CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-259

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-259 Correction of label review dated March 21, 2001

Methylphenidate HCl (Metadate™ CD Capsules); 20 mg modified release capsules

Sponsor:	Celltech Americas Inc. (formerly Medeva Americas Inc.), 755 Jefferson Road, P.O. Box 1710, Rochester, NY 14603-1710
Submission Date:	February 13, March 19, 2001
Reviewer:	Maria Sunzel, Ph.D.
Indication:	Attention Deficit/Hyperactivity Disorder (ADHD)

CORRECTION: REVIEW OF RESPONSE TO LABEL PROPOSAL DATED MARCH 21, 2001

A minor modification is necessary for the OCPB label review for Metadate CD (NDA 21-259) dated March 21, 2001. In the review (3/21/01) the early C_{max} for the 20 mg dose was erroneously given as ———— it should be **8.6 (±2.2) ng/mL**.

One value (subject 44, actual C_{max1} =13.2956 ng/mL was entered as 12.2956 ng/mL, therefore the mean ± SD value should be adjusted (data from Attachment 2 in review dated 3/21/01).

The sponsor has otherwise accepted the proposed label text (review dated March 21, 2001), therefore no further action is needed.

Maria Sunzel, Ph.D., _____

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

c.c.: NDA 21-259, HFD-120 (Laughren, Glass) , HFD-860 (Uppoor, Sunzel)

/s/

Maria Sunzel
3/22/01 05:49:11 PM
BIOPHARMACEUTICS

Venkata Ramana Uppoor
3/22/01 05:57:24 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-259 Label Review

Methylphenidate HCl (Metadate™ CD Capsules); 20 mg modified release capsules

Sponsor:	Celltech Americas Inc. (formerly Medeva Americas Inc.), 755 Jefferson Road, P.O. Box 1710, Rochester, NY 14603-1710
Submission Date:	February 13, March 19, 2001
Reviewer:	Maria Sunzel, Ph.D.
Indication:	Attention Deficit/Hyperactivity Disorder (ADHD)

REVIEW OF RESPONSE TO LABEL PROPOSAL

Celltech Americas Inc. received an Approvable Letter for Metadate™ CD Capsules (methylphenidate HCl; 20 mg modified release capsules) from FDA on February 2, 2001. The sponsor sent in a complete response to the Approvable Letter on February 13, 2001 that included a counter–proposal to the label proposed by the FDA.

In the Clinical Pharmacology section, one outstanding issue was not resolved, namely the description of time to peak methylphenidate concentration (t_{max}) in the target population. The FDA proposal for the text in question was as follows:

*"METADATE CD was administered as repeated once-daily doses of 20 mg or 40 mg to children aged 7-12 years with ADHD for one week. After a dose of 20 mg, the mean (±SD) early C_{max} was 8.6 (±2.6) ng/mL, the later C_{max} was 9.6 (±3.8) ng/mL and AUC_{0-9h} was 63.0 (±16.8) ng.h/mL. The corresponding values after a 40 mg dose were 15.4 (±8.1) ng/mL, 17.0 (±4.4) ng/mL and 120 (±39.6) ng.h/mL, respectively. The early peak concentrations were reached about **2 hours** after dose intake, and the second peak concentrations were reached about **5 hours** after dose intake. The means for C_{max} and AUC following a dose of 20 mg were slightly lower than those seen with 10 mg of the immediate-release formulation, dosed at 0 and 4 hours."*

The sponsor's counterproposals for the early and later t_{max} values are 1.5 hours and 4.5 hours, respectively. Their rationale for the change is to match the text and a figure depicting the average plasma concentration-time profiles from the study that is also included in the label (Study MAI 1001-002; see Attachment 1). Since the label text regarding the observed t_{max} values is based on the mean values from the t_{max} values from each individual, and the figure only describes the mean plasma concentration-time profile for each dose, there is a slight discrepancy between the t_{max} values in the figure and the text.

This issue was discussed with the sponsor in a telecon (March 14, 2001), and the FDA proposal was to either include the range for the early and late t_{max} values, or alternatively, the median values, instead of the mean values of t_{max} currently proposed by FDA. The observed C_{max} and t_{max} values cited in the label originates from the study report, where the values were chosen from fixed time intervals, the early values were the highest in the 0-3 h time interval, and the later values were the highest in the 4.5-9 h time interval. The sponsor now proposes the use of the actual values from the plasma concentration-time profiles observed in the study, not values generated from the fixed time intervals. The sponsor was requested to provide tabulations of the t_{max} values, including summary statistics, in support for the proposed changes. The sponsor provided the requested data by fax on March 19, and proposed the use of the median values for t_{max}, 1.5 h and 4.5 h, respectively.

The proposal is acceptable, and will depict the data in a more accurate manner. However, the use of actual t_{max} values from the plasma concentration-time profiles observed in the study, instead of

the t_{max} values generated from fixed time intervals, warrants a change in the C_{max} values in a corresponding way. Comparisons of the C_{max} and t_{max} values, using both approaches (fixed time intervals *vs.* actual values) are tabulated in Attachment 2.

Recommendation:
The Office of Clinical Pharmacology and Biopharmaceutics proposes the following labeling text for the proposed paragraph (**revisions**, ~~previous text~~):

METADATE CD was administered as repeated once-daily doses of 20 mg or 40 mg to children aged 7-12 years with ADHD for one week. After a dose of 20 mg, the mean (±SD) early C_{max} was **8.5 (±2.1)** [redacted] ng/mL, the later C_{max} was **10.9 (±3.9)*** [redacted] ng/mL and $AUC_{0\text{-}9h}$ was 63.0 (±16.8) ng.h/mL. The corresponding values after a 40 mg dose were **16.8 (±5.1)** [redacted] ng/mL, **15.1 (±5.8)*** [redacted] ng/mL and 120 (±39.6) ng.h/mL, respectively. The early peak concentrations (median) were reached about **1.5** [redacted] hours after dose intake, and the second peak concentrations (median) were reached about **4.5** [redacted] hours after dose intake. The means for C_{max} and AUC following a dose of 20 mg were slightly lower than those seen with 10 mg of the immediate-release formulation, dosed at 0 and 4 hours.
*25-30% of the subjects had only one observed peak (C_{max}) concentration of methylphenidate

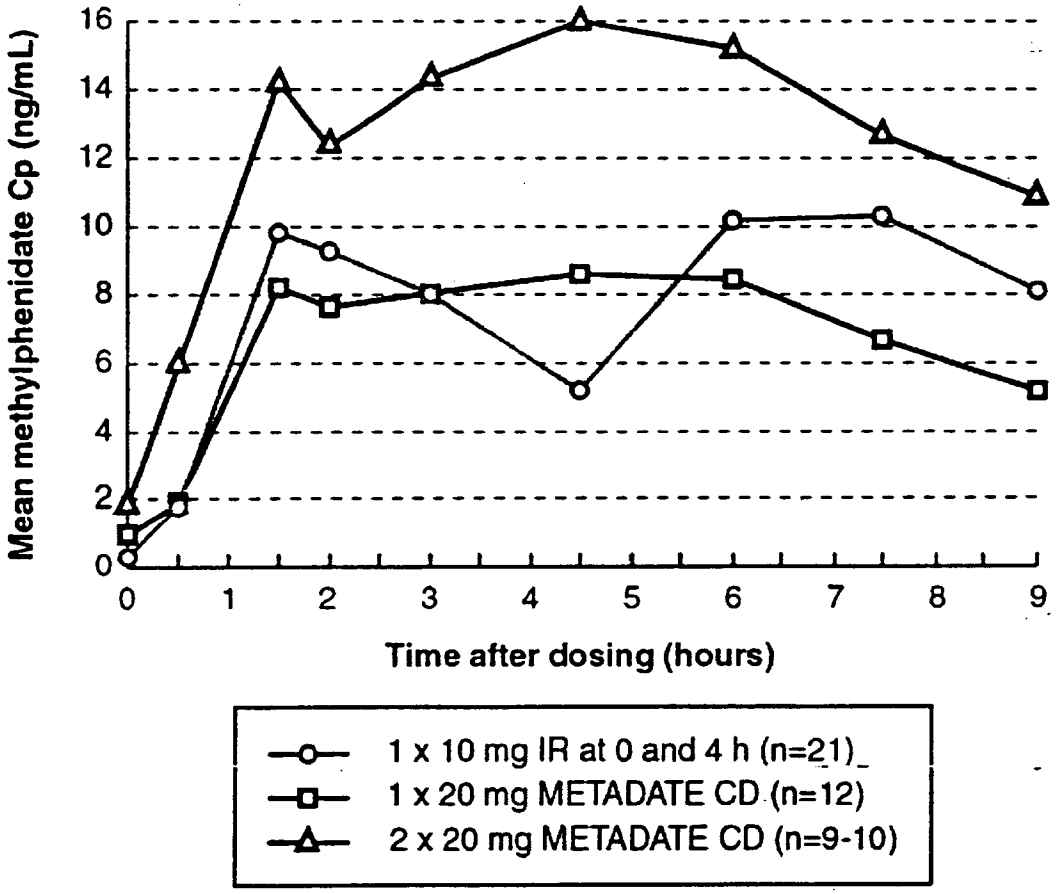
Maria Sunzel, Ph.D., _____

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

c.c.: NDA 21-259, HFD-120 (Laughren, Glass) , HFD-860 (Mehta, Uppoor, Sunzel)

FIGURE 1

Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Children with ADHD



ATTACHMENT 2

MAI 1001-02
20 mg

	Fixed time periods (0-3h, 4.5-9h)				Actual 1st & 2nd Cmax				
Subject	Cmax1	tmax1	Cmax2	tmax2	Cmax1	tmax1	Cmax2	tmax2	
4	6.9727	1.5	8.4712	4.5	6.9727	1.5	8.4712	4.5	same as fixed
5	9.8026	3	9.6226	6	8.5372	1.5	9.8026	3	
11	8.5521	2	8.106	6	8.5521	2	8.106	6	same as fixed
12	11.7715	1.5	9.1628	4.5	11.7715	1.5	11.265	3	
14	4.4157	3	6.2892	4.5	6.2892	4.5			one peak
18	6.5012	1.5	4.9624	7.5	6.5012	1.5	5.3204	3	
27	8.8964	1.5	10.6248	4.5	8.8964	1.5	10.6248	4.5	same as fixed
31	9.31	1.5	7.7588	4.5	9.31	1.5			one peak
35	7.0076	3	6.0324	4.5	7.0076	3			one peak
42	6.4356	3	18.114	6	6.1908	1.5	18.114	6	
44	14.108	3	15.538	4.5	12.2956	1.5	15.538	4.5	
46	9.9936	1.5	10.9036	4.5	9.9936	1.5	10.9036	4.5	same as fixed
mean	**8.65**	**2.17**	**9.63**	**5.13**	**8.53**	**1.92**	**10.91**	**4.33**	
SD	**2.63**	**0.75**	**3.85**	**1.00**	**2.07**	**0.93**	**3.87**	**1.17**	
median	**8.72**	**1.75**	**8.82**	**4.50**	**8.54**	**1.50**	**10.62**	**4.50**	
min									
max									
n	**12**	**12**	**12**	**12**	**12**	**12**	**9**	**9**	

25% of the subjects (3of 12) only showed one peak

MAI 1001-02
40 mg

	Fixed time periods (0-3h, 4.5-9h)				Actual 1st & 2nd Cmax				
Subject	Cmax1	tmax1	Cmax2	tmax2	Cmax1	tmax1	Cmax2	tmax2	
1	16.3545	1.5	15.907	4.5	16.3545	1.5	15.907	4.5	same as fixed
3	15.6675	3	22.248	6	22.248	6			one peak
10	10.701	3	11.1125	4.5	11.1125	4.5	7.0171	9	
15	27.0284	1.5	22.9132	4.5	27.0284	1.5	24.49	3	
16	10.8004	3	15.8036	4.5	15.8036	4.5			one peak
28	13.586	1.5	14.334	6	13.586	1.5	14.334	6	same as fixed
36	11.3392	1.5	12.022	4.5	11.3392	1.5	12.022	4.5	same as fixed
37	14.068	3	17.2104	6	17.2104	6			one peak
47	17.0608	3	15.59	4.5	16.4216	1.5	17.0608	3	
mean	**15.18**	**2.33**	**16.35**	**5.00**	**16.79**	**3.17**	**15.14**	**5.00**	
SD	**5.04**	**0.79**	**4.03**	**0.75**	**5.10**	**2.05**	**5.80**	**2.26**	
median	**14.07**	**3.00**	**15.80**	**4.50**	**16.35**	**1.50**	**15.12**	**4.50**	
min									
max									
n	**9**	**9**	**9**	**9**	**9**	**9**	**6**	**6**	

33% of the subjects (3 of 9) only showed one peak

/s/

Maria Sunzel
3/21/01 10:09:13 AM
BIOPHARMACEUTICS

Venkata Ramana Uppoor
3/21/01 11:46:18 AM
BIOPHARMACEUTICS

· HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	(HFD 860) **Tracking/Action Sheet for Formal/Informal Consults**

From: Maria Sunzel, Ph.D.			To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE: 3/1/01	IND No.: N/A Serial No.: N/A	NDA No. 21-259	DATE OF DOCUMENT 2/13/01	MAR 1 2001
NAME OF DRUG **Metadate™ CD** (20 mg IR/ER capsules, methylphenidate)	PRIORITY CONSIDERATION S		Date of informal/Formal Consult: 2/15/01	IC COMPLETED MAR 0 2 2001

NAME OF THE SPONSOR: **Medeva Pharmaceuticals, Rochester, NY**

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUES

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW)*: **[Labeling amendment, dissolution specs.]**
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ **See comments below**
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor received an Approvable Letter for Metadate™ CD (methylphenidate HCl, 20 mg IR/ER capsules) on Feb. 2, 2001. In response to the letter, the sponsor has submitted a response to pharmaceutical issues and the proposed label text.

1. The Office of Clinical Pharmacology and Biopharmaceutics agrees to the proposed modifications to our recommended *in vitro* dissolution specifications (4 h: —— %, 12 h: —— %). The final dissolution method specifications are provided on page 1 of the attachment.
2. Please see attachment for comments (page 1) on the minor revisions to the proposed label text (Page 3-7) provided by the sponsor.

Please forward the labeling comments to the medical reviewer.

SIGNATURE OF REVIEWER: /S/	Date 3/1/01
SIGNATURE OF TEAM LEADER:	Date 03/01/01
c.c.: NDA 21-259; HFD-120 (Laughren, Glass); HFD-860; TL: R Uppoor; DD: M. Mehta	**Project Manager: Anna-Marie Homonnay Date** _____

1. Final dissolution method specifications

The final dissolution method specifications for METADATE™ CD, 20 mg *d,l-threo*-methylphenidate HCl capsules, are as follows:

Dissolution apparatus: USP Paddle Apparatus II
Rotation speed: 50 rpm
Medium and volume: Water, 500 mL
Medium Temperature: 37 ± 0.5°C

Time Interval	Specification (% of label)
1 h	—
2 h	—
4 h	—
8 h	—
12 h	—

2. Comments on the sponsor's proposed CLINICAL PHARMACOLOGY label (see the following pages of Attachment, pages 3-7, for the actual label text)

Sponsor's revision no. 5 (Attachment, page 3): Acceptable

Sponsor's revision no. 6 (Attachment, page 4): The sponsor has added a new sentence at the beginning of the paragraph. This addition is acceptable. (The same text appears in Alza's label for Concerta. Medeva has also performed a study with an oral solution of methylphenidate that showed rapid absorption, i.e. the sponsor has shown that the drug is rapidly absorbed.)

Sponsor's revision no. 7 (Attachment, page 4): Acceptable

Sponsor's revision no. 8 (Attachment, page 4): Acceptable

FDA revision (Attachment, page 4): 2nd paragraph (repeated dosing in children): Correction of the units for $AUC_{0\text{-}9h}$:to 'ng.h/mL' (not 'ng/h.mL', this mistake appears twice)

Sponsor's revision no. 9 (Attachment, page 4): Please keep the text proposed by FDA, i.e. '— hours' and —hours', respectively. The sponsor proposes to use the t_{max} values depicted in Figure 1 of the label (Figure 1 not shown in Attachment p. 4). However, the t_{max} in the graph does not fully reflect the average t_{max} calculated from the individual data, although the difference is small. The actual average t_{max} for 20 mg was 2.2±0.7 h and 5.1±1.0 h, respectively. The actual average t_{max} for 40 mg was 1.9±1.0 h and 5.2±0.8 h, respectively.

Sponsor's revision no. 10 (Attachment, page 5): Please use 't_{max}' which is standard pharmacokinetic nomenclature (for reference, see: Clinical Pharmacokinetics Preferred Symbols, Clin. Pharmacokinet. 1999: 37(1) 87-89)

Sponsor's revision no. 11 (Attachment, page 5): Acceptable

Sponsor's revision no. 12 (Attachment, page 5): Please, do not include text proposed by the sponsor. Since the text was re-inserted to explain the text regarding a maximum plasma concentration of 23 ng/mL in a single subject, we propose to also delete the sentence regarding this individual. Please delete the following sentences from the sponsor's proposed text: —

[ ]

The time delay in the absorption, as well as the increase in C_{max} and AUC is still captured in the label text.

Sponsor's revision no. 13 (Attachment, page 5): Acceptable

Sponsor's revision no. 14 (Attachment, page 6): Acceptable

Sponsor's revision no. 15 (Attachment, page 6): Acceptable

FDA revision (Attachment, page 6): **Special Populations**, *Gender:* The pharmacokinetics of methylphenidate after a single dose of METADATE CD ~~was~~ **were** similar between...
Correction: 'was' is changed to 'were'.

FDA revision (Attachment, page 7): **Special Populations**, *Age:* The pharmacokinetics of methylphenidate after METADATE CD administration ~~has~~ **have** not been studied in children less than 6 years of age.

Correction 1st sentence: 'has' is changed to 'have'. Please delete the 2nd (last) sentence for the section **Special Populations**, *Age*. The sentence was inserted by FDA, but should be deleted. The reference is not thoroughly convincing, and this is not standard label text for the other methylphenidate product labels.

FDA revision (Attachment, page 7): **Special Populations**, *Renal and Hepatic Insufficiency:* The pharmacokinetics of methylphenidate after METADATE CD administration ~~has~~ **have** not been studied in patients with renal or hepatic insufficiency.
Correction: 'has' is changed to 'have'.

WITHHOLD 5 PAGE (S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
NDA 21-259

Methylphenidate HCl ; 20 mg modified release capsules	
Sponsor:	Medeva Americas Inc., 755 Jefferson Road, P.O. Box 1710, Rochester, NY 14603-1710
Submission Dates:	March 31, June 26, December 15, and December 27, 2000
Reviewer:	Maria Sunzel, Ph.D.
Indication:	Attention Deficit/Hyperactivity Disorder (ADHD)

EXECUTIVE SUMMARY

The racemic *d,l-threo*-methylphenidate hydrochloride (*d,l*-MPH) is currently marketed for treatment of attention deficit/ hyperactivity disorders (ADHD) in children > 6 years of age, and narcolepsy, in daily doses up to 60 mg as immediate and extended release formulations. The sponsor has submitted an NDA for MPH HCl as an extended release formulation (20 mg) that consists of encapsulated immediate-release (IR) beads (30%, 6 mg) and extended-release (ER) beads (70%, 14 mg), to be given up to a maximal once-daily dose of 60 mg (3x20 mg). This formulation is proposed to eliminate the need for a mid-day dose. The sponsor has provided four supportive clinical pharmacology studies in adults and children with ADHD. The sponsor is also seeking approval of an *in vitro-in vivo* correlation for the new dosage form. Two *in vitro* metabolism (cytochrome P450) studies were also submitted. The NDA contains one pivotal placebo-controlled efficacy and safety study in children.

The issues regarding this submission are;

- Are the pharmacokinetics of methylphenidate adequately characterized after oral doses of the extended release formulation compared to the IR product?
- Is dose dumping ruled out for the ER capsule?
- Are the *in vitro-in vivo* correlation and the *in vitro* dissolution specifications for the pharmaceutical formulation acceptable?

It was shown that MPH administered as the 20 mg MPH HCl extended release formulation

1. Gives a plasma concentration-time profile that is characterized by a sharp initial increase (immediate release portion) followed by a prolonged absorption (t_{max} about 5 h)
2. Is influenced by concomitant food intake (C_{max} increased by 30%, AUC by 17%, and t_{max} prolonged by about 1 hour under fed conditions)
3. Shows dose proportional increases in C_{max} and AUC after repeated doses in children with ADHD (20 and 40 mg/day) without any indication of dose dumping
4. Shows minimal accumulation after repeated doses in children with ADHD (C_{min} about 1 ng/mL after 40 mg qd for 7 days)
5. Shows similar efficacy (SKAMP and CLAM ratings) after daily doses of 20 mg or 40 mg compared to 10 mg IR tablets administered b.i.d. (20 mg/day) that could not be correlated to plasma MPH concentrations

The *in vitro-in vivo* correlation (IVIVC) of the extended release formulation was not found acceptable. It was also shown that MPH does not inhibit cytochrome P450 isoenzymes *in vitro* at concentrations corresponding to therapeutic levels.

In conclusion, the characterization of the pharmacokinetics of MPH administered as the 20 mg MPH HCl extended release formulation was found to be acceptable. Revisions of the proposed label and *in vitro* dissolution specifications are recommended.

TABLE OF CONTENTS

BACKGROUND

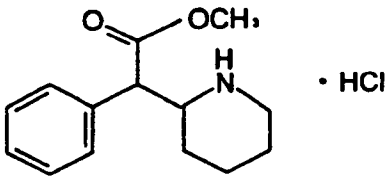
The racemic *d,l-threo*-methylphenidate hydrochloride (*d,l*-MPH) has been marketed in the US since 1955 for various indications, and is currently marketed for treatment of attention deficit/ hyperactivity disorders (ADHD) and narcolepsy, in daily doses up to 60 mg as immediate and sustained release formulations. The sustained release formulation (Ritalin® SR) has been reported to have shorter duration of action than the immediate release formulations dosed twice or three times daily. The sponsor, Medeva, has two generic extended release formulations (Metadate ER 10 and 20 mg tablets) approved, that were shown to be bioequivalent to Ritalin® SR tablets.

Medeva has submitted an NDA for MPH HCl as a modified release formulation (20 mg) that consists of immediate-release beads (30%, 6 mg) and extended-release beads (70%, 14 mg) in a capsule. The sponsor is seeking approval of this dosage form based on one pivotal placebo-controlled efficacy and safety study in children (active treatment 20-60 mg/daily; n=155). Further, the sponsor has provided four supportive clinical pharmacology studies and is seeking approval of an *in vitro-in vivo* correlation (IVIVC) for the pharmaceutical formulation.

The currently proposed trade name, Metadate™ apsules, where denotes Modified Release, is not acceptable according to new Office of Post-Marketing Drug Risk Assessment (OPDRA). Since an acceptable trade name is not yet available, Metadat capsules, or parts of the name, are used in the present review.

Methylphenidate (MPH)

Methylphenidate (MPH), the methyl ester of α-phenyl-2-piperidineacetic acid, is a sympathomimetic agent classified as a mild CNS stimulant. MPH is a racemic mixture. The *d*-MPH is active whereas *l*-MPH is pharmacologically inactive.



[$C_{14}H_{19}NO_2$ HCl; mw: 269.77; freely soluble in water and methanol, soluble in alcohol, slightly soluble in chloroform and acetone]

While the mechanism of therapeutic efficacy in ADHD is uncertain, a number of neurotransmitter systems are altered by both acute and chronic MPH administration. In addition, MPH has been reported to affect endocrine, metabolic, and cardiovascular function in laboratory animals. Although MPH undergoes extensive metabolism, the pharmacological action of MPH in humans is attributed to the parent compound.

Basic Pharmacokinetic Properties of MPH (literature data)

Absorption of racemic methylphenidate (MPH) is rapid and almost complete. Following oral administration of 40 mg of *d,l-threo*-MPH, the peak plasma concentration of *d*-MPH is approximately 18 ng/mL which is almost 6 fold higher than *l*-MPH. The t_{max} of MPH following oral administration is between 1 to 3 hours. The absolute bioavailability of *d*- and *l*-MPH is 22 ± 8% and 5 ± 3%, respectively.

The volume of distribution at steady state for *d*- and *l*-MPH following 10 mg *d,l*-threo-MPH i.v. dose in healthy volunteers is 2.65 ± 1.1 L/kg and 1.80 ± 0.91 L/kg, respectively. The plasma protein binding of MPH is 15%.

The predominant metabolic pathway of MPH is de-esterification to form the corresponding carboxylic acid metabolite, alpha-phenyl-2-piperidineacetic acid (PPA), also called ritalinic acid. After oral administration of MPH, about 90% of the radioactivity is recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose. PPA is pharmacologically inactive, and does not cross the blood-brain-barrier and has no CNS activity.

The systemic clearance of *d*- and *l*-MPH is 0.4 ± 0.12 and 0.73 ± 0.28 L/hr/kg. The half-life of *d*- and *l*-MPH is 6 ± 1.7 and 3.6 ± 1.1 hours, respectively.

The pharmacokinetics of MPH in children are comparable with those of adults. Gender has no effect on the pharmacokinetics of MPH. The effect of renal and hepatic impairment on the pharmacokinetics of MPH has not been established.

1. RELATIVE BIOAVAILABILITY/BIOEQUIVALENCE

The pharmacokinetics of the commercially intended MR capsule formulation, and two other test formulations of 25 mg methylphenidate were compared to the two commercially available formulations of Ritalin®. [Study #1]. This was a single dose, randomized, 6-way cross-over study in healthy adult volunteers (18-50 years). Twenty-two subjects were enrolled, and 18 subjects (10M/8F) completed all periods of the study.

The three test formulations consisted of different ratios of immediate release (IR) and extended release (ER) encapsulated beads. The different ratios of beads that were investigated were a slow release pattern (IR:ER), intermediate release pattern (30:70 IR:ER) and more rapid release pattern IR:ER). The commercially available formulations were the immediate release (IR) tablet, given as a single 10 mg dose and 10 mg at 0 and 4 h after the first dose (1x10 mg at 8 a.m. and 12 noon, tot. 20 mg), and the sustained release (SR) tablet, given as a single dose of 20 mg. All test formulations had a slower *in vitro* release profile than the Ritalin-SR formulation, with ≤85% released at 12 h, compared to 100% at 12 h for the Ritalin SR formulation. These aspects are described in Section 10 (*in vitro-in vivo* correlation). All formulations were administered in the morning, after an over-night fast. Frequent blood samples were collected up to 24 h post-dose. The samples were analyzed by ? or further details regarding the bioanalytical assay, see Section 7.

The resulting mean plasma concentration-time profiles are shown in Figure 1.1.

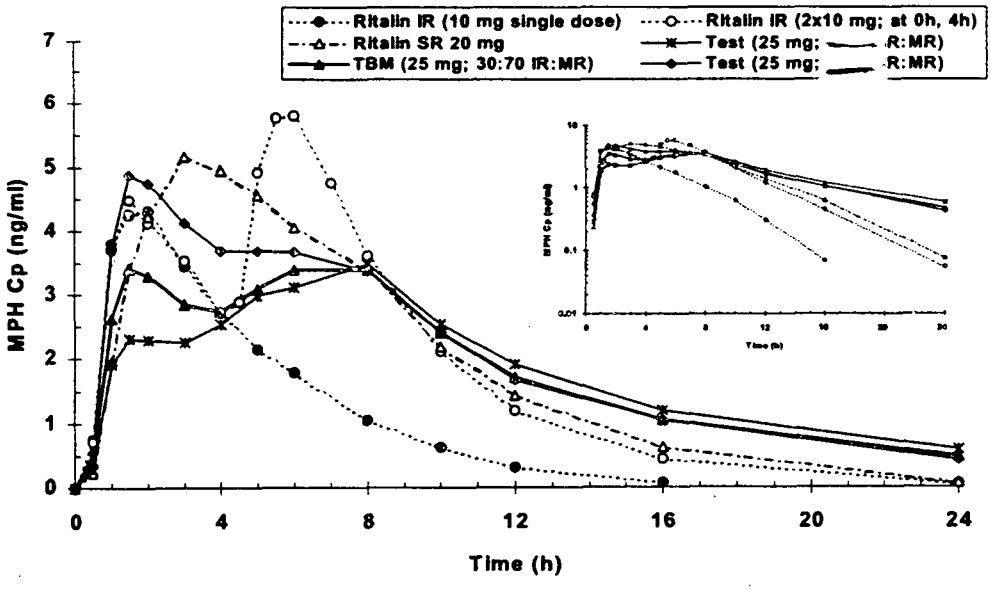


FIGURE 1.1 Mean methylphenidate plasma concentrations after single, oral doses of three test formulations of the MR capsule (25 mg), Ritalin (10 mg as a single dose or at 0 and 4 h), and Ritalin-SR (20 mg). The to-be-marketed (TBM) formulation is indicated by a thicker, solid line. The small insert shows the corresponding log-linear MPH plasma-concentration *vs.* time curve. Actual values are shown (not adjusted for different doses).

The pharmacokinetic parameters after administration of the test formulation with an intermediate release pattern (MR capsule 30:70 IR:ER beads), the Ritalin IR (at 0 and 4 h), and Ritalin-SR

formulations are shown in Table 1.1. The variability (coefficient of variation) of AUC and C_{max} was rather high, about 40%, for all treatments. The pharmacokinetic parameters for the other two test formulations are given in Appendix 2, Study #1.

TABLE 1.1 Pharmacokinetic parameters (mean ± SD) after a single, oral dose of the commercially intended MR capsule (25 mg; 30:70 IR:ER beads), Ritalin (10 mg at 0 and 4 h), and Ritalin-SR (20 mg). The AUC and C_{max} values are not adjusted for differences in dose.

Parameter	MR capsule (25 mg) n=19	Ritalin (10 mg at 0 and 4 h) n=20	Ritalin-SR (20 mg) n=19
C_{max} (ng/mL)	3.94 ± 1.61	6.38 ± 2.38	5.53 ± 2.38
t_{max} (h)	4.1 ± 2.8	5.2 ± 1.4	3.2 ± 1.1
AUC_{0-24h} (ng.h/mL)	44.1 ± 19.7	43.8 ± 18.0	44.7 ± 21.3
$AUC_{0-\infty}$ (ng.h/mL)	49.9 ± 22.7	45.8 ± 18.2	47.2 ± 22.0
C_{24h}* (ng/mL)	0.49 ± 0.35	0.06 ± 0.13	0.08 ± 0.16
t½ (h)	6.8 ± 1.5	2.9 ± 0.8	3.4 ± 0.7

*Methylphenidate plasma concentration 24 h post-dose

The MPH plasma concentrations were higher for the MR capsules compared to the Ritalin formulations after 24 h post-dose, as shown in Figure 1.1. The t½ was longer (6.8 h) after the administration of the MR capsule compared to the Ritalin formulations (approximately t½ 3 h after IR at 0 and 4 h and SR), indicating that absorption process is (in part) reflected in the terminal decline of the plasma concentration *vs.* time curve. This indicates that the absorption of the MR capsule (ER beads) is prolonged compared to the Ritalin formulations.

The pharmacokinetics of MPH were similar between female and male subjects.

The 90% confidence intervals, including the point estimates following an ANOVA analysis, for AUC and C_{max} (log-transformed values) for the MR capsule (test) with intermediate release pattern (30:70 IR:ER beads) with the Ritalin-SR and IR formulations (reference), are given in Table 1.2.

TABLE 1.2 Point estimates and 90% confidence intervals for Cmax and AUC for one test formulation and the reference formulations. The test formulation is the MR capsule with intermediate release profile and the reference formulations are commercially available extended (SR) and immediate (IR) Ritalin formulations. The AUC and C_{max} values were not adjusted for differences in dose when constructing the intervals.

	90% confidence intervals (ANOVA)	
Comparison	Point estimate (%)	Lower Limit-Upper Limit (%)
C_{max}		
25 mg MR (30:70) *vs.* 20 mg Ritalin-SR	72.2	62.4 – 82.1
25 mg MR (30:70) *vs.* 2x10 mg Ritalin IR	62.6	57.3 – 68.4
$AUC_{0-\infty}$		
25 mg MR (30:70) *vs.* 20 mg Ritalin-SR	109.9	103.3 – 117.0
25 mg MR (30:70) *vs.* 2x10 mg Ritalin IR	110.8	104.2 – 117.9

As shown in Table 1.2, the MR capsule (30:70 IR:ER beads; test) was not bioequivalent to the Ritalin preparations (reference) with regard to C_{max}. Also, the MR capsule contained 25 mg, i.e., a

25% higher dose than the Ritalin formulations, but this was not reflected in a correspondingly higher AUC. It should be noted that the 90% confidence intervals were calculated from parameters that were unadjusted for a higher dose. In fact, the point estimates of the confidence intervals were only 9-10% higher than the Ritalin formulations, indicating that the MR capsule is not bioequivalent to the Ritalin immediate release or the sustained release formulations.

Comments

The MR capsule (30:70 IR:ER beads; test) was not bioequivalent to the Ritalin preparations (reference) with regard to C_{max}. Also, the 25% higher dose content compared to the Ritalin formulations, was not reflected in a correspondingly higher AUC. The sponsor states that absorption of methylphenidate ceases after 12 h, and that 15% less drug is delivered *in vivo* with the slower releasing MR capsule. The explanation is supported by *in vitro* dissolution data according to the sponsor, where the MR capsule has a —— lissolution at 12 h, compared to the Ritalin preparations, that has been shown to have an *in vitro* dissolution of —— at 12 hours. The reviewer disagrees with this conclusion, since the difference in terminal t½ between the test and reference formulations indicates that absorption of MPH is ongoing also after 12 h post-dose. The AUC values do indicate that the MR capsule delivers less drug compared to the Ritalin tablets. The cause of the lower *in vivo* MPH exposure (AUC) may reside with sub-optimal release of drug from the ER beads.

The plasma concentrations 24 h after dose intake were higher (mean 0.5 ng/mL) for the MR capsule (30:70 IR:ER beads) compared to the Ritalin-SR formulation (0.1 ng/mL). However, accumulation of MPH above these low levels is unlikely, and therefore not considered important for the clinical effects.

The MR capsule (30:70 IR:ER beads) was selected as the formulation intended for commercial purposes, and a 20 mg MR capsule, a 25% lower dose than in this study, was used throughout the drug development program.

2. FOOD EFFECT

The effect of high fat meal (FDA breakfast, approx. 1000 kcal) on the pharmacokinetics of MPH was evaluated following an oral single dose of 2 x 20 mg of the to-be-marketed MR capsule (30:70 IR:ER beads) given to adult healthy volunteers (11 M/7 F, 20-50 years of age) [Study #2].

Plasma samples for MPH analysis were collected pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 14 and 24 h after dose intake. The samples were analyzed by a validated ———— ———— For further details regarding the analytical assay, see Section 7.

The mean plasma concentration – time curves during fasting and fed conditions are shown in Figure 2.1.

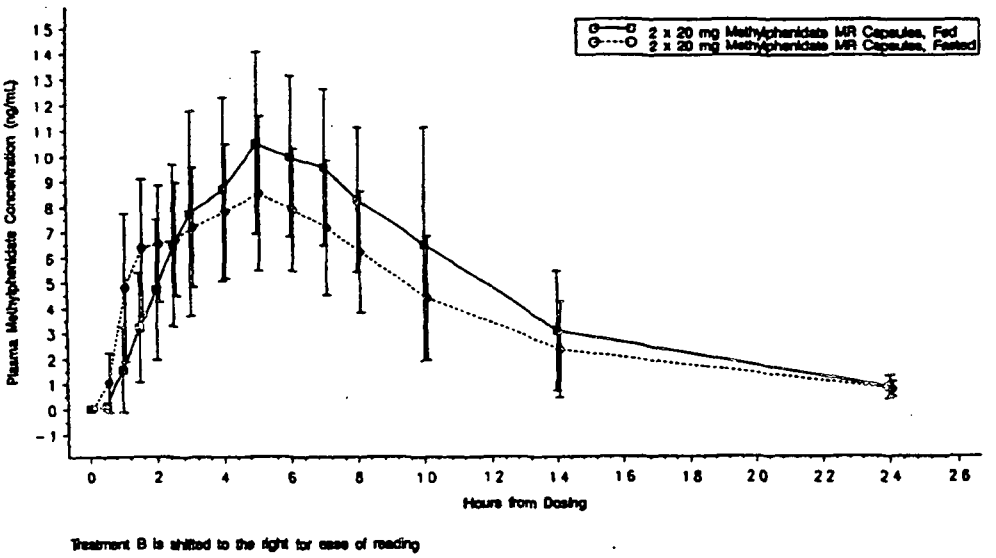


FIGURE 2.1 Mean ± SD methylphenidate plasma concentrations after an oral, single dose of 40 mg (2 x 20 mg) of the to-be-marketed MR capsule during fasting and fed conditions (n=18; dashed line = fasting; solid line = fed).

Overall, food increased the C_{max} of the to-be-marketed MR formulation by 30% and AUC by 17% (point estimates of the ratio of C_{max}). The t_{max} was prolonged approximately by an hour under fed conditions. Figure 2.2 shows the individual changes of C_{max} and t_{max} after an over-night fast and after a high-fat breakfast. There was no clear difference between male and female adult subjects.

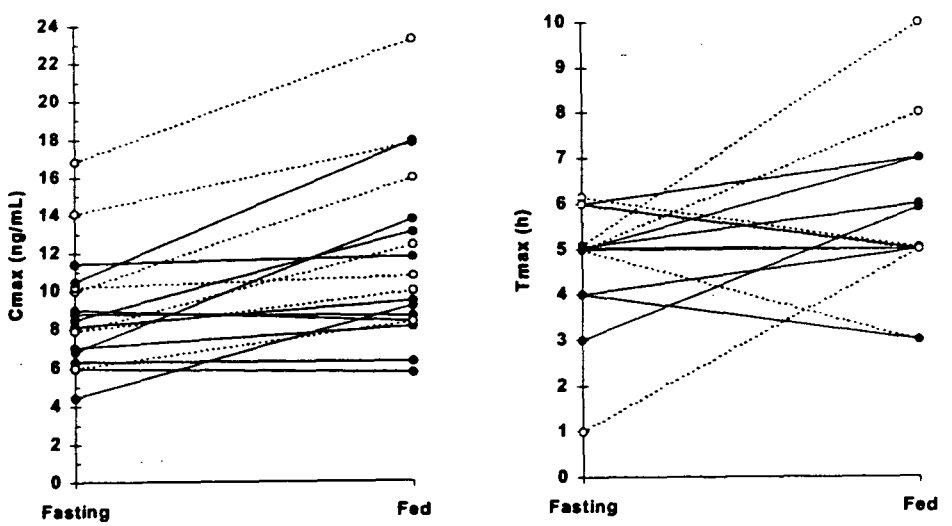


FIGURE 2.2 Methylphenidate C_{max} and t_{max} after an oral, single dose of 40 mg (2 x 20 mg) of the to-be-marketed MR capsule during fasting and fed conditions (n=18; dashed lines, open symbols = females; solid lines, filled symbols = males).

The pharmacokinetic parameters are shown in Table 2.1.

TABLE 2.1 Pharmacokinetic parameters of *d-threo*-MPH after a single dose of 30:70 IR:ER MR formulation (racemic MPH) under fed and fasting conditions.

Parameter	Fasting (2x20 mg) Mean ± SD (range: min-max)	Fed (2x20 mg) Mean ± SD (range: min-max)	90% Confidence Interval* (fasting as reference) Point estimate (upper – lower limit)
n	18	18	
C_{max} (ng/mL)	8.9 ± 3.0 (4.4 – 16.8)	11.7 ± 4.6 (5.7 – 23.3)	132.3 (119.6 – 144.6)
t_{max} (h)	4.8 ± 1.2 (1.0 – 6.15)	5.7 ± 1.7 (3.0 – 10.0)	
AUC $_{0-inf}$ (ng*h/mL)	99.7 ± 41.3 (57.0 – 230.3)	116.5 ± 48.0 (65.6 – 263.6)	116.8 (111.1-122.4)

*Based on log-transformed parameters

Comments

The study results indicate that concomitant food intake influences the rate of absorption, which may alter effect of the immediate release (IR) component of the MR formulation. The changes in time to peak plasma concentrations were variable in the studied population. The t_{max} was increased by ≥1 h (maximal increase 5 h) in nine subjects, and was unchanged or shorter (maximal decrease 2 h) in the other 9 subjects. Since the rapid, initial increase in MPH plasma concentrations resulting from the IR beads of the formulation is considered essential for the overall effect of this formulation intended for an o.d. dosing regimen, concomitant food intake should be avoided due to the variability. However, the AUCs' were similar during fasting and fed conditions, within bioequivalence criteria, during fed and fasting conditions, which ensures that the total exposure to MPH is not influenced by food.

3. DOSE PROPORTIONALITY

The active isomer, *d*-methylphenidate (MPH) HCl dose linearity was investigated in 12 healthy, male volunteers, following single dose of 10, 20, 30, 40, and 60 mg *d,l-threo*-MPH HCl. [Study #3]. The subjects also received 5, 10, 15, 20 and 30 mg doses of the single enantiomer, *d-threo*-MPH HCl. The age of the subjects ranged from 20 to 42 years (mean 28 years). The subjects received MPH as an oral solution (racemate or single isomer) after an overnight fast. Two subjects did not complete the study. Plasma samples were collected up to 24 h post-dose, and concentrations of the active moiety, *d*-MPH were measured in plasma. For further details regarding the analytical assay, see Section 7. The study indicated that *d*-MPH is linear over the dose range of 10 to 60 mg when given as *d,l-threo*-MPH HCl, and linearity was also demonstrated over the dose range of 5 to 30 mg when given as *d*-MPH HCl. Figure 3.1 depicts AUC *vs.* dose. A similar relationship was observed for C_{max} *vs.* dose.

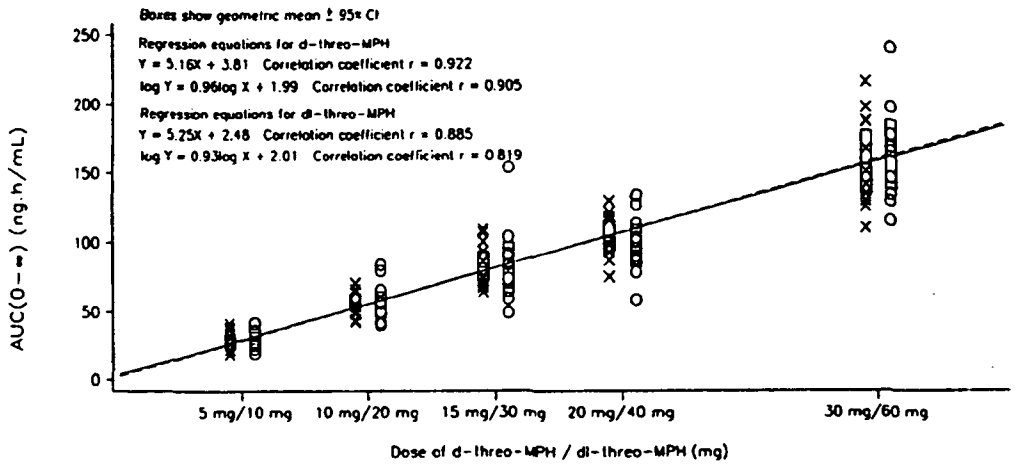


FIGURE 3.1 Methylphenidate $AUC_{0\text{-}inf}$ *vs.* dose. Oral doses of MPH as a solution were administered as *d-threo*-MPH (x) or as the racemate, *d,l-threo*-MPH (o) to 10 healthy, male volunteers.

The pharmacokinetic parameters after single doses of the racemic MPH are shown in Table 3.1.

TABLE 3.1 Pharmacokinetic parameters (arithmetic mean ± SD) of *d*-MPH (active enantiomer) following single doses of 10, 20, 30, 40, and 60 mg *d,l-threo*-MPH HCl (racemate) as an oral solution.

Parameters	10 mg	20 mg	30 mg	40 mg	60 mg
***d*-MPH:**					
No. of subjects	10	11	11	11	10
C_{max} (ng/mL)	6.2 ± 1.5	11.1 ± 3.3	17.0 ± 6.3	19.2 ± 4.4	33.9 ± 14.6
t_{max} (h)	1.5 ± 0.3	1.5 ± 0.4	1.9 ± 0.9	2.0 ± 0.8	1.6 ± 0.4
t½ (h)	3.2 ± 1.0	2.9 ± 0.6	2.7 ± 0.5	2.6 ± 0.5	2.8 ± 0.5
$AUC_{(0\text{-}24h)}$ (ng*h/mL)	22.1 ± 5.7	48.1 ± 14.9	78.4 ± 27.5	90.4 ± 20.3	153.6 ± 34.2
$AUC_{(0\text{-}inf)}$ (ng*h/mL)	30.0 ± 7.9	55.4 ± 15.3	85.0 ± 27.7	98.2 ± 21.7	164.3 ± 36.5

The other enantiomer, *l-threo*-MPH, was only quantifiable in plasma up to 3 h post-dose after administration of *d,l-threo*-MPH HCl (racemate), as an oral solution. Therefore, no pharmacokinetic parameters were calculated for the inactive isomer.

Comments

The pharmacokinetics of *d*-MPH were linear for oral doses of 10-60 mg of the racemic MPH as a solution. However, the sponsor has not performed the study with the MR capsule, i.e. the formulation that this NDA submission concerns. It has not been shown that the 20 mg MR capsule shows proportional increases in AUC and C_{max} up to the highest dose of the proposed dose range in the sponsor's label (20-60 mg). The AUC and C_{max} showed dose-proportional increases between 20 and 40 mg for the MR formulation intended for commercial use (see Section 4, multiple dose in this review). The doses in the proposed label have been used in the phase III clinical study where the to-be-marketed 20 mg MPH MR capsule (30:70 IR:ER beads) was used in the dose range of 20-60 mg/day.

Further, cross-study comparisons indicate that the MR capsule is approximately 100% bioavailable (Study #2, fasting, 2x20 mg) compared to oral solution. Hence, the linearity information generated using oral solution can be extrapolated to the MR capsule.

4. MULTIPLE DOSE

A double-blind, randomized, multiple dose study was conducted in 25 children with ADHD (21 males and 4 females; age = 7-12 years, mean 10 ± 1.4 years) [Study #4]. Study #4 is also described in Section 5, Pharmacodynamics. 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, and the second contained a ratio of 30:70 IR:ER beads.

After screening visits to determine eligibility, qualified subjects entered into the trial that consisted of two stages. In Stage I, one-week regimens of encapsulated 10 mg of MPH IR tablets b.i.d. (dose intake after breakfast and lunch) and placebo b.i.d. were compared in a randomized, balanced crossover design. 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 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).

Blood samples for plasma analysis of MPH were collected on Day 7, the last day, of each of the four 1-week study periods, at 0, 0.5, 1.5, 2, 3, 4.5, 6, 7.5 and 9 h after the morning dose. For further details regarding the analytical assay, see Section 7.

The pharmacokinetic evaluation was performed on data from subjects assigned to a modified-intent-to-treat (MITT) population, and also on data from subjects assigned to in a per protocol (PP) population. The MITT population includes a subset of patients who had efficacy evaluations for all four sessions (n=22). The per protocol (PP) population for the pharmacokinetic evaluation included the subset of MITT patients and who were not identified as placebo responders in Stage I, and had plasma MPH concentration data from the four sessions.

The mean plasma concentration-time curves of MPH after the different treatments are shown in Figure 4.1.

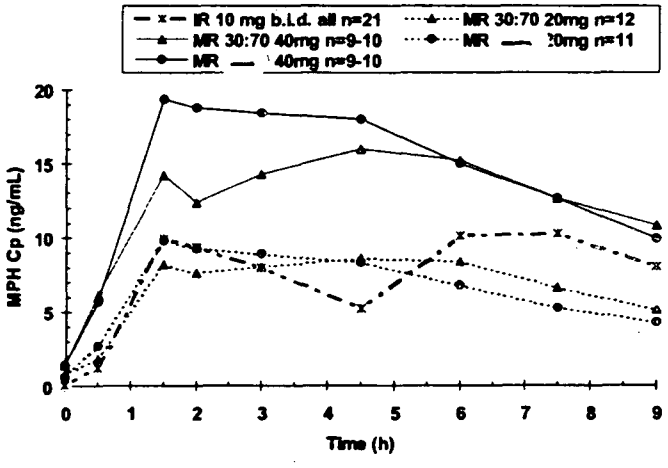


FIGURE 4.1. Mean MPH plasma concentration-time curves on Day 7 after once daily (MR capsules, 20 or 40 mg q.d.) or twice daily (10 mg IR tablets at 0 and 4 h) repeated doses of MPH in children with ADHD. Doses are administered after meal intake.

The pharmacokinetic parameters after repeated doses of 20 and 40 mg doses of the 30:70 IR:ER capsules and the 2x10 mg IR tablets (administered at 0 and 4 h) on Day 7 are shown in Table 4.1.

TABLE 4.1 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**	**40 mg**
No. Patients:			
MITT pop.	19-20	12	9
PP pop.	*13-14*	*10*	*5*
C_{trough}# (ng/mL)	0.10 ± 0.15	0.76 ± 0.45	1.41 ± 1.03
	0.08 ± 0.13	*0.68 ± 0.40*	*1.22 ± 1.15*
C_{max1}* (ng/mL)	10.0 ± 3.3	8.6 ± 2.6	15.4 ± 8.1
	10.2 ± 2.9	*8.3 ± 2.1*	*17.2 ± 10.3*
t_{max1}* (h)	1.9 ± 0.5	2.2 ± 0.7	1.9 ± 1.0
	1.9 ± 0.5	*2.2 ± 0.7*	*1.7 ± 1.1*
C_{max2}** (ng/mL)	11.4 ± 3.4	9.6 ± 3.8	17.0 ± 4.4
	11.9 ± 3.3	*9.5 ± 3.4*	*18.7 ± 3.3*
t_{max2}** (h)	7.2 ± 1.1	5.1 ± 1.0	5.2 ± 0.8
	6.8 ± 0.8	*5.0 ± 0.7*	*5.1 ± 0.8*
AUC_{0-9h} (ng.h/mL)	65.7 ± 21.5	63.0 ± 16.8	119.7 ± 39.6
	65.8 ± 21.5	*61.5 ± 12.4*	*138.4 ± 37.8*

*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 Day 7

As shown in Table 4.1, 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 (t_{max1}) was also comparable, indicating that the immediate release portion of the 30:70 IR:ER capsule and the IR tablet is similar in performance. The second peak (t_{max2}) 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.

Since the study was performed in the target population, children with ADHD, the number of plasma samples drawn were limited. Therefore, the terminal t½ was not calculated, since MPH plasma levels were not determined at time points beyond 9 h post-dose.

Comments
It was shown that the pharmacokinetics was linear between 20 and 40 mg for the 30:70 IR:ER MR formulation in the target population, children aged 7-12 years, with ADHD. Both the immediate release tablets and the MR capsules intended for commercial use were administered after breakfast, and the formulations gave peak concentrations at similar times after dose intake. The patients were instructed to eat breakfast prior to dose-intake, but standardization or description of the meal composition is not given. Most patients had residual MPH concentrations

in the through sample after repeated dose intake of the MR formulations. However, the through 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.

5. PHARMACODYNAMICS

One clinical study (Study #4) was conducted in patients with ADHD to evaluate the influence of two different release profiles on efficacy of MPH. The pharmacokinetics after repeated dosing in this Study #4 is described in the previous section (Section 4). 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

This was a double-blind, randomized, placebo controlled, balanced, 4-week, crossover study where 40 children aged 7-12 years, diagnosed with ADHD (1 of 3 DSM-IV criteria, and need of MPH) were to be enrolled. Twenty-seven subjects were randomized and 25 subjects (21M/4F) completed the full trial. All MPH or placebo doses were blinded; the oral dosage form was a capsule. The study was divided in two stages. After two screening visits, the patients entered Stage I, where one-week regimens of 10 mg of MPH IR b.i.d. and placebo (dose intake after breakfast and lunch) were compared. 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.

Behavioral measures, which were used to assess pharmacodynamic responses, were the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale, the PERMP (permanent products of a math test), and the Conners, Loney, and Milich questionnaire (CLAM).

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 pharmacokinetics of MPH after the different treatments was also determined during the laboratory classroom sessions. (see Section 4).

The efficacy measurements were:

1. The SKAMP 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 ten items describing classroom behavior, and each item is rated on a 7-point impairment scale (none, slight, mild, moderate, severe, very severe, or maximal). Ratings of subsets of items are averaged to provide the Deportment and Attention scores.

2. The PERMP (permanent products of a math test) was completed by the subject, which was 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 ratings were completed by the regular teacher and a parent on three 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 were averaged to provide three scores: the Conners Global Index, the Loney/Milich Inattention/Overactivity Index (I/O) and the Aggression/Defiance Index (A/D).

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. 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 did not tolerate placebo, 1 patient did not attend 1 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.

Comparisons were made between and among formulations, where 95% confidence intervals were constructed for the mean differences for the efficacy. A split-plot analysis of variance (ANOVA) was used for the SKAMP and PERMP assessments on the laboratory school days. Comparisons between means by t-test were done when analyses of variance results showed significant F-ratios.

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 5.1. Figure 5.1 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.

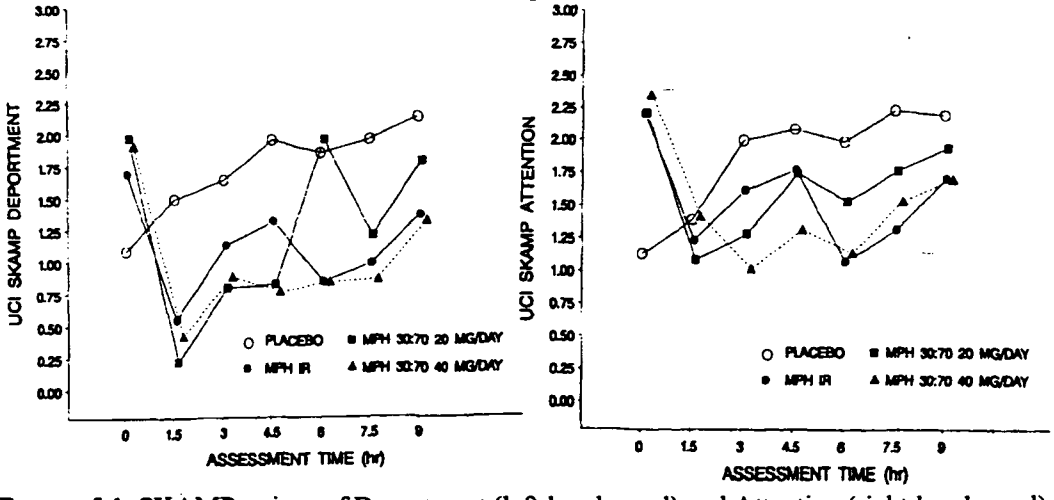


FIGURE 5.1. SKAMP ratings of Deportment (left-hand panel) and Attention (right-hand panel) on Day 7 after once daily (MR capsules, 20 or 40 mg q.d.) or twice daily (10 mg IR tablets or placebo at 0 and 4 h) repeated doses of MPH in children with ADHD. Doses are administered after meal intake.

Both MR formulations gave a statistically significant improvement ($p<0.01$) compared to placebo for the SKAMP ratings, and gave a response comparable to the 10 mg b.i.d. dose of IR tablets.

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. 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.

CLAM
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). Both MR formulations gave a statistically significant improvement ($p<0.01$) compared to placebo treatment for the CLAM ratings performed by the regular teacher.

Pharmacokinetic-pharmacodynamic (PK/PD) relationship
The relationships between the individual scores of peak SKAMP Attention *vs.* individual C_{max} values on the morning and afternoon on Day 7 after MPH doses (30:70 IR:ER MR capsule) are shown in Figure 5.2.

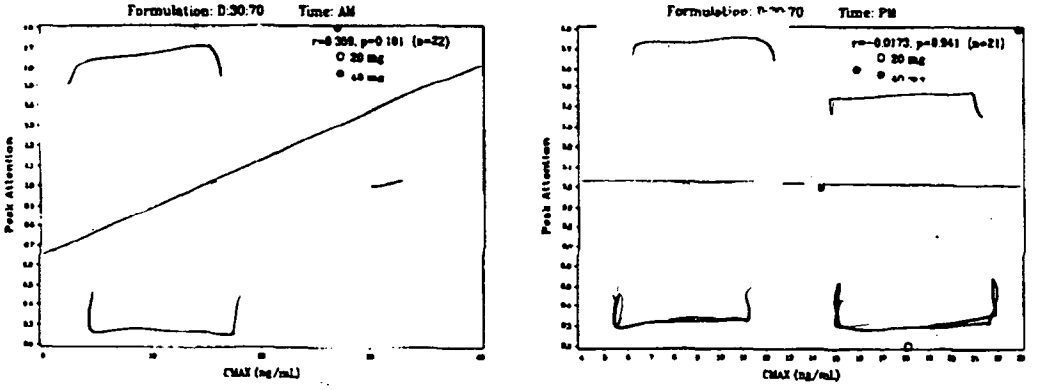


FIGURE 5.2 Individual peak SKAMP ratings of Attention vs. a.m. C_{max} (left-hand panel) and p.m. C_{max} (right-hand panel) on Day 7 after once daily repeated doses of MPH as a 30:70 IR:ER MR capsule (20 mg: unfilled circles, or 40 mg: filled circles) in children with ADHD.

The relationships between the individual scores of average SKAMP (Attention and Deportment) *vs.* individual AUC values after MPH doses (30:70 IR:ER MR capsule) are shown in Figure 5.3.

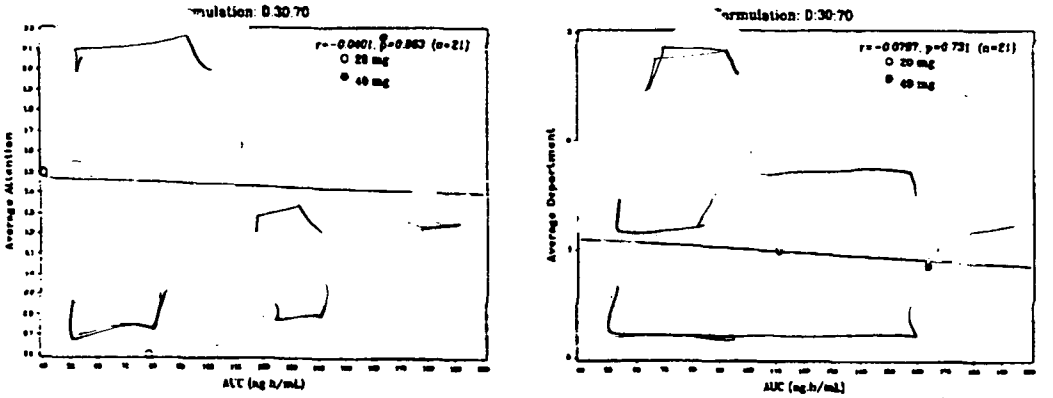


FIGURE 5.3 Individual average SKAMP ratings of Attention *vs.* AUC (left-hand panel) and Deportment *vs.* AUC (right-hand panel) on Day 7 after once daily repeated doses of MPH (30:70 IR:ER MR capsule; 20 mg: unfilled circles, or 40 mg: filled circles) in children with ADHD.

Since there was only a slight or no trend of lower scores (improvement) of the SKAMP ratings in relation to the observed AUC or C_{max} values, no attempt to model the PK/PD relationship was made.

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).

6. *IN VITRO* METABOLISM AND INHIBITION POTENTIAL

The metabolism and inhibition potential of MPH by cytochrome P450 isoenzymes were investigated *in vitro* [Studies #5 and #6].

Methylphenidate, as the racemate or the *d*-, and *l*-enantiomers, was not metabolized *in vitro* using human liver microsomes from three liver donors [Study #5].

Methylphenidate, as the racemate or the *d*-, and *l*-enantiomers, did not inhibit cytochrome P450 isoenzymes CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 at MPH concentrations up to 10 µM (23.4 ng/mL as MPH). At racemic MPH concentrations of 100 µM (234.4 ng/mL as MPH) there was a weak inhibition of CYP2C9 (19% inhibition), 2C19 (44% inhibition) and 2D6 (65% inhibition). At the same MPH concentration (100 µM) there was a <15% inhibition of CYP3A4, 2E1 and 1A2, i.e. limited inhibition was observed [Study #6].

Comments
Racemic MPH was not metabolized by cytochrome P450 isoenzymes. The weak inhibition observed on the isoenzymes CYP2C9, 2C19 and 2D6 were only observed at concentrations that exceed therapeutic MPH concentrations by more than 7-fold. The highest maximal concentration (C_{max}) observed with the 30:70 IR:ER MR formulation was 31.2 ng/mL at 0.5 h after dose intake Study #4, Subject 39, 40 mg dose). Therefore, it is unlikely that MPH would have any inhibitory potential on co-administered drugs that are metabolized by CYP isoenzymes, at therapeutic doses.

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8. DRUG FORMULATION

The 30:70 IR:ER MR (modified release) capsule in this NDA contains 20 mg of *d,l-threo*-methylphenidate, i.e. only one strength is included in the application. The hard gelatin capsules ——— contain two types of beads, immediate release (30%; 6 mg) and extended release (70%; 14 mg) beads. The final drug product will be packaged in 30 count blister cards.

Three lots of the 30:70 IR:ER MR capsule were used in clinical studies. A batch size of ——— capsules (production batch size) was used in the phase II/III trials. The details of drug formulation can be found in Study #7 in Appendix 2.

9. *IN VITRO* DISSOLUTION

The proposed *in vitro* dissolution specifications were determined under the following conditions:

Dissolution apparatus: USP Paddle Apparatus II
Rotation speed: 50 rpm
Medium and volume: Water, 500 mL
Medium Temperature: 37 ± 0.5°C

The apparatus, rotation speed and medium are according to the current USP monograph (USP 24-NF 19) for drug release tests of methylphenidate HCL extended release tablets. For the sampling procedure, two mL solution was withdrawn from vessel and filtered (70 µ Full-Flow Vankel filter), before analysis. was used for the MPH HCl analysis.

The Sponsor has set the following cumulative drug release specifications for the 20 mg 30:70 IR:ER MR (modified release) capsule (MPH HCl):

Time Intervals	Specification (% of label)
1 h	
2 h	
4 h	
8 h	
12 h	

Information regarding the influence of different pHs on the *in vitro* release profiles of the MPH HCl extended release capsules are described in Appendix 2, Study #8.

The investigations of influence of pH show that ——— is an acceptable medium for the *in vitro* dissolution test method. The dissolution specifications for the 4 h and 12 h time points should be revised, and the proposed revisions are described in Section 11, comment 3.

10. *IN VITRO-IN VIVO* CORRELATION (FORMULATION)

The Sponsor has submitted data to support an *in vitro–in vivo* correlation (IVIVC) for the methylphenidate (MPH) HCl Immediate Release:Extended Release (IR:ER) formulation (Study #9). A deconvolution method was used for calculation of the fraction absorbed drug in 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. The data used to construct the IVIVCs is shown in Table 10.1.

TABLE 10.1 Data used for the IVIVC (IR:ER formulations).

Lot# / Formulation	Strength* (mg)	Study	No. Subjects
EA 458 / 30:70 IR:ER (medium release rate)	7.5 + 17.5	MAI 1001-1 (Study # 1)	18
EA 459 / 40:60 IR:ER (fast release rate)	10 + 15	MAI 1001-1 (Study # 1)	18
EA 460 / 20:80 IR:ER (slow release rate)	5 + 20	MAI 1001-1 (Study # 1)	18
EA 542 / 30:70 IR:ER (medium release rate)	6 + 14	MAI 1001-2 (Study # 4)	12
EA 543 / 40:60 IR:ER (fast release rate)	8 + 12	MAI 1001-2 (Study # 4)	11

Data from each pharmacokinetic study was evaluated and reported as a separate IVIVC report. The *in vitro* dissolution data from each lot 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, 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, to serve as a basis for acceptance of an IVIVC.

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 lower number of capsules used in the tests 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.

In addition to the data submitted with the original NDA, the sponsor provided additional data upon request (12/27/00). The sponsor provided data regarding prediction errors between observed and predicted C_{max} and AUC, an external validation, and predictions of C_{max} and AUC by use of the IVIVC on the proposed *in vitro* dissolution specifications. A more detailed description regarding the requested data is found in Appendix 2, Study #9.

The sponsor states that an adequate level A IVIVC has been established, as shown in Figure 10.1. Figure 10.1 depicts the IVIVC where the data points from the first hour (immediate release portion) were excluded from the IVIVC.

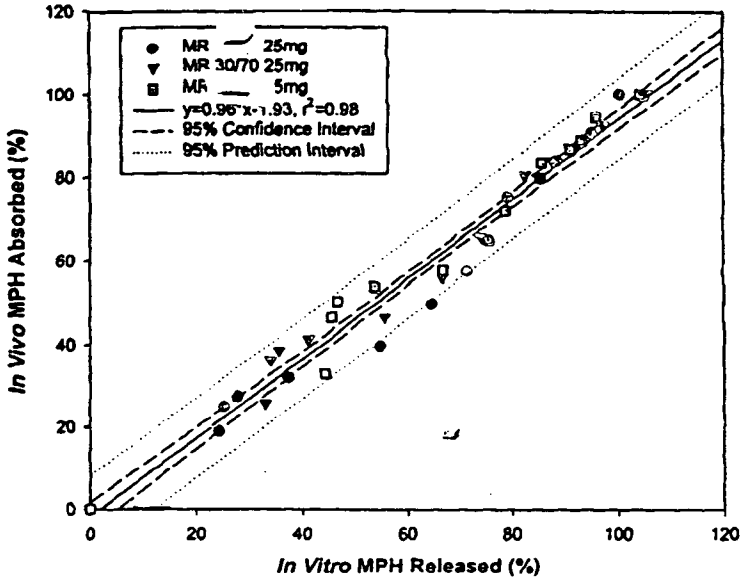


Figure 10.1 *In vitro-in vivo* correlation (IVIVC) of methylphenidate released *in vitro* (%) and absorbed *in vivo* corrected for bioavailability (%) for the MR formulations. Data points from the first hour (immediate release portion) are excluded in the IVIVC.

The internal predictability of the IVIVC, where the predicted parameters were compared to the observed C_{max} and AUC, are depicted in Table 10.2. The predictions were performed by use of the IVIVC depicted in Figure 10.1.

Table 10.2 Internal predictability of C_{max} and AUC for the MR formulations (25 mg MPH HCl)

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

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

The sponsor also performed an external predictability evaluation of the IVIVC, by use of data from Study #2 (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. AUC and C_{max} were underestimated by 17.90% and 32.5%, respectively, when the IVIVC was used in the predictions of the pharmacokinetic parameters.

The upper and lower limits of the *in vitro* dissolution specifications (Section 9) were also used to predict C_{max} and AUC, by use of the IVIVC. 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. In addition, the numerical values of the average C_{max} and AUC were about 2-fold higher, 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 results 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*.

11. OVERALL COMMENTS

The sponsor has performed four pharmacokinetic studies, three in healthy adult male and female volunteers, and one study in the intended patient population, children diagnosed with ADHD. These studies adequately characterized the pharmacokinetics of methylphenidate (MPH) after single and repeated administration of the 20 mg 30:70 IR:ER capsule. The sponsor has also shown that *d,l-threo*-methylphenidate is not metabolized by, and does not inhibit cytochrome P450 isoenzymes at therapeutic plasma drug concentrations *in vitro*.

1. The sponsor did not characterize the pharmacokinetics of the highest recommended dose 60 mg (3x20 mg 30:70 IR:ER capsule). The 40 mg (2x20 mg capsule) dose was investigated (food effects, repeated dosing in children with ADHD). A dose-proportional increase in C_{max} and AUC was established after 10-60 mg MPH as an oral solution. The 60 mg dose was used in the pivotal clinical study. The relative bioavailability of the extended release capsule and the oral solution is approximately 100% (40 mg; cross-study comparison) and the sponsor has satisfied the CFR requirement for the approval of the 20 mg ER strength. Therefore, a characterization of the pharmacokinetics of 3x20 mg is not required.

2. An *in vitro-in vivo* correlation (IVIVC) of the pharmaceutical formulation was developed, but not deemed acceptable. The external predictability yielded prediction errors that were greater than 10% for both C_{max} (PE 33%) and AUC (PE 18%) for the to-be-marketed 30:70 IR:ER formulation. The results 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. Although the internal predictability was acceptable based on the formulations with slow (—— R:ER) and medium (30:70 IR:ER) release rates, their release profiles were not sufficiently different to conclude an adequate IVIVC.

   In addition, 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.

   Since the IVIVC is not deemed to be acceptable at this point in time, this IVIVC cannot be used to justify *in vitro* dissolution specifications.

3. The following revised *in vitro* dissolution specifications are proposed for the 20 mg (*d,l-threo*-methylphenidate HCl) 30:70 IR:ER MR (modified release) capsule (unless adequate justification based on an acceptable IVIVC is provided by the sponsor):

   Dissolution apparatus: USP Paddle Apparatus II
   Rotation speed: 50 rpm
   Medium and volume: Water, 500 mL
   Medium Temperature: 37 ± 0.5°C

Time Interval	Specification (% of label)
1 h	——
2 h	——
4 h	——
8 h	——
12 h	——

The 4-hour and 12-hour time points have been revised from ——% and ——%, to ——% and ——%, respectively.

12. LABELING COMMENTS

The Sponsor is requested to make revisions to the submitted labeling. The sponsor has proposed label text based on values taken from the mean plasma concentration-time profiles. The proposed revisions are based on the arithmetic mean values from the calculated pharmacokinetic parameters from the studies.

The revised figure in the CLINICAL PHARMACOLOGY; Pharmacokinetics section is proposed to only contain data from the study in pediatric patients. The original figure contained data from too many sources, [redacted] Therefore it is advised that the [redacted] curve be not included in this figure. The methylphenidate concentrations should be depicted as arithmetic means in the graph.

The sponsor's proposed label for the CLINICAL PHARMACOLOGY; Pharmacokinetics section is shown below, including changes recommended by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

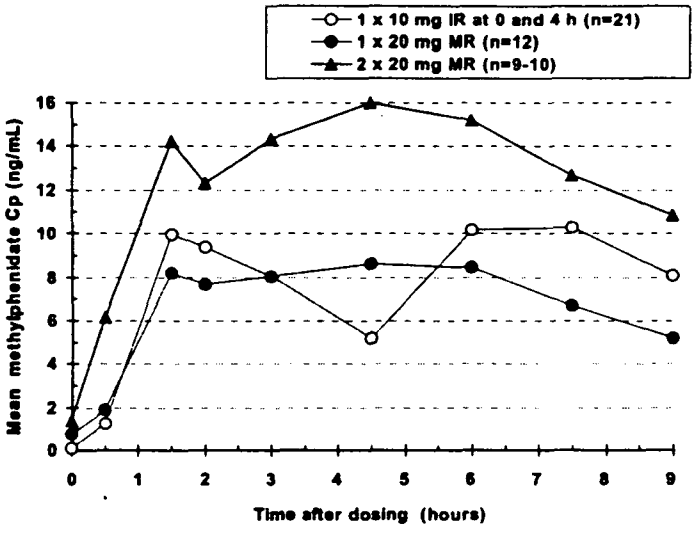
The sponsor's proposal, with revisions recommended by OCPB (~~deletions~~, **changes**):

CLINICAL PHARMACOLOGY:
Pharmacokinetics:
The pharmacokinetics of the methylphenidate hydrochloride [redacted] formulation has been studied in healthy adult volunteers and in children with attention deficit hyperactivity disorder (ADHD).

Absorption and Distribution
Methylphenidate [redacted] has a plasma/time concentration profile showing two phases of drug release with a sharp, initial slope similar to a methylphenidate immediate-release tablet, and a second rising portion approximately three hours later, followed by a gradual decline [redacted] (See figure below.)

Please exchange the figure below with the figure following immediately after this graph.

Comparison of immediate release (IR) and modified release (MR) formulations after repeated doses of methylphenidate HCl in children with ADHD



METADATE MR was administered as repeated once-daily doses of 20 mg or 40 mgto children aged 7-12 years with ADHD for one week. After a dose of 20 mg, the mean (±SD) early C_{max} was 8.6 (±2.6) ng/mL, the later Cmax was 9.6 (±3.8) ng/mL and AUC_{0-9h} was 63.0 (±16.8) ng/h.mL, respectively. The corresponding values after a 40 mg dose were 15.4 (±8.1) ng/mL, 17.0 (±4.4) ng/mL and 120 (±39.6) ng/h.mL, respectively. The early peak concentrations were reached about 2 hours after dose intake, and the second peak concentrations were reached about 5 hours after dose intake.

[ ]

The —— -mean for C_{max} and AUC following a dose of 20 mg were slightly lower than those seen with 10 mg of the immediate-release formulation, dosed at 0 and 4 hours. ——

[ ]

<u>Dose Proportionality</u>

Following a **single oral** doses of 10-60 mg **methylphenidate free base** ——**as** a solution ——— given to ten healthy **male** volunteers, **C_{max} and AUC increased proportionally with increasing doses. After the 60 mg dose, t_{max}** —— **was reached** 1.5 hours **post-dose, with** ——— **a mean C_{max} of 31.8 ng/mL (range 24.7 - 40.9 ng/mL)** ———

Following one week of repeated once-daily doses of 20 mg or 40 mg to children aged 7-12 years with ADHD, C_{max} and AUC were proportional to the administered dose.

Food Effects

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of a dose of 40 mg, the presence of food delayed the early peak **by approximately 1 hour (range –2 to 5 hours delay).** The plasma levels rose rapidly following the **food induced** delay **in absorption.**

. Overall, increased the C_{max} of by about 30% and AUC by about 17%, on average (see Dosage and Administration).

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily via de-esterification to alpha-phenyl-piperidine acetic acid (ritalinic acid). The metabolite has little or no pharmacologic activity.

***In vitro* studies showed that methylphenidate was not metabolized by cytochrome P450 isoenzymes, and did not inhibit cytochrome P450 isoenzymes at clinically observed plasma drug concentrations.**

The **mean terminal half-life ($t_{½}$)** of methylphenidate following administration of METADATE MR **($t_{½}$=6.8 h)** is slower than the **mean terminal** $t_{½}$ following administration of methylphenidate hydrochloride immediate-release tablets **($t_{½}$=2.9 h)** and methylphenidate hydrochloride sustained-release tablets **($t_{½}$=3.4 h) in healthy adult volunteers.** This suggests that the elimination process observed for METADATE MR is controlled by the release rate of methylphenidate from the release formulation, **and that the drug absorption is the rate limiting process.**

Special Populations

Gender: The pharmacokinetics of methylphenidate after a single dose of was similar between adult men and women.

Race: The influence of race on the pharmacokinetics of methylphenidate after administration has not been studied.

Age: The pharmacokinetics of methylphenidate after administration has not been studied in children less than 6 years of age.

Renal and Hepatic Insufficiency: The pharmacokinetics of methylphenidate after administration has not been studied in patients with renal or hepatic insufficiency.

13. RECOMMENDATION

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics, provided that the sponsor accepts the dissolution specifications and labeling changes.

Please forward the comments regarding the IVIVC (Overall comment no. 2, in Section 11), the revised dissolution specifications (Overall comment no. 3, in Section 11), and the labeling revisions to the Sponsor.

Maria Sunzel, Ph.D., _____

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

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics
OCPB Briefing Date: January 5, 2001
Attendees: Drs. M Mehta, C Sahajwalla, R Uppoor, G Fetterly, and S Al-Habet

c.c.: NDA 21-259, HFD-120, HFD-860 (Mehta, Uppoor, Sunzel), HFD-340 (Viswanathan), CDR (Biopharm) and FOI files (HFD-19)

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APPENDIX 2

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 (.5 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
MA1 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] [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

STUDY #1. (REPORT MAI-1001-01): COMPARISON OF MPH PHARMACOKINETICS OF THREE TEST FORMULATIONS *VS.* COMMERCIALLY AVAILABLE FORMULATIONS

Medeva Americas, Inc.
Methylphenidate Protocol MAI 1001-01

SYNOPSIS

TITLE: A Single Dose, Bioavailability Study, Comparing Five Different Formulations of Methylphenidate (Existing IR and SR Formulations, and New Modified Release Formulations)

SPONSOR: Medeva Development
Three Glenhardie Corporate Center
1265 Drummers Lane, Suite 300
Wayne, PA 19087

STUDY SITE: [redacted]

INVESTIGATOR: [redacted]

OBJECTIVES: The objective of this study was to evaluate the bioavailability of three new modified release (MR) capsule formulations of methylphenidate, compared to the marketed immediate (IR) and sustained release (SR) methylphenidate tablets, following single dose administration to healthy adult subjects.

STUDY DESIGN: The study included 6 periods of one and a half days each (9 total days of confinement) over approximately 5 weeks. The study had an open-label, randomized, six-period crossover design. Twenty-two (22) subjects were enrolled; 18 subjects completed all 6 treatments.

TREATMENTS:

A: Ritalin® 10mg IR tablets (Methylphenidate HCl)
Ciba-Geigy
Lot # 1T192333-A
Exp Date 01-May-2001

Subjects randomized to Treatment A received a single oral dose of one Ritalin® 10 mg tablet with 240 ml of room temperature tap water following a 10 hour fast.

B: Ritalin® 10 mg IR tablet (Methylphenidate HCl)
Ciba-Geigy
Lot # 1T192333-B
Exp Date 01-May-2001

Subjects randomized to Treatment B received a single oral dose of one Ritalin® 10 mg tablet with 240 ml of room temperature tap water following a 10 hour fast. The first dose was then followed 4 hours later by a second oral dose of one Ritalin® 10 mg tablet.

C: Ritalin-SR® 20 mg tablet (Methylphenidate HCl)
Ciba-Geigy
Lot # 1T193044
Exp Date 01-July-1998

Subjects randomized to Treatment C received a single oral dose of one Ritalin-SR® 20 mg tablet with 240 ml of room temperature tap water following a 10 hour fast.

D: Methylphenidate HCl 25 mg modified release capsule
—— (IR: extended release (ER))
Lot # EA-460
Exp Date n/a

Subjects randomized to Treatment D received a single oral dose of one Methylphenidate HCl 25 mg —— capsule with 240 ml of room temperature tap water following a 10 hour fast.

E: Methylphenidate HCl 25 mg modified release capsule
(30:70) (IR:ER)
Lot # EA-458
Exp Date n/a

Subjects randomized to Treatment E received a single oral dose of one Methylphenidate HCl 25 mg (30:70) capsule with 240 ml of room temperature tap water following a 10 hour fast.

F: Methylphenidate HCl 25 mg modified release capsule
—— (IR:ER)
Lot # EA-459
Exp Date n/a

Subjects randomized to Treatment F received a single oral dose of one Methylphenidate HCl 25 mg —— capsule with 240 ml of room temperature tap water following a 10 hour fast.

PK MEASURES AND METHODS: Pharmacokinetic assessments were made by measuring serial plasma methylphenidate concentrations at predose (0 hour), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours postdose. Noncompartmental pharmacokinetic parameters were calculated for each subject and treatment. Differences between concentration profiles were discussed. Parameter values of C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, K_{el}, $T_{1/2el}$, and T_{max} were also compared between treatments.

Study #1 cont.

Medeva Americas, Inc.
Methylphenidate Protocol MAI 1001-01

RESULTS: The pharmacokinetic parameters for each treatment are summarized in the following tables:

Mean Methylphenidate Pharmacokinetic Parameters, Treatments A, B and C

Pharmacokinetic Parameters	Treatment A Arithmetic Mean (SD)	Treatment B Arithmetic Mean (SD)	Treatment C Arithmetic Mean (SD)
C_{max} (ng/ml)	4.82 (1.83)	6.38 (2.38)	5.53 (2.38)
T_{max} (hr)	1.9 (1.0)	5.2 (1.4)	3.2 (1.1)
AUC_{0-t} (ng*hr/ml)	22.5 (9.45)	43.8 (18.0)	44.7 (21.3)
$AUC_{0-\infty}$ (ng*hr/ml)	24.3 (9.62)	45.8 (18.2)	47.2 (22.0)
$T_{1/2el}$	2.90 (0.637)	2.93 (0.789)	3.41 (0.674)
K_{el}	0.250 (0.0558)	0.251 (0.0584)	0.212 (0.0455)

Treatment A= 1 x 10 mg Methylphenidate IR Tablet.
Treatment B= 1 x 10 mg Methylphenidate IR Tablet at 0 and 4 hours (20 mg total).
Treatment C= 1 X 20 mg Methylphenidate SR Tablet.

Mean Methylphenidate Pharmacokinetic Parameters, Treatments D, E and F

Pharmacokinetic Parameters	Treatment D Arithmetic Mean (SD)	Treatment E Arithmetic Mean (SD)	Treatment F Arithmetic Mean (SD)
C_{max} (ng/ml)	3.66 (1.33)	3.94 (1.61)	5.19 (2.12)
T_{max} (hr)	6.9 (2.2)	4.1 (2.8)	2.0 (1.5)
AUC_{0-t} (ng*hr/ml)	43.5 (17.3)	44.1 (19.7)	49.0 (21.1)
$AUC_{0-\infty}$ (ng*hr/ml)	50.8 (22.0)	49.9 (22.7)	54.9 (25.5)
$T_{1/2el}$	7.20 (1.80)	6.80 (1.53)	6.33 (2.45)
K_{el}	0.103 (0.0280)	0.108 (0.0280)	0.122 (0.0380)

Treatment D= 1 X 25 mg Methylphenidate Modified Release Capsule (mmediate Release: Extended Release).
Treatment E= 1 X 25 mg Methylphenidate Modified Release Capsule (30:70 Immediate Release: Extended Release).
Treatment F= 1 X 25 mg Methylphenidate Modified Release Capsule (mmediate Release: Extended Release).

Given the composition of the modified release dosage forms with varying fractions of IR (immediate release) and ER (extended release) formulations, a listing of both maximum plasma peak values after each treatment seems desirable. Since this type of analysis cannot be performed by non-compartmental pharmacokinetic analysis, maximum plasma levels (see following table) are listed as obtained from the mean plasma profiles (actual numbers will deviate slightly from the above tables, since no smoothing operation was employed).

Mean Methylphenidate Peak Plasma Pharmacokinetic Parameters

	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Treatment F
C_{max} 1 (ng/ml)	4.31	4.48	5.16	2.33	3.43	4.88
T_{max} 1 (hrs)	2.0	1.5	3.0	1.5	1.5	1.5
C_{max} 2 (ng/ml)	-	5.8	-	3.49	3.40	3.37*
T_{max} 2 (hrs)	-	6.0	-	8.0	8.0	8.0*

* estimated from the plasma curves with the IR portion removed.

Dose-proportionality was established for all treatment phases for both the IR and ER portions, after taking into account the fraction of the dose that had not been released from the ER portion in the modified-release formulations after 12 hours. These data were also analyzed for the fraction of the dose released between 4-8 hours.

Study #1 cont.

Medeva Americas, Inc.
Methylphenidate protocol MAI 1001-01

Table 1 Demographic Information

Sub. No.	Init.	Smoking Habits	Drop-outs	Sex	Age	Height (cm)	Weight (kg)	Frame	Race
1		15-19 CIGARETTES A DAY	1	M	42	186.0	82.0	Medium	Cauc
2		0-4 CIGARETTES A DAY	2	M	39	181.0	70.0	Medium	Cauc
3		10-14 CIGARETTES A DAY		F	38	164.0	54.0	Small	Cauc
4		5-9 CIGARETTES A DAY		M	27	185.0	89.0	Large	Cauc
5		NON-SMOKER		M	50	168.0	77.0	Large	Hisp
6		10-14 CIGARETTES A DAY		M	41	184.0	80.0	Large	Cauc
7		0-4 CIGARETTES A DAY		M	19	170.0	79.0	Large	Cauc
8		1-2 PACKS OF CIGARETTES A DAY		M	45	182.0	71.5	Medium	Cauc
9		1-2 PACKS OF CIGARETTES A DAY		M	24	184.0	78.0	Medium	Cauc
10		NON-SMOKER		F	18	163.0	67.0	Large	Cauc
11		NON-SMOKER		F	34	171.0	61.5	Medium	Cauc
12		10-14 CIGARETTES A DAY		M	31	183.0	82.5	Medium	Cauc
14		NON-SMOKER		F	38	163.0	52.0	Small	Hisp
16		5-9 CIGARETTES A DAY	16	M	29	179.0	83.0	Large	Cauc
17		NON-SMOKER		F	24	163.0	53.0	Small	Hisp
18		5-9 CIGARETTES A DAY		F	33	163.0	72.5	Large	Cauc
19		NON-SMOKER		M	22	178.0	69.5	Medium	Blck
20		5-9 CIGARETTES A DAY		M	29	178.0	66.0	Medium	Cauc
21		NON-SMOKER		M	20	178.0	67.0	Medium	Blck
22		0-4 CIGARETTES A DAY		F	20	159.0	50.5	Small	Cauc
23		NON-SMOKER		F	39	175.0	85.5	Large	Cauc
24		5-9 CIGARETTES A DAY	24	M	43	175.0	75.0	Medium	Cauc
Mean			14M/8F		32.0	174.2	71.2		
Std. Dev.					9.5	8.7	11.4		
Range:									
Minimum					18	159.0	50.5		
Maximum					50	186.0	89.0		

completed all periods:
10M/8F

Study #1 cont.

Pharmacokinetics by gender: Upper panel: Male subjects; Lower panel: Female subjects

Males		Treatment					
Parameter	Data	A	B	C	D	E	F
AUC(0-INF)	Average	25.48	48.56	51.01	53.43	53.51	57.28
	S.D.	11.37	19.56	22.92	24.13	25.22	25.48
	N	13	12	11	12	11	12
	Minimum						
	Maximum						
AUC(0-t)	Average	23.55	46.47	48.51	44.72	46.54	51.56
	S.D.	11.13	19.41	22.86	18.20	21.44	22.54
	N	13	12	11	12	11	12
	Minimum						
	Maximum						
Cmax	Average	4.51	6.35	5.59	3.59	4.09	4.96
	S.D.	1.90	2.35	2.52	1.49	1.76	1.95
	N	13	12	11	12	11	12
	Minimum						
	Maximum						
Kel	Average	0.2382	0.2313	0.1999	0.0953	0.0961	0.1126
	S.D.	0.0529	0.0576	0.0520	0.0240	0.0183	0.0271
	N	13	12	11	12	11	12
	Minimum						
	Maximum						
T1/2el	Average	3.05	3.19	3.64	7.69	7.43	6.44
	S.D.	0.69	0.88	0.74	1.87	1.30	1.33
	N	13	12	11	12	11	12
	Minimum						
	Maximum						
Tmax	Average	2.2	5.3	3.3	7.7	5.2	2.3
	S.D.	1.2	1.4	1.2	1.2	2.8	1.8
	N	13	12	11	12	11	12
	Minimum						
	Maximum						

Females		Treatment					
Parameter	Data	A	B	C	D	E	F
AUC(0-INF)	Average	22.47	41.51	41.90	46.75	44.99	51.29
	S.D.	6.03	16.18	20.87	19.21	19.35	26.65
	N	8	8	8	8	8	8
	Minimum						
	Maximum						
AUC(0-t)	Average	20.92	39.69	39.36	41.74	40.68	45.19
	S.D.	6.24	16.17	19.11	16.84	17.76	19.66
	N	8	8	8	8	8	8
	Minimum						
	Maximum						
Cmax	Average	5.33	6.41	5.44	3.76	3.75	5.53
	S.D.	1.70	2.58	2.34	1.14	1.48	2.45
	N	8	8	8	8	8	8
	Minimum						
	Maximum						
Kel	Average	0.2691	0.2813	0.2280	0.1137	0.1235	0.1358
	S.D.	0.0586	0.0480	0.0306	0.0313	0.0322	0.0488
	N	8	8	8	8	8	8
	Minimum						
	Maximum						
T1/2el	Average	2.67	2.52	3.09	6.45	5.93	6.14
	S.D.	0.50	0.39	0.42	1.49	1.41	3.66
	N	8	8	8	8	8	8
	Minimum						
	Maximum						
Tmax	Average	1.6	5.1	2.9	5.8	2.6	1.5
	S.D.	0.4	1.5	1.0	3.0	2.1	0.5
	N	8	8	8	8	8	8
	Minimum						
	Maximum						

STUDY #2. (REPORT MAI-1001-05): FED VS. FASTING CONDITIONS

Medeva Development
Methylphenidate Protocol MAI 1001-05

REPORT SYNOPSIS

TITLE:	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
SPONSOR:	Medeva Development 1265 Glenhardie Corporate Center Wayne, PA 19087
STUDY SITE:	[redacted]
INVESTIGATOR:	[redacted]
OBJECTIVE:	The objective of this study was to compare the oral bioavailability of a methylphenidate modified-release 20 mg capsule after a single 40 mg (2x20 mg) dose following a high fat meal (FDA's definition) or under fasting conditions in 18 healthy adult subjects.
STUDY DESIGN:	This Phase I study had a randomized open-label, single-dose, two-way crossover fed versus fasted design.
TREATMENTS:	A,B: Methylphenidate HCl MR 20 mg capsules (30% IR:70% ER) Manufactured for Medeva Lot No. EA-604

Subjects randomized to Treatment A received a single oral dose of two 20 mg Methylphenidate HCl MR capsules taken with 240 ml of water approximately five minutes after a high-fat breakfast.

Subjects randomized to Treatment B received a single oral dose of two 20 mg Methylphenidate HCl MR capsules taken with 240 ml of water in a fasting condition.

(NDA volume 1.36-1.39)