" as the modifier. Therefore, the established name of the product should be Methylphenidate Hydrochloride Extended-release Capsules. Once the established name is revised the modifier which represents ' would be meaningless.

2. also a common medical abbreviation for the following: maddox rod, magnetic resonance, manifest refraction, may repeat, measles-rubela, medical rectus, medical record, mental retardation, milliroentgen, mitral regurgitation, and moderate resistance. The use of the modifier ' may cause confusion in the hospital setting where ' might be interpreted as " on an inpatient prescription order resulting in the administration of an additional dose of the medication.

For these reasons, we do not recommend use of the modifier

III. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name '

OPDRA would appreciate feedback of the final outcome of this consult and are willing to meet with the Division for further discussion if needed. If you have any questions concerning this review, please contact Carol Holquist, R.Ph. at 301-827-3244.

/S/ 6/27/00

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/ 6/27/00

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

Original New Drug Application

Capsules, 20 mg
(methylphenidate hydrochloride modified-release capsules)

13.A. PATENT INFORMATION

Methylphenidate Hydrochloride Modified-Release Capsules represent a modification of a listed drug in terms of a new dosage form and unique drug-release pattern, for which clinical investigations, other than bioavailability or bioequivalence studies, are essential to its approval. This 505(b)(2) application relies on the Agency's previous finding of safety and efficacy for the following listed drugs:

- Ritalin® (methylphenidate hydrochloride tablets, USP) 5, 10, 20 mg, manufactured by Novartis, NDA 10-187.

- Ritalin-SR® (methylphenidate hydrochloride USP, sustained-release tablets) 20 mg, manufactured by Novartis, NDA 18-029.

U.S. Patent No. 4,137,300 for Ritalin-SR® has expired. The period of marketing exclusivity for this product expired on September 24, 1986.

There is no listed drug that is pharmaceutically equivalent to the drug product for which this application is submitted.

The undersigned hereby declares that there are no known relevant patents that claim the drug product or the use of the drug product for which approval is sought.

Helen Wiley, Esq.
General Counsel

Original New Drug Application

Capsules, 20 mg
(methylphenidate hydrochloride modified-release capsules)

13.B. MARKET EXCLUSIVITY STATEMENT

Pursuant to 21 CFR 314.50(j), Medeva hereby claims that the drug product subject of this application is entitled to three (3) years of market exclusivity from the date of approval of this application, in accordance with 21 CFR 314.108(b)(4). Medeva certifies that the clinical investigations included in this application meet the definition of "new clinical investigations" per 21 CFR 314.108(a) in that they have not been previously submitted to FDA, and thus have not been relied on by FDA to demonstrate substantial evidence of safety or efficacy of a previously approved drug product. Further, the clinical investigations included in this application are essential to approval of Capsules, as there is no other available evidence of the safety and efficacy of this particular drug product. These clinical investigations were sponsored by Medeva under IND 52,318.

Original New Drug Application

Capsules, 20 mg
(methylphenidate hydrochloride modified-release capsules)

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14. PATENT CERTIFICATION

Paragraph II Certification

Medeva certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 4,137,300 for Ritalin-SR® (methylphenidate hydrochloride USP sustained-release tablets) 20 mg, manufactured by Novartis, the listed drug on which Medeva relies upon the Agency's previous finding of safety and efficacy for the approval of this application, has expired, and therefore will not be infringed by the manufacture, use or sale of methylphenidate hydrochloride modified-release capsules, 20 mg, for which this application is submitted.

Helen P. Wiley, Esq.
General Counsel