CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-278

MEDICAL REVIEW

COMPLETED OCT 0 5 2001

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-278 (No. 039) Submission Date: September 14, 2001
Name of Drug:	*d-threo*-methylphenidate (dexmethylphenidate) HCl; "TRADENAME" 2.5 mg, 5 mg and 10 mg tablets (immediate release)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor:	Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059
Reviewer:	Maria Sunzel, Ph.D.
Team leader:	Ramana Uppoor, Ph.D.
OCPB Division:	Pharmaceutical Evaluation 1 (HFD-860)
ORM Division:	Neuropharmacological Drug Products (HFD-120)

Sponsor's response to the Agency's Approvable Letter dated 08/21/2001

This review evaluates the sponsor's counterproposal of currently retaining the originally proposed *in vitro* dissolution specifications for the dexmethylphenidate immediate release tablets, and recommends retaining the Agency's revised dissolution specifications. The review also gives a comment to the medical reviewer regarding the sponsor's labeling proposal to increase the maximal dose from 20 mg/day to 30 mg/day, but does not address the Clinical Pharmacology section of the label, since the sponsor accepted the Agency's proposed label revisions.

***In Vitro* Dissolution Specifications**

The Agency's proposal:

In the review of NDA 21-278 (addendum dated 08/07/2001), the Office of Clinical Pharmacology & Biopharmaceutics (OCPB) found the sponsor's *in vitro* dissolution method acceptable. However, OCPB recommended a change in the dissolution specifications from Q = [ ] in 45 minutes to Q = [ ] in 30 minutes (see below).

[ ]

In the original NDA (submitted in October 2000), [ ] was the tablet manufacturer. In March 2001, the sponsor switched manufacturing sites to [ ] submitted new *in vitro* dissolution data (July 30, 2001) from recently manufactured batches at the [ ] The Agency's recommended *in vitro* dissolution specifications were based on data from both the old and new manufacturing sites.

The sponsor's new counterproposal:

The sponsor proposes to retain the sampling time of 45 min (Q = [ ] until *in vitro* dissolution data from accelerated, intermediate and long-term stability tests from the new manufacturing site [ ] is available.

The *in vitro* dissolution data from the ongoing stability tests will include a 30-min time point in addition to the 45-min time point, and this data will be included in the first Annual Report to NDA 21-278. If the *in vitro* dissolution data from the stability batches support a change to Q = [ ] at 30 min, the sponsor commits to changing the dissolution specifications in accordance with

the Agency's proposed Q = [redacted] at 30 min. In that case, the new, revised, *in vitro* dissolution specifications will be included in this first Annual Report to the NDA. For further details regarding the sponsor's proposal, see Attachment 1.

Comments - *In Vitro* Dissolution Specifications

The Office of Clinical Pharmacology & Biopharmaceutics (OCPB) maintains the recommendation of a revised *in vitro* dissolution specification of Q = [redacted] dissolved at **30 min**, and does not accept the sponsor's proposed retention of a Q = [redacted] at 45 min as an interim specification. It should be noted that the USP monograph specification of Q = [redacted] at 45 min describes the *in vitro* specifications for *d,l-threo*-methylphenidate, not for dexmethylphenidate.

The proposed Q = [redacted] dissolved at 30 min, may serve as an interim specification until the *in vitro* dissolution data is available from the accelerated, intermediate and long-term stability batches specified by the sponsor. If the specified stability batches fail to meet a Q = [redacted] at 30 minutes, the sponsor can submit the new *in vitro* dissolution data together with the revised *in vitro* dissolution specifications. A discussion regarding the potential impact on the *in vivo* performance of the tablets is requested to justify the change of the *in vitro* specification. The new data and revised *in vitro* dissolution specifications, including the justification regarding the *in vivo* performance of the change should be submitted as a supplement, at the same time as the first annual report to NDA 21-278. This supplement should be a separate submission from the annual report.

Labeling (increase in maximum daily dose)

The sponsor's labeling change (DOSAGE AND ADMINISTRATION) that increases the maximum daily dose from 20 mg/day [redacted] is not supported by any pharmacokinetic data submitted in NDA 21-278. Direct pharmacokinetic comparisons between dexmethylphenidate (*d*-MPH) and racemic methylphenidate (*d,l*-MPH) were performed in single doses up of 2.5-10 mg of *d*-MPH and 5-20 mg of *d,l*-MPH, respectively. The steady state pharmacokinetics of *d*-MPH after repeated doses of 20 mg/day (10 mg BID) were described in the NDA. A summary of the human pharmacokinetic and clinical studies (including doses) in NDA 21-278 is found in Attachment 2.

Comments – Labeling

The sponsor's labeling change (DOSAGE AND ADMINISTRATION) that increases the maximum daily dose from 20 mg/day [redacted] is not supported by the pharmacokinetic or clinical data submitted in NDA 21-278.

The pharmacokinetics of *d*-MPH were comparable to *d,l*-MPH, and C_{max} and AUC of *d*-MPH increased proportionally to dose up to 10 mg of *d*-MPH. Only very minor drug accumulation was observed after repeated doses of *d*-MPH (20 mg/day). Although it is likely that the pharmacokinetics of *d*-MPH is linear up to [redacted] this has not been demonstrated in NDA 21-278. The proposed maximum daily dose of [redacted] was not included in the clinical efficacy studies.

Therefore, we recommend that the maximum daily dose of 20 mg/day in the label be retained, since the higher dosing regimen of [redacted] is not supported by pharmacokinetic or clinical studies submitted in NDA 21-278.

Recommendation:

The sponsor's proposed *in vitro* dissolution specifications are not acceptable to the Office of Clinical Pharmacology and Biopharmaceutics, and the specifications should be maintained as Q = [redacted] at 30 min. Please forward the comments regarding the *in vitro* dissolution specifications to the sponsor.

There are no pharmacokinetic or clinical data to support the proposed label change to increase the maximum daily dose to [redacted]. Therefore we recommend that the originally proposed maximum daily dexmethylphenidate dose of 20 mg/day be retained. Please forward the comments regarding the labeling to the medical reviewer.

Maria Sunzel, Ph.D. /S/ 10/04/01

RD/FT Initialed by Ramana Uppoor, Ph.D. /S/ 10/04/01

cc: NDA 21-278, HFD-120 (Wheelous, Glass, Klein), HFD-860 (Mehta, Uppoor, Sunzel)

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

ATTACHMENT 2

Table of pharmacokinetic studies & doses in NDA-21-278 (original review dated 07/30/01, p 23):

Study No.	Population	N [M / F]	Ethnicity	Mean Age (yrs) [Range]	Design	Dose(s)
97-M-01	Children, ADHD	32[1] [32 / 0]	25 Caucasian 2 Black 3 Hispanic 2 Other	10.3 [9 - 12]	Single dose, double-blind, placebo- and active-controlled, 7-way crossover, pharmacokinetic, pharmacodynamic and safety study[1]	Placebo *d*-MPH: 2.5, 5, and 10 mg *d,l*-MPH: 5, 10, and 20 mg
d-MPH-PK-99-001	Children, ADHD	12 [8 / 4]	8 Caucasian 1 Black 2 Other 1 Hispanic	11 [7 – 16]	Single and multiple dose pharmacokinetics	First period: 10 mg single *d*-MPH dose Second period: 10 mg *d*-MPH b.i.d. for 6 ½ days
d-MPH-PK-00-001	Healthy, adult volunteers	15 [9 / 6]	14 Caucasian 1 Asian	30 [20 – 44]	Single dose, two-way crossover, bioequivalence study with and without food	Fed state: 20 mg single *d*-MPH dose Fasted state: 20 mg single *d*-MPH dose
TOTAL	–	59 [49/10]	47 Caucasian 3 Black 4 Hispanic 1 Asian 4 Other	[7 - 44]	–	–

[1] 31 patients evaluated for pharmacokinetics. Subjects received single doses of the investigational product 1 week apart, however, during the intervening time between clinic visits, they continued to be treated with racemic MPH.

Table of all clinical studies in NDA 21-278:

Study No.	Description	Drug(s) Tested/Regimen	Number of Subjects	Treatment Duration
Clinical Pharmacology Studies				
97-M-01	Single dose, double-blind, placebo and active controlled, crossover study of pk in children	Single doses of : *d*-mph: 2.5, 5, & 10 mg d,l-MPH (5,10 & 20 mg)	N=32	Single doses
PK-99-001	Single and multiple dose pk study in children	*d*-mph: 10 mg bid	N=12	6 ½ days
PK-00-001	Single dose, crossover, food effects in adults	*d*-mph: 2-single doses of 20 mg (fasting & fed)	N=15	Single doses
Placebo Controlled Studies				
97-M-02	Double-blind, pbo-controlled, 4 week study with 1 week pbo lead in	*d*-MPH: 5-20 mg/day *d,l*-MPH: 10-40 mg/day	Total: n= 132 d-MPH: n=44 d,l-MPH: n=46 placebo: n=42	4 weeks with 1 wk pbo lead in
97-M-03	A: Open label B: Withdrawal phase: 2 week placebo controlled C: Open label	A: 5-20 mg/day (titrated to effective dose) B:*d*-MPH 2.5-10 mg bid	N=89	A: 6 weeks:open label B: 2 weeks: withdrawal C: 44 weeks: open label
Open Label Studies				
97-M-04	Open-label, 1 year in children with ADHD		N=187	1 year
97-M-05	Open-label, 6 month safety study in children with ADHD		N=361	6 month

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-278	Brand Name	[redacted]
OCPB Division I	HFD-860	Generic Name	[redacted]enidate HCl
Medical Division	HFD-120	Drug Class	Centrally acting sympathomimetic
OCPB Reviewer	Maria Sunzel, Ph.D.	Indication(s)	Attention deficit/ hyper-activity disorder (ADHD)
OCPB Team Leader	Ramana Uppoor, Ph.D.	Dosage Form	Tablets (IR): 2.5, 5, 10 mg strengths
		Dosing Regimen	Start 5 mg/day, max dose 20 mg/day; b.i.d. (0 & 4 h)
Dates of Submission	Oct. 25, 2000, Jan. 12, Jan. 30, Jun. 15, Jun. 25, Jul. 10, 2001	Route of Administration	Oral
Estimated Due Date of OCPB Review	July, 2001	Sponsor	Celgene Corp
PDUFA Due Date	August 25, 2001	Priority Classification	S
Division Due Date	August 3, 2001		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	(X, in separate sections)	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	X (food)	1	1	
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	X	1+1	1+1	
multiple dose:	X	1 (also single d)	1	
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:	X (not final formulation)		X	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X (effects of primary drug		X	CYP tested (comment for information only)

Clin. Pharm. and Biopharm. information (continued)				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
Subpopulation studies -				
ethnicity:				
gender:	X		X	
pediatrics:	X		X	
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X		X	The sponsor collected PK/PD data, but no attempt to model a PK/PD relationship was made
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X		X	(comparison *d- vs d,l*-MPH)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	2	2	
(IVIVC):	Not applicable			
Bio-waiver request based on BCS				
BCS class			X	May be Class I
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X		X	
Total Number of Studies	3 (CP)+ 3 (In vitro)		3 (CP)+ 3 (In vitro)	

Brief description of NDA	This is the 1st NDA submission of the active enantiomer, *d-threo*-methylphenidate for the treatment of ADHD. The sponsor has also performed two pivotal placebo-controlled clinical trials in children with ADHD (6-17 years old; n=221). The safety of *d*-methylphenidate has been documented in open-label extensions (0.5-1 year) of the pivotal trials. In these pivotal studies the clinical trial tablets (all strengths) were used (same tablet batch used in the food effect study and the pivotal trials). The different tablet strengths are not compositionally proportional. The 2.5 mg tablet deviates more in composition than the other two tablet strengths (5 & 10 mg).

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	X	
Comments sent to firm?	X	Data requests were sent to sponsor, all requests were fulfilled (attachment not included in final review)
QBR questions (key issues to be considered)		
Other comments or information not included above	The dose proportionality study was performed with a capsule formulation of d-MPH, with a reference capsule formulation of d,l-MPH (crushed Ritalin tablets). No link (bioequivalence) was established between the capsule and the tablet formulations. All PK data relevant to the tablet formulation was determined after 10 mg doses (single and repeated doses). During the review all available data will be utilized for comparisons between capsule and tablet. The sponsor was informed that a bioequivalence study was not required between the clinical and to-be-marketed tablet formulations, since the only difference is the addition of dye to the commercial formulation. The PK information provided is somewhat limited, but sponsor was informed that if the PK is comparable between *d,l*-MPH and the single isomer, data from *d,l*-MPH can be utilized. The PK was found to be comparable. The sponsor has provided literature data for basic PK of racemic MPH, which is considered acceptable. The 2.5 mg tablet is compositionally dissimilar to the other tablets, and no PK information is available for the 2.5 (or 5) mg strength. The 5 mg is compositionally similar to the 10 mg tablet. Thus, existing data is acceptable for the 5 mg tablet. The sponsor will be contacted to discuss if any data is available for BCS classification.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-278, HFD-850 (Electronic Entry /Lee), HFD-120 (T Wheelous), HFD-860 (Uppoor, Mehta, Sahajwalla),

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-278

d-threo-methylphenidate HCl [redacted] Ritadex™); 2.5 mg, 5 mg and 10 mg tablets

Indication:	Attention Deficit/Hyperactivity Disorder (ADHD)
Sponsor:	Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059
Submission Dates:	Oct. 25 2000, Jan. 12, Jan. 30, Jun. 15, Jun. 25, Jul. 10, 2001
Reviewer:	Maria Sunzel, Ph.D.
Team leader:	Ramana Uppoor, Ph.D.

Division of Pharmaceutical Evaluation 1 (HFD-860)

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1. RECOMMENDATION

From a pharmacokinetic point of view this NDA is not acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB), until the sponsor provides dissolution data on tablets manufactured at a new site, compared to the manufacturing site provided in the NDA. Since OCPB has not received the data for the to-be-marketed formulations (see Comments) nothing can be said about the to-be-marketed product, and the dissolution specifications cannot be set at this point in time.

Therefore, only an approvable action is recommended from OCPB.

Please forward the proposed labeling revisions (page 14) to the sponsor, as appropriate.

2. COMMENT

In March 2001, the sponsor notified the FDA that the manufacturing site for the drug product filed in the original NDA [redacted] was being changed to [redacted] Therefore, comparative *in vitro* dissolution profiles for all dosage strengths have been requested for the tablets produced at the old and new sites. The sponsor intends to submit the requested data by the end of July 2001. Therefore the *in vitro* dissolution specifications of the intended commercial formulations have not been set, or included, in this review.

3. EXECUTIVE SUMMARY

The racemic *d,l-threo*-methylphenidate HCl (*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 the active enantiomer, *d-threo*-methylphenidate HCl (*d*-MPH) as immediate release (IR) tablets (2.5 mg, 5 mg and 10 mg strengths), to be given orally twice daily, as a morning and a mid-day dose, with a maximum recommended daily dose of 20 mg. This is the first submission seeking approval for the single enantiomer, *d*-MPH, for the treatment of ADHD. Dexmethylphenidate HCl is the recently assigned USAN name for this compound (correspondence 5/21/01). Throughout this review, the former name is used, i.e. *d-threo*-methylphenidate (or *d*-MPH), instead of dexmethylphenidate. The sponsor has also submitted a change in the proposed trade name on 6/25/01, where [redacted]

In March 2001, the sponsor notified the FDA that the manufacturing site for the drug product filed in the original NDA [redacted] was being changed to [redacted] Therefore, comparative *in vitro* dissolution profiles for all dosage strengths have been requested for the tablets produced at the old and new sites. It has also been communicated by the sponsor (fax 7/6/01) that Novartis is Celgene's licensee.

The sponsor has provided three supportive clinical pharmacology studies in adult volunteers and children with ADHD. It was previously agreed that if the pharmacokinetics (PK) are comparable between *d,l*-MPH and the single isomer, data from *d,l*-MPH can be utilized. The sponsor has provided literature data for basic PK of racemic MPH, which is considered acceptable. One *in vitro* inhibition (cytochrome P450) study was also submitted. The clinical parts of the NDA contain two pivotal placebo-controlled efficacy and safety studies, and two open-label safety studies in children.

The issues regarding this submission are;

- Are the pharmacokinetics of the single enantiomer *d*-MPH comparable to that of the *d*-MPH administered as the racemate?
- Does concomitant food intake influence the pharmacokinetics of *d*-MPH?
- Does *d*-MPH accumulate in the body after repeated dosing?
- Is there a sex difference in the pharmacokinetics of *d*-MPH?
- Does *d*-MPH inhibit cytochrome P450 isoenzymes *in vitro*?
- Are all tablet strengths, although not compositionally proportional, approvable?
- Are the clinical and to-be-marketed tablets similar in performance?

It was shown that *d*-MPH

1. Gives plasma concentration-time profiles after single doses (2.5, 5, 10 mg) that are similar to that of the racemate (*d,l*-MPH), with no (or minor) *in vivo* interconversion to the *l*-enantiomer
2. Shows dose proportional increases in C_{max} and AUC after single doses in children with ADHD (capsule formulation, 2.5, 5, 10 mg)
3. Is not influenced by concomitant food intake (10 mg IR to-be-marketed tablets), although t_{max} is delayed by 1 hour after concomitant food intake ($t_{max,\ fasting}$ = 1.5 h; $t_{max,\ fed}$ = 2.9 h)
4. Shows no accumulation after repeated doses in children with ADHD (10 mg IR to-be-marketed tablets b.i.d for 7 days)
5. Gives comparable mean C_{max} and AUC values in boys and girls (mean age about 10 years), but 20-35% higher mean C_{max} and 26-36% higher mean AUC values in adult female compared to adult male volunteers, after adjustment for body weight. Mean t_{max} and t½ were similar between adult males and females.
6. Does not inhibit cytochrome P450 isoenzymes *in vitro* (at concentrations 10-fold higher than therapeutic levels)
7. The tablet formulations of 2.5 mg, 5 mg and 10 mg, although not compositionally proportional, are approvable (pharmacokinetic characteristics available for the 10 mg tablet; all strengths used in efficacy trials, *in vitro* dissolution data partly available)
8. No data has been provided to show that the clinical and the to-be-marketed formulation (new site) are comparable

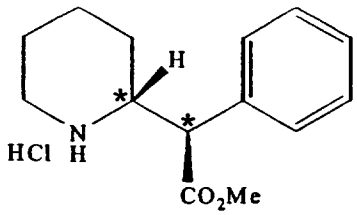
In conclusion, the characterization of the pharmacokinetics of *d*-MPH was found to be acceptable. *In vitro* dissolution specifications have not been set for the to-be-marketed tablet formulations, due to lack of data. Revisions of the proposed label are recommended.

4. INTRODUCTION, CHEMISTRY, AND PHARMACEUTICS

What are the pharmacological and chemical properties of d-MPH? What indication, dosage and administration has the sponsor included in the application? What are the pharmaceutical properties of the dosage forms?

Methylphenidate (MPH) is a sympathomimetic agent classified as a mild CNS stimulant. All currently approved formulations contain the racemic mixture of *d,l-threo*-MPH. This is the first submission seeking approval for the single enantiomer, *d-threo*-MPH HCl (USAN name: dexmethylphenidate HCl).

4.1. Chemistry



* = Asymmetric carbon centers

d-threo-MPH hydrochloride (HCl) is (R,R')-(+)-methyl-α-phenyl-2-piperidineacetate HCl, with the molecular formula $C_{14}H_{19}NO_2$ HCl; mw: 269.77; specific rotation: +88°, and is freely soluble in water and methanol, soluble in alcohol, and slightly soluble in chloroform and acetone.

4.2. Proposed mechanism of action and indication

d-threo-MPH HCl (*d*-MPH), is the more pharmacologically active enantiomer of the *d*- and *l*-enantiomers, blocks the re-uptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space. The mode of the therapeutic action is not known. The sought indication is treatment of Attention-Deficit/ Hyperactivity Disorder (ADHD) in children > 6 years of age.

4.3. Proposed dosage and administration

The proposed dosage of [redacted] is twice daily (approximately 4 h apart), once in the morning and once mid-day, and may be administered with or without food.

The dosage of *d*-MPH should be individualized. The recommended starting dose of *d*-MPH for new patients is 5 mg/day (2.5 mg BID). For patients currently using MPH, the recommended starting dose of *d*-MPH is half the dose of *d,l*-MPH. Dosage may be adjusted in 2.5 to 5 mg increments to a maximum of 20 mg/day (10 mg BID), at weekly intervals.

4.4. Formulation

The sponsor intends to market three strengths of an immediate release (IR) tablet formulation. Three different dose strengths have been used in the clinical trials supporting this NDA. Also, three different formulations were used during the development.

The first capsule formulation (Formulation 1) was only used in one early clinical pharmacology study where the pharmacokinetics of *d*-MPH were compared to the racemate, *d,l*-MPH. In most of the clinical trials, *d*-MPH was administered as an immediate release (IR) tablet (Formulation 2). The to-be-marketed drug product (Formulation 3) is identical to Formulation 2, except for the inclusion of dyes. The to-be-marketed IR tablets contain 2.5 mg, 5 mg, and 10 mg of *d*-MPH, respectively. The proposed commercial tablets contain D&C Yellow lake #10 (5 mg) and FD&C blue no 1 #5516 aluminum lake (2.5 mg), while the 10 mg tablet strength does not contain dye. It was agreed in the end-of-phase 2 CMC meeting (1/14/1998), that no *in vivo* bioequivalence testing is required to support this difference between Formulations 2 and 3 and that *in vitro* dissolution testing would suffice.

The compositions of the to-be-marketed IR tablets are depicted in Table 4.1. As shown in Table 4.1 the tablets are not compositionally proportional. Further information regarding the pharmaceutical formulations, including batch sizes, that were used in the human trials, and the compositions of Formulations 1 and 2, are included in Appendix 1.

TABLE 4.1. Composition of the 2.5 mg, 5 mg and 10 mg *d*-MPH hydrochloride tablets (Formulation 3), proposed commercial formulation (2 million tablets scale).

	2.5 mg tablet			5 mg tablet			10 mg tablet		
	% w/w	mg per tablet	kg per batch	% w/w	mg per tablet	kg per batch	% w/w	mg per tablet	kg per batch
d-threo-methylphenidate HCl									
Pregelatinized starch, NF									
Lactose monohydrate, NF									
Sodium starch glycolate, NF									
Microcrystalline cellulose, NF									
Magnesium stearate, NF									
D&C yellow lake #10									
FD&C blue no.1 #5516 aluminum lake									
Total									

[1] Not applicable

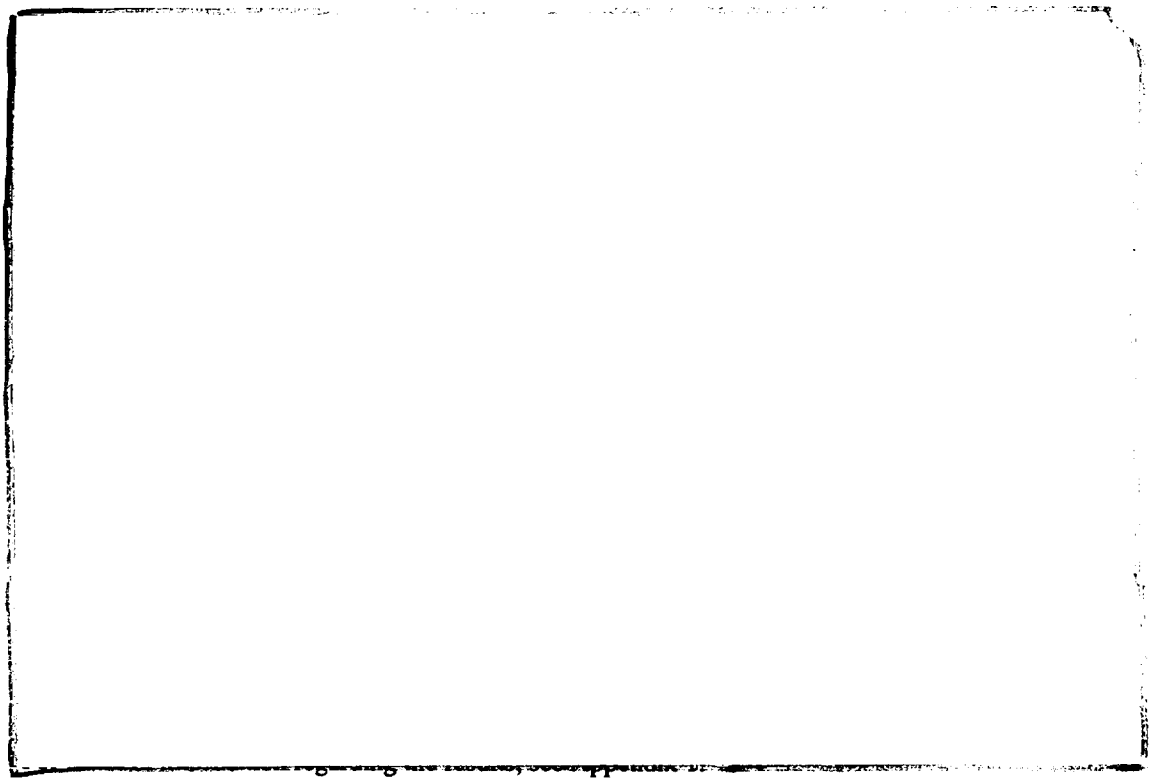
The 10 mg strength of the to-be-marketed formulation of *d*-MPH was administered in two of the pharmacokinetic trials (Studies # 3 and #4), while the lower strengths (2.5 mg and 5 mg) were only administered in the clinical efficacy studies (see Appendix 1, Tables 3 and 4).

The 2.5 mg tablet is the dosage strength that differs the most in composition, while there are less pronounced compositional differences between the 5 and 10 mg tablet strengths. In addition to the provided *in vitro* dissolution data (see Section 4.5), the to-be-marketed formulations of all tablet strengths have been used in the clinical efficacy trials (see Appendix 1), although *in vivo* pharmacokinetic data is only available after administration of the 10 mg to-be-marketed tablet.

In March 2001, the sponsor notified the FDA that the manufacturing site for the drug product (Formulations 2 and 3) filed in the original NDA was being changed to Therefore, comparative *in vitro* dissolution profiles for all dosage strengths have been requested for the tablets produced at the old and new sites. The sponsor intends to submit these comparative *in vitro* dissolution profiles for the to-be-marketed tablet strengths on July 30, 2001. Therefore the *in vitro* dissolution specifications of the intended commercial formulations have not been reviewed or approved to date.

The drug substance used for the data provided in NDA 21-278 (clinical trials and primary chemistry and stability lots) was manufactured by In agreement with FDA, the sponsor also qualified a second manufacturer (see section 4.5 Dissolution specifications). The sponsor has currently withdrawn as drug substance manufacturer.

4.5. Dissolution method



5. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

What pharmacokinetic and pharmacodynamic properties of d-MPH have been investigated? Are the bioanalytical methods that were used considered adequate?

5.1 Pharmacological effects of *d*-MPH and *d,l*-MPH in children with ADHD

The improvement of symptoms of children diagnosed with ADHD was measured according to behavioral rating scales (subjective measures), and a mathematical test (objective measure). The Conners, Loney and Milich (CLAM) rating scale is a standard scale, which measures inattention/ over-activity and aggression/defiance. The two tests were used in a double-blind study where 32 boys, 7-12 years of age, participated. The tests were performed pre-dose and 3-5 times over 8 h, after single doses (capsule formulations) of 2.5, 5, and 10 mg of *d*-MPH and equipotent doses of the racemate *d,l*-MPH (5, 10, 20 mg) [Study #3].

The dose-response relationships (math test, CLAM rating scale) were linear, parallel (e.g. equipotent with regard to *d*-MPH) and had a similar duration of effect after corresponding doses of *d*-MPH and *d,l*-MPH [Study #3].

There was a dose-related anorectic effect, where a higher degree of appetite suppression (50% reduction of food intake at lunch) was observed after the highest dose of MPH (10 or 20 mg). A similar degree of anorexia was observed after the single doses of either *d*- or *d,l*-MPH [Study #3].

An increase in systolic BP (max average +20 mmHg) and heart rate, HR, (max average +30 bpm) 0-4 h after dose intake was observed in 12 children that received 10 mg *d*-MPH (to-be-marketed

tablet) as a single dose followed by repeated daily doses for one week (10 mg BID). These increases were similar after both single and repeated doses, and corresponded to the *d*-MPH plasma concentration – time profiles [Study #4]. Comparable increases in BP and HR have been described in the literature after oral doses of *d,l*-MPH.

5.2 Absorption and distribution
Peak plasma concentrations (C_{max}) of *d*-MPH were rapidly achieved after both single and repeated doses of the to-be-marketed IR tablet (10 mg), where t_{max} was attained about 1 h after dose intake in both children an adults [Studies #2 and #4].

The plasma protein binding of MPH has been reported to be about 15% [literature data, limited method descriptions].

5.3 BCS Classification
According to the Biopharmaceutics (BCS) Guidance, waivers may be granted if a drug is classified as a Class 1 (high solubility – high permeability) substance (*Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, August 2000*).

5.4 Dose proportionality
Dose proportional increases of C_{max} and AUC of *d*-MPH were observed after single doses of 2.5, 5, and 10 mg of *d*-MPH and equipotent doses of the racemate *d,l*-MPH (5, 10, 20 mg), as shown

in Figure 5.1. The single isomer and the racemate were administered as capsule formulations in boys (age 9-12 years; n=30) diagnosed with ADHD [Study #3].

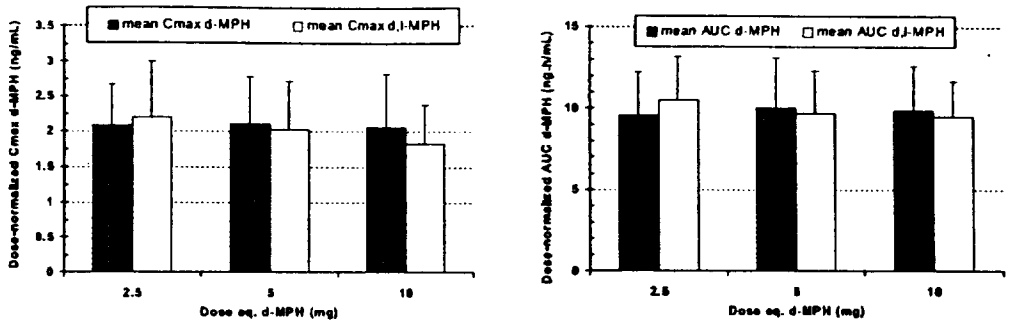


FIGURE 5.1. Dose normalized (mean + SD) C_{max} (left panel) and $AUC_{0\text{-}inf}$ (right panel) values of d-MPH after administration of the isomer, *d*-MPH (solid bars), and the racemate, *d,l*-MPH (unfilled bars). The *d,l*-MPH doses (5, 10, and 20 mg) are expressed as *d*-MPH equivalents.

A corresponding study was not performed with the to-be-marketed (TBM) immediate release (IR) tablet formulation. However, a comparison of the pharmacokinetic parameters, shows that similar values were obtained after a single dose of 10 mg as the capsule formulation and the TBM IR formulations, as shown in Table 5.1 [Studies #3 and #4].

TABLE 5.1. Pharmacokinetic parameters (mean ± SD) after single doses of 10 mg *d*-MPH as a capsule or the TBM IR tablet in children diagnosed with ADHD [Studies #3 and #4].

Parameter	**Capsule 10 mg *d*-MPH**	**TBM IR Tablet 10 mg *d*-MPH**
C_{max} **(ng/mL)**	20.6 ± 7.7 (n=30)	21.4 ± 6.5 (n=9)
t_{max} **(h)**	1.8 ± 1.3 (n=30)	1.1 ± 0.4 (n=9)
$AUC_{0\text{-}t}$ **(ng.h/mL)**	85.5 ± 29.3 (n=30)	82.4 ± 20.6 (n=9)
$AUC_{0\text{-}inf}$ **(ng.h/mL)**	98.7 ± 27.7 (n=28)	88.6 ± 20.2 (n=9)
t½ (h)	2.4 ± 0.4 (n=28)	2.3 ± 0.4 (n=9)

5.5 Food effects

There were no significant effects of concomitant food intake (high fat 'FDA breakfast') compared to the fasting state on C_{max} and AUC of *d*-MPH after a single dose of the to-be marketed IR tablet (2x10 mg; n=15 adult healthy volunteers), as shown in Figure 5.2 [Study #2]. The mean ratios (fed/fasting states) for both AUC and C_{max} of *d*-MPH (active moiety) and *d*-RA (inactive moiety) were within the 'no effect' limits 80-125% (90% CI). There was a delay in time to reach peak plasma concentrations after concomitant food intake ($t_{max,fed}$ 2.9 h, $t_{max,fasting}$ 1.5 h), that had only a slight effect on C_{max} (<5% decrease on average with food compared to the fasting state).

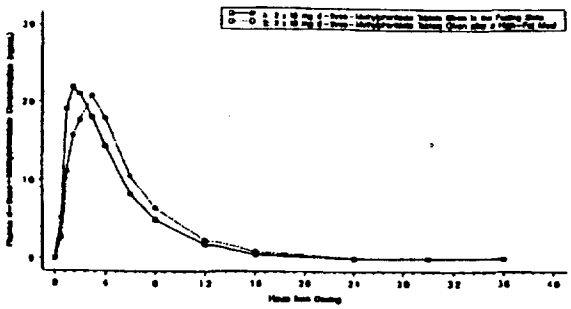


FIGURE 5.2. Mean Cp-time profiles of *d*-MPH in healthy adult subjects (n=15) after 20 mg (2x10 mg) *d*-MPH HCl in the fasting state (solid line) and after a high fat breakfast (dashed line).

The effects of food were studied in an adequate number of patients, at an adequate dose level [Study #2].

5.6 Metabolism and elimination

In humans, MPH is metabolized primarily via de-esterification to α-phenyl-piperidine acetic acid (ritalinic acid = RA). RA has little or no pharmacologic activity. The metabolism of MPH to RA has been reported to be stereospecific, where *d*- and *l*-enantiomers of MPH are converted to their respective *d*- and *l*-metabolites of RA [literature data].

No, or very minor, *in vivo* inter-conversion between enantiomers (MPH and the inactive metabolites) were observed in the three studies included in this submission, indicating that the metabolism of *d*-MPH to *d*-RA is stereospecific [Studies #2, #3, #4].

In vitro, no significant inhibition was observed on the activity of P450 CYP 1A2, 2A6, 2C19, 2D6 2E1 or 3A4 by either enantiomer or racemate of MPH. There was a 20-30% inhibition of CYP2D6 by *d*- MPH, *l*-MPH and *d,l*-MPH at the highest tested concentration (100 μM=27,000 ng/mL). The concentrations of the enantiomers and racemate of MPH were greatly above the therapeutic concentrations of MPH, with the lowest tested concentration (270 ng/mL) being about 10-fold higher than C_{max} observed after a dose of 10 mg *d*-MPH or 20 mg *d,l*-MPH (~20 ng/mL). Although the concentrations of the MPH moieties were not optimally chosen in the *in vitro* inhibition study, the reviewer agrees with the sponsor, that it is unlikely that *d*- MPH inhibits the tested P450 isoenzymes at therapeutic plasma concentrations [Study #1].

The elimination half-life, t½, of *d*-MPH was approximately 3 h, after both *d*-MPH (single and repeated doses) or *d,l*-MPH administrations (single doses) in all three studies. The t½ of *d*-MPH was also comparable after dosing with the capsule and the to-be marketed IR tablets, and in adults and children with ADHD [Studies #2, #3, #4].

The t½ of the corresponding metabolite *d*-RA was determined to be approximately 6 h in children, and about 8 h in adults. However, the t½ of *d*-RA may be similar irrespective of age, since there is a discrepancy in study designs between the studies in children and adults. In children the last plasma sample was collected at 10 h or 12 h, whereas the drug concentrations were followed up to 36 h post-dose in adults, which is likely to influence the calculations of t½ of *d*-RA.

5.7 Special populations

Gender:

The pharmacokinetics of *d*-MPH were similar between girls and boys diagnosed with ADHD after a single and repeated doses of 10 mg of the to-be-marketed IR tablet, as shown in Table 5.2 [Study #4].

TABLE 5.2. *Demographics* and pharmacokinetic parameters (mean ± SD) of *d*-MPH in girls and boys after a single dose of 10 mg (1x10 mg) and repeated doses (2x10 mg Days 2-7, PK on Day 8 a.m. dose; 1x10 mg) of *d*-MPH HCl.

Parameter	Single Dose		Repeated Doses	
	Girls (n=4)	Boys (n=5)	Girls (n=4)	Boys (n=5)
Age (years)	*9.5 ± 2.1*	*10.4 ± 2.9*	*9.5 ± 2.1*	*10.4 ± 2.9*
Height (cm)	*138.3 ± 9.8*	*146.6 ± 19.4*	*138.3 ± 9.8*	*146.6 ± 19.4*
Weight (kg)	*32.8 ± 6.5*	*40.6 ± 13.8*	*32.8 ± 6.5*	*40.6 ± 13.8*
C_{max} (ng/mL)	22.7 ± 7.8	20.4 ± 5.6	25.9 ± 10.6	24.4 ± 10.9
t_{max} (h)	1.0 ± 0.4	1.3 ± 0.4	1.2 ± 0.5	1.2 ± 0.3
AUC $_{0-t}$ (ng.h/mL)	85.2 ± 25.5	80.1 ± 18.6	90.8 ± 29.2	90.1 ± 23.1
AUC $_{0-inf}$ (ng.h/mL)	89.1 ± 26.6	88.1 ± 17.0	93.4 ± 29.3	93.6 ± 23.1
t½ (h)	2.0 ± 0.3	2.5 ± 0.4	2.1 ± 0.4	2.2 ± 0.3

Although the number of female subjects in the pediatric target population is very small, no obvious sex related differences were observed in the pharmacokinetics of *d*-MPH after single and repeated doses of *d*-MPH administered as the to-be-marketed tablet (10 mg tablet strength).

However, adult female volunteers had 20-35% higher mean C_{max} and 26-37% higher mean AUC values compared to male volunteers after adjustment for body weight, although t_{max} and t½ were comparable between adult males and females. This may indicate that adult females have a somewhat higher bioavailability of *d*-MPH compared to adult male volunteers [Study #2].

Race, age, renal and hepatic impairment:

The influence of race on the pharmacokinetics of *d*-MPH was not investigated, since there were an insufficient number of non-Caucasian subjects included in the different studies.

The potential influence of old age, renal or hepatic impairment on the pharmacokinetics of *d*-MPH was not investigated in any study in this submission.

5.8 Bioanalytical methods

Two different bioanalytical methods were used to determine the plasma concentrations of *d*- and *l*-MPH, and the metabolites, *d*-ritalinic acid (RA) and *l*-RA, in plasma.

The limits of quantitation (LOQ) and range of linearity of the calibration curves for the analytes used in the different assay methods are given in Table 5.3. For further details regarding the performance and validation of the analytical methods for the plasma samples, please refer to Appendix 2, Section #5 of this review.

TABLE 5.3. Limits of quantitation (LOQ) and range of linearity of the calibration curves for the analytes of the [redacted] assay methods used for the studies in this NDA.

Study	Method	Analyte	LOQ (ng/mL)	Linearity (ng/mL)
#3	[redacted]	*d*-MPH	0.5	[redacted]
		l-MPH	0.5	
		d-RA	10	
		l-RA	10	
#2 & #4	[redacted]	*d*-MPH	0.5	
		l-MPH	0.05	
		d-RA	5	
		l-RA	5	

The bioanalytical assays used in the different studies were found to be adequately validated.

6. COMMENT TO THE MEDICAL OFFICER

The pharmacokinetics of *d*-MPH were similar between female (n=4) and male (n=5) pediatric patients 12 years old or younger. However, adult females (n=6) had 55-76% higher C_{max} and 64-79% higher $AUC_{0\text{-}inf}$ values compared to the adult male (n=9) volunteers, during both fasting and fed conditions. After dose adjustment based on body weight (mg/kg), this difference became less pronounced with a 25%-37% increase in $AUC_{0\text{-}inf}$ and a 20%-35% increase in C_{max}. The t_{max} and t½ estimates were comparable between adult males and females. Although the difference is less pronounced after adjustment for body weight, *d*-MPH will be administered as fixed doses as currently proposed in the label, and dosing will not be based on a mg/kg basis. Therefore it is expected that adult females will have higher plasma levels than adult males, with levels that may be comparable to those observed in the present study [Study #2].

The observed finding, although based on a small number of adult females and males, has been included in the proposed revisions of the 'Pharmacokinetics/Special populations/gender' subsection.

7. LABELING RECOMMENDATIONS

The Sponsor is requested to make revisions to the submitted labeling. The complete proposed label is included in Appendix 3. The sections of the sponsor's proposed label for the CLINICAL PHARMACOLOGY; Pharmacokinetics section where changes are recommended by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) are shown below.

The sponsor's proposed label, with revisions recommended by OCPB (~~deletions~~, **changes**, [*comments*]):

PHARMACOKINETICS

Absorption

Dexmethylphenidate hydrochloride is readily [redacted] absorbed following oral administration of [redacted] In patients with ADHD, plasma dexmethylphenidate concentrations increase rapidly, reaching a maximum at about 1 to 1½ hours post-dose. No differences in the pharmacokinetics of [redacted] were noted following single and repeated twice daily dosing indicating no significant drug accumulation. [redacted]

When given **as capsules** in single doses of 2.5 mg, 5 mg, and 10 mg to children, C_{max} and $AUC_{0\text{-}inf}$ of dexmethylphenidate were proportional to dose. In the same study, plasma dexmethylphenidate levels were comparable to those achieved following single *dl-threo*-methylphenidate HCl doses given **as capsules** in twice the total mg amount (equimolar with respect to dexmethylphenidate HCl).

Food Effects

In a single dose study conducted in adults, coadministration of with a **high fat breakfast** resulted in a dexmethylphenidate t_{max} of 2.9 hours post-dose as compared to 1.5 hours post-dose when given in a fasting state. C_{max} and $AUC_{0\text{-}inf}$ were comparable in both the fasted and non-fasted states.

Distribution

Plasma dexmethylphenidate concentrations in children decline exponentially following oral administration of

Metabolism and Excretion

In humans, dexmethylphenidate is metabolized primarily to *d*-α-phenyl-piperidine acetic acid (also known as *d*-ritalinic acid) by de-esterification. This metabolite has little or no pharmacologic activity. There is little or no *in vivo* interconversion to the *l-threo*-enantiomer **minute** levels of *l-threo*-methylphenidate detectable **in a few samples** in only 2 of 58 children and adults.

After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accountable for approximately 80% of the dose.

***In vitro* studies showed that dexmethylphenidate did not inhibit cytochrome P450 isoenzymes.**

The mean plasma **elimination** half-life **of dexmethylphenidate** is approximately 2.2 hours.

Special Populations

Gender

In a single dose study conducted in adults, the mean dexmethylphenidate AUC_{0-inf} values (adjusted for body weight) following single [redacted] were 25-35% higher in adult female volunteers (n=6) compared to male volunteers (n=9). Both t_{max} and $t_{1/2}$ were comparable between the adult males and females.

Race

There is insufficient experience with the use of [redacted] to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of dexmethylphenidate after [redacted] administration have not been studied in children less than 6 years of age.

When single doses of [redacted] were given to children between the ages of 6 to 12 years and healthy adult volunteers, C_{max} of dexmethylphenidate was similar, however children showed somewhat lower AUCs compared to the adults.

Renal Insufficiency

There is no experience with the use of [redacted] in patients with renal insufficiency. After oral administration of radiolabeled racemic methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of [redacted] Since very little unchanged drug is excreted in the urine, renal insufficiency is expected to have little effect on the pharmacokinetics of [redacted]

Hepatic Insufficiency

There is no experience with the use of [redacted] in patients with hepatic insufficiency.

(Drug Interactions – refer to Precautions)
(END OF LABEL – PHARMACOKINETICS Section)

8. SIGNATURES

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: July 27, 2001
Attendees: Drs. C Sahajwalla, H Malinowski, R Uppoor and Ms. M Roychowdhury

c.c.: NDA 21-278, HFD-120 (Katz, Laughren, Glass), HFD-860 (Mehta, Sahajwalla, Uppoor, Sunzel)

APPENDIX 1: PHARMACEUTICS

Pharmaceutical formulations used in clinical trials

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Three different pharmaceutical formulations have been used in the clinical trials supporting NDA 21-278.

The first capsule formulation (Formulation 1) was only used in one early clinical pharmacology study where the pharmacokinetics of *d*-MPH was compared to the racemate, *d,l*-MPH [redacted] capsule was used, and the capsules were manufactured by [redacted]

In most of the clinical trials, *d*-MPH was administered as an immediate release (IR) tablet (Formulation 2).

The to-be-marketed drug product (Formulation 3) is identical to Formulation 2, except for the inclusion of dyes (see Table 4.1 in the summary review, Section 4.4). The proposed commercial tablets contain D&C Yellow lake #10 (5 mg) and FD&C blue no 1 #5516 aluminum lake (2.5 mg), while the 10 mg tablet strength does not contain dye. It was agreed in the end-of-phase 2 CMC meeting (1/14/1998), that no *in vivo* bioequivalence testing is required to support this difference; *in vitro* dissolution testing would suffice.

In March 2001, the sponsor notified the FDA that the manufacturing site for the drug product (Formulations 2 and 3) filed in the original NDA [redacted] was being changed to [redacted] Therefore, comparative *in vitro* dissolution profiles [redacted] for all dosage strengths have been requested for the tablets produced at the old and new sites. The sponsor intends to submit these comparative *in vitro* dissolution profiles for the to-be-marketed tablet strengths [redacted] on July 30, 2001, therefore the *in vitro* dissolution specifications have not been reviewed to date.

The composition of Formulations 1 and 2 are shown in Tables 1 and 2, respectively. The composition of Formulation 3 is included in the summary review (Table 4.1, Section 4.4).

The batch numbers, batch sizes and formulations used in the pharmacokinetic trials (covered by this review) and clinical trials in humans are summarized in Tables 3 and 4, respectively.

TABLE 1. Formulation 1: Composition of *d*-MPH capsules administered in Study # 3 (Study 97-M-01) Placebo capsules contained only anhydrous lactose.

Component	2.5 mg			5 mg			10 mg		
	% w/w	mg per capsule	g per batch[1]	% w/w	mg per capsule	g per batch[2]	% w/w	mg per capsule	g per batch[3]
d-*threo*-methylphenidate HCl	[redacted]								
Lactose Anhydrous, NF									
Fill Weight									

[1] For a batch of 2100 capsules.
[2] For a batch of 1650 capsules.
[3] For a batch of 1500 capsules.

TABLE 2. Formulation 2: Composition of *d*-MPH IR tablets

Component	2.5 mg			5 mg			10 mg		
	% w/w	mg per tablet	kg per batch[1]	% w/w	mg per tablet	kg per batch[1]	% w/w	mg per tablet	kg per batch[1]
d-*threo*-methylphenidate HCl									
Pregelatinized starch, NF									
Lactose Monohydrate, NF									
Sodium starch glycolate, NF									
Microcrystalline cellulose, NF									
Magnesium stearate, NF									
D&C yellow lake #10									
Fill Weight									

TABLE 3. Identification of the *d*-MPH formulations used in pharmacokinetic studies.

Study Number	Lot/Batch Number	Dosage Form and Strength	Batch Size	Drug Substance Batch	Formulation Code
Studies in Children					
97-M-01	960058 960086 960060	2.5 mg capsules 5 mg capsules 10 mg capsules			1
d-MPH-PK-99-001	039723	10 mg tablets			3
Study in Adults					
d-MPH-PK-00-001	039723	10 mg tablets			3

TABLE 4. Identification of the *d*-MPH formulations used in clinical studies*.

Study Numbers	Lot/Batch Number	Dosage Form and Strength	Batch Size	Drug Substance Batch	Formulation Code
97-M-02	078618 078619 078617	2.5 mg tablets 5 mg tablets 10 mg tablets			2
97-M-03	078618 039719 078619 108661* 128693 078617 039723	2.5 mg tablets " 5 mg tablets " " 10 mg tablets "			2 3 2 2 3 2 3
97-M-04	078618 039719 078619 108661* 128693 078617 039723	2.5 mg tablets " 5 mg tablets " " 10 mg tablets "			2 3 2 2 3 2 3
97-M-05	078618 039719 078619 108661* 128693 078617 039723	2.5 mg tablets " 5 mg tablets " " 10 mg tablets "			2 3 2 2 3 2 3

* Placebo-controlled studies: 97-M-02 & 97-M-03; Open label studies: 97-M-04 (1 year safety) & 97-M-05 (6 months safety)

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APPENDIX 2: REVIEW OF INDIVIDUAL STUDIES AND BIOANALYTICAL METHODS

Summary of studies (Tables)

Table of human studies included in NDA 21-278 (the table is included in the medical review, and was prepared and kindly provided by Dr. Roberta Glass).

Study No.	Description	Drug(s) Tested/Regimen	Number of Subjects	Treatment Duration
Clinical Pharmacology Studies				
97-M-01	Single dose, double-blind, placebo and active controlled, crossover study of pk in children	Single doses of : *d*-mph: 2.5, 5, & 10 mg d,l-MPH (5,10 & 20 mg)	N=32	Single doses
PK-99-001	Single and multiple dose pk study in children	*d*-mph: 10 mg bid	N=12	6 ½ days
PK-00-001	Single dose, crossover, food effects in adults	*d*-mph: 2-single doses of 20 mg (fasting & fed)	N=15	Single doses
Placebo Controlled Studies				
97-M-02	Double-blind, pbo-controlled, 4 week study with 1 week pbo lead in	*d*-MPH: 5-20 mg/day *d,l*-MPH: 10-40 mg/day	Total: n= 132 d-MPH: n=44 d,l-MPH: n=46 placebo: n=42	4 weeks with 1 wk pbo lead in
97-M-03	A: Open label B: Withdrawal phase: 2 week placebo controlled C: Open label	A: 5-20 mg/day (titrated to effective dose) B:*d*-MPH 2.5-10 mg bid	N=89	A: 6 weeks:open label B: 2 weeks: withdrawal C: 44 weeks: open label
Open Label Studies				
97-M-04	Open-label, 1 year in children with ADHD		N=187	1 year
97-M-05	Open-label, 6 month safety study in children with ADHD		N=361	6 month

Overview of Celgene-sponsored clinical pharmacology studies:

Study No.	Population	N [M / F]	Ethnicity	Mean Age (yrs) [Range]	Design	Dose(s)
97-M-01	Children, ADHD	32[1] [32 / 0]	25 Caucasian 2 Black 3 Hispanic 2 Other	10.3 [9 - 12]	Single dose, double-blind, placebo- and active-controlled, 7-way crossover, pharmacokinetic, pharmacodynamic and safety study[1]	Placebo *d*-MPH: 2.5, 5, and 10 mg *d,l*-MPH: 5, 10, and 20 mg
d-MPH-PK-99-001	Children, ADHD	12 [8 / 4]	8 Caucasian 1 Black 2 Other 1 Hispanic	11 [7 – 16]	Single and multiple dose pharmacokinetics	First period: 10 mg single *d*-MPH dose Second period: 10 mg *d*-MPH b.i.d. for 6 ½ days
d-MPH-PK-00-001	Healthy, adult volunteers	15 [9 / 6]	14 Caucasian 1 Asian	30 [20 – 44]	Single dose, two-way crossover, bioequivalence study with and without food	Fed state: 20 mg single *d*-MPH dose Fasted state: 20 mg single *d*-MPH dose
TOTAL	–	59 [49/10]	47 Caucasian 3 Black 4 Hispanic 1 Asian 4 Other	[7 - 44]	–	–

[1] 31 patients evaluated for pharmacokinetics. Subjects received single doses of the investigational product 1 week apart, however, during the intervening time between clinic visits, they continued to be treated with racemic MPH.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Study # 2. Report *d*-MPH-PK-00-001: A single dose, two-way crossover bioequivalence study of *d-threo*-methylphenidate hydrochloride (*d*-MPH) with and without food when administered to healthy adult volunteers.

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Study Objective:

- To determine the relative bioavailability of 20 mg *d-threo*-methylphenidate HCl (*d*-MPH; 2x10 mg IR tablet) after a high-fat breakfast (test) and in the fasting state (reference).

Study Methods:

This study had a single dose, open, randomized, 2-way crossover design, with a 7-day washout period between treatments. A total of 15 healthy, adult volunteers (6 F/9 M; 14 Caucasian, 1 Asian; mean age 30, range 20-44 years; weight 71.7 ± 13.7 kg, [redacted] were enrolled and completed the study. The subjects were administered 20 mg *d*-MPH [redacted] tablet, the to-be-marketed formulation) after an over-night fast. The dose was administered in the fasting state (reference), or immediately after a high-fat meal ("FDA" breakfast), and blood samples for plasma analysis were collected frequently up to 36 h post-dose (14 samples/treatment). Safety assessments (physical examination and clinical laboratory tests) were performed pre-dose and at the end of the study. Adverse events were monitored throughout the investigational periods.

The plasma samples were analyzed for *d*- and *l*-MPH, and the inactive metabolites [redacted] For details regarding the bioanalysis, see Section #5 of Appendix 2 of this review. The pharmacokinetic parameters were calculated by use of non-compartmental methods, and statistical comparisons were performed (90% confidence intervals; ANOVA).

Results:

Measurable *d*-MPH and [redacted] plasma concentrations were obtained after dose intake, but *l*-MPH and [redacted] concentrations were not measurable, indicating that no *in vivo* inter-conversion between enantiomers took place. Plasma concentration (Cp) -time profiles of *d*-MPH with and without concomitant food intake are shown in Figure 1-2.

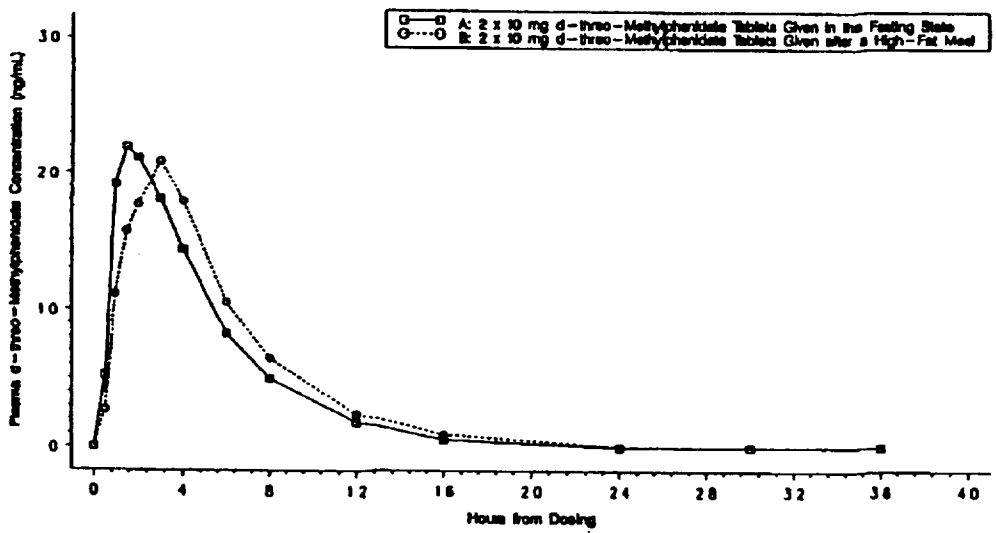

FIGURE 1-2. Mean Cp-time profiles of *d*-MPH in healthy adult subjects (n=15) after 20 mg (2x10 mg) *d*-MPH HCl in the fasting state (solid line) and after a high fat breakfast (dashed line).

The effects of food on AUC and C_{max} of *d*-MPH (active moiety) and *d*-RA (inactive moiety) are not considered significant, since the mean ratios (fed/fasting) were within the limits 80-125% (90% CI), as shown in Table 1-2.

TABLE 1-2. Point estimates and 90% confidence intervals (CI) of C_{max} and AUC (fed/fasting) of *d*-MPH and *d*-RA in adult subjects (n=15) after a single dose of 20 mg (2x10 mg) *d*-MPH HCl.

	d-MPH		*d*-RA (inactive metabolite)	
Parameter	**Point estimate (%)**	**90%CI**	**Point estimate (%)**	**90%CI**
C_{max}	96.0	88.2 – 104.6	86.7	82.3 – 91.3
AUC_{0-t}	112.5	106.0 – 119.3	100.2	96.7 – 103.8
AUC_{0-inf}	111.9	105.9 – 118.2	101.2	97.6 – 104.9

The pharmacokinetic parameters of *d*-MPH and *d*-RA after a single oral dose of 20 mg *d*-MPH HCL in the fasting and fed state are shown in Table 2-2. There was a delay in time to reach peak plasma concentrations after concomitant food intake compared to the fasting state ($t_{max,fed}$ 2.9 ± 0.8 h, $t_{max,fasting}$ 1.5 ± 0.5 h).

TABLE 2-2. Pharmacokinetic parameters (mean ± SD) of *d*-MPH and *d*-RA in adult subjects (n=15) after a single dose of 20 mg (2x10 mg) *d*-MPH HCl under fed and fasting conditions.

Parameter	***d*-MPH**		***d*-RA (inactive metabolite)**	
	Fed	**Fasting**	**Fed**	**Fasting**
C_{max} (ng/mL)	22.1 ± 6.9	23.7 ± 9.9	219.0 ± 39.0	255.4 ± 57.3
t_{max} (h)	2.9 ± 0.8	1.5 ± 0.5	3.3 ± 0.7	1.9 ± 0.7
AUC_{0-t} (ng.h/mL)	127.8 ± 48.8	116.8 ± 54.6	2502 ± 416.0	2503 ± 407.3
AUC_{0-inf} (ng.h/mL)	131.9 ± 49.7	120.9 ± 55.3	2648 ± 417.0	2628 ± 430.5
t½ (h)	2.8 ± 0.3	2.7 ± 0.3	8.3 ± 0.9	8.1 ± 0.9

Six (6) female and 9 male adult volunteers participated in the study. Interestingly, the female subjects had 55-76% higher C_{max} and 64-79% higher AUC_{0-inf} values compared to the male volunteers, during both fasting and fed conditions. After dose adjustment based on body weight (mg/kg), this difference became less pronounced with a 26%-37% increase in AUC_{0-inf} and a 20%-35% increase in C_{max}, as shown in Table 2-3.

TABLE 2-3. Pharmacokinetic parameters (mean ± SD) of *d*-MPH female (n=6) and male (n=9) adult subjects after a single dose of 20 mg (2x10 mg) *d*-MPH HCl under fasting and fed conditions. The % increase in C_{max} and AUC values for females compared to males are given within parentheses, the values are unadjusted or adjusted based on body weight (mg/kg).

Parameter	**FASTING**		**FED**	
	Females (n=6)	**Males (n=9)**	**Females (n=6)**	**Males (n=9)**
Body weight (kg)	60.4 ± 4.7	79.2 ± 12.4	*See fasting*	*See fasting*
Dose/kg	0.33 ± 0.03	0.26 ± 0.04	*See fasting*	*See fasting*
C_{max} (ng/mL)	**32.0 ± 9.4 (+76%)**	**18.2 ± 5.6**	**28.1 ± 4.8 (+55%)**	**18.1 ± 4.9**
C_{max} /(dose/kg)	**96.0 ± 28.3 (+35%)**	**71.8 ± 19.3**	**84.4 ± 12.5 (+20%)**	**70.6 ± 15.9**
t_{max} (h)	1.4 ± 0.4	1.7 ± 0.6	2.6 ± 0.7	3.1 ± 0.9
AUC_{0-t} (ng.h/mL)	159.7 ± 55.9	88.1 ± 31.0	167.4 ± 45.3	101.4 ± 30.4
AUC_{0-inf} (ng.h/mL)	**164.3 ± 56.3 (+79%)**	**91.9 ± 31.9**	**172.0 ± 45.9 (+64%)**	**105.2 ± 31.7**
AUC_{0-inf} /(dose/kg)	**488.2 ± 148.8 (+37%)**	**355.2 ± 100.9**	**511.6 ±106.3 (+26%)**	**407.0 ± 98.1**
t½ (h)	2.7 ± 0.3	2.7 ± 0.3	2.8 ± 0.5	2.8 ± 0.2

In total, 32 mild or moderate adverse events (AEs) were reported, where 17 AEs (n=6) were reported after dose intake in the fasting state, and 15 AEs (n=8) during fed conditions. The most commonly reported AEs were dry mouth (n=6, 40%), nervousness (n=5, 33%), and somnolence (n=4, 27%). Vital signs, ECG, and clinical laboratory tests were comparable between treatments, and no particular safety concerns were reported or recorded.

Comments:
No *in vivo* inter-conversion between enantiomers (MPH and the inactive metabolites) occurred, indicating that the metabolism of *d*-MPH to *d*-RA is stereospecific.

There were no significant effects of concomitant food intake compared to the fasting state. The mean ratios (fed/fasting states) for both AUC and C_{max} of *d*-MPH (active moiety) and *d*-RA (inactive moiety) were within the 'no effect' limits 80-125% (90% CI). There was a delay in time to reach peak plasma concentrations after concomitant food intake ($t_{max,fed}$ 2.9 h, $t_{max,fasting}$ 1.5 h), that had a slight effect on C_{max} (<5% decrease on average with food compared to fasting). The effects of food were studied in an adequate number of patients, at an adequate dose level. Therefore, it can be concluded that the to-be-marketed IR tablet can be administered irrespective of food, and that no special dosing recommendations are required.

Female volunteers had 20-35% higher C_{max} and 26-37% higher AUC values compared to male volunteers, although t_{max} and t½ were comparable between males and females. This may indicate that adult females have a somewhat higher bioavailability of *d*-MPH compared to adult male volunteers.

APPEARS THIS WAY
ON ORIGINAL

Study # 3. Report 97-M-01: Comparative pharmacokinetics, pharmacodynamics, and safety of single doses of *d-threo*-methylphenidate hydrochloride and *d,l-threo*-methylphenidate hydrochloride in children with Attention Deficit/Hyperactivity Disorder.

NDA Volume 1.31-1.34

Study Objectives:

Primary:
1. Compare the pharmacokinetics of the isomers of methylphenidate (MPH) and its major metabolites after single doses of MPH administered as *d-* or *d,l*-MPH.
2. To evaluate the potential *in vivo* conversion of *d-* to *l*-MPH, and metabolism of *d*-MPH after administration of *d-* and *d,l*-MPH.
3. To evaluate the safety after single doses of *d*-MPH and *d,l*-MPH.

Secondary:
1. To determine the tendency of single doses of *d*-MPH and *d,l*-MPH to induce adverse events (AEs), such as headache, stomachache and appetite suppression.
2. To compare the pharmacodynamics/activity of single doses of *d*-MPH to that of *d,l*-MPH and placebo.

Study Methods:

This was a double-blind, randomized, placebo-controlled, multi-center (n=3), cross-over study in boys diagnosed with ADHD (according to DSM-IV) that were receiving *d,l*-MPH therapy (≥20 mg/day for at least one month). Three dose levels of the single isomer *(d-)* MPH (2.5, 5, 10 mg) were compared to three dose levels of racemic *(d,l-)* MPH (5, 10, 20 mg). After a 1-week single-blind, placebo run-in phase, single doses of study medication (*d*-MPH, *d,l*-MPH and placebo) were administered weekly over 8 weeks. After the run-in week of placebo treatment and the first investigational day, the patients continued their regular *d,l*-MPH therapy between investigational days. An extra visit was scheduled in the protocol, to allow for completion of the medication sequence, in case a patient missed a session. If the patient had completed the full sequence, he was randomly assigned to a replicate of one treatment.

A total of 36 patients (n=12/center), 7-12 years of age, were to be enrolled in this double-blind study. The patients at each center were divided into two groups (n=6/group) and randomized to start the dosing regimen with either *d*-MPH or *d,l*-MPH. Within each treatment regimen (*d-* or *d,l*-MPH) the patients were receiving low, mid and high doses in random order. Placebo was given during one investigational day between the two dosing regimens, before the patient was crossed over to the second dosing regimen of either *d*-MPH or *d,l*-MPH (low, mid and high dose).

The study medication was administered as capsules (Formulation 1), which contained 2.5, 5 and 10 mg *d*-MPH, and 5, 10 and 20 mg *d,l*-MPH (*d,l*-MPH formulated from crushed 20 mg Ritalin tablets) or matching placebo.

Blood samples for plasma analysis were collected frequently up to 10 h post-dose (pre-dose, 0.5, 1, 1.5, 2, 4, 8 and 10 h) on each of the 9 investigational days. The plasma samples were analyzed for *d-* and *l*-MPH, and the metabolites *d*-ritalinic acid (RA) and *l*-RA. For details regarding the bioanalysis, see Section #5 of Appendix 2 of this review. Pharmacokinetic (PK) parameters (AUC, C_{max}, t_{max}, $t_{½}$) were calculated (non-compartmental methods) for each analyte, if measurable plasma concentrations were attained.

Two psychometric tests were used to assess the pharmacodynamics (PD) of MPH in this study, and were performed by teachers. The first test was a mathematical test (50 arithmetic problems) that was performed pre-dose, and at 1, 2, 4, 6, and 8 h post dose. The second test was the Conners, Loney and Milich (CLAM) rating scale, which subjectively measures inattention/over-

activity and aggression/defiance (sum of a 0-3 score for 16 items). The CLAM ratings were made during each investigational day at 2, 3.5 and 6 h after dose-intake.

Food consumption (weight of food consumed at lunch) and vital signs (BP, HR measured pre-dose, 2, 4 and 8 h) were monitored on each investigational day. Adverse events were monitored throughout the study and a physical examination was performed at each visit. Clinical laboratory tests were performed at baseline and at the end of each double blind dosing period (visits no 4 & 8).

Results:
The sponsor submitted the original study report to the IND [redacted] in March 1998. Both the PK and PD data was subsequently reanalyzed (original plasma concentrations were used in the calculations), and new, revised study reports were submitted in NDA 21-278. The decision to reanalyze the data was taken when the NDA was prepared, since the SAS data sets were not formatted to allow easy identification of the original data. The sponsor decided to have all data from the study reanalyzed by two different contract research organizations (PK: [redacted] The revised reports contain the methods and results from these re-analyses. The original results differ somewhat from the revised results, but similar conclusions are made in all reports. Since no major dissimilarities exist between the reports, the revised reports were used in this review.

Demographics:
A total of 37 subjects were screened, 32 male patients received study drug (entered the double-blind part), and 30 subjects were included in the PK summary evaluations. One subject withdrew consent after the first visit of the double blind part of the study. One subject (Patient no. 3-10; 11 years old) had repeated elevated levels of *d*-MPH, *d*- and *l*-RA in the pre-dose plasma samples, indicating that he took his regular medication also on the investigational days, therefore his data was not included in the analyses (the data was reported separately).

The mean ± SD (range) age was 10.3±1.1 (9-12) years, and the mean ± SD (range) height was 144±11 (127-168) cm. Body weight was not reported. The majority of the subjects were Caucasian (n=25; 2 Black, 3 Hispanic, 1 Native American, and 1 subject of 'other' ethnic origin). The demographics and number of participating subjects were similar between the 3 centers.

Pharmacokinetics:
The last visit of the trial was a 'catch-up' visit, where subjects could receive a dose that was previously missed, or if all treatments had been received per protocol, a duplicate of an earlier dose was administered according to the protocol randomization list. The sponsor has included two analyses for the average data, one where data from replicate doses was included, and one where the data from the replicate doses are not included. Since most subjects did not receive a duplicate dose (only 0-3 patients received one replicate dose of either *d*-MPH or *d,l*-MPH at each dose level), the non-replicate data is used in the review.

The pharmacokinetic parameters after the *d*-MPH and *d,l*-MPH administrations are given in Table 1-3 (*d*-MPH) and Table 2-3 (*d*-RA).

As shown in the two tables, the pharmacokinetics of the *d*-isomer, as well as its metabolite, *d*-RA, were very similar after administration of MPH as the racemate or the single isomer, indicating that concomitant administration of *l*-MPH does not influence the pharmacokinetics of *d*-MPH.

TABLE 1-3. Pharmacokinetic parameters (mean ± SD (n)) of d-MPH in boys (age 9-12 years) after single doses of *d*-MPH HCl (2.5 mg, 5 mg, 10 mg) or the racemate, *d,l*-MPH HCl, (5 mg, 10 mg, 20 mg) administered as capsules.

Parameter	2.5 mg *d*-MPH	5 mg *d,l*-MPH	5 mg *d*-MPH	10 mg *d,l*-MPH	10 mg *d*-MPH	20 mg *d,l*-MPH
C_{max} (ng/mL)	5.2 ± 1.5 (n=30)	5.5 ± 2.0 (n=29)	10.5 ± 3.4 (n=30)	10.1 ± 3.5 (n=30)	20.6 ± 7.7 (n=30)	18.3 ± 5.5 (n=30)
t_{max} (h)	1.7 ± 1.1 (n=30)	1.6 ± 1.1 (n=29)	1.3 ± 0.7 (n=30)	1.8 ± 1.0 (n=30)	1.8 ± 1.3 (n=30)	2.0 ± 1.2 (n=30)
$AUC_{0\text{-}10h}$ (ng.h/mL)	19.8 ± 7.2 (n=30)	21.3 ± 7.4 (n=29)	45.2 ± 13.7 (n=30)	43.4 ± 13.2 (n=30)	85.5 ± 29.3 (n=30)	85.2 ± 19.5 (n=30)
$AUC_{0\text{-}inf}$ (ng.h/mL)	23.9 ± 6.7 (n=25)	26.4 ± 6.6 (n=25)	50.1 ± 15.5 (n=30)	48.4 ± 13.4 (n=30)	98.7 ± 27.7 (n=28)	95.0 ± 21.9 (n=29)
t½ (h)	2.4 ± 0.4 (n=25)	2.5 ± 0.6 (n=25)	2.5 ± 0.5 (n=30)	2.4 ± 0.4 (n=30)	2.4 ± 0.4 (n=28)	2.4 ± 0.5 (n=29)

TABLE 2-3. Pharmacokinetic parameters (mean ± SD (n)) of d-RA (metabolite) in boys (age 9-12 years) after single doses of *d*-MPH HCl (2.5 mg, 5 mg, 10 mg) or the racemate, *d,l*-MPH HCl, (5 mg, 10 mg, 20 mg) administered as capsules.

Parameter	2.5 mg *d*-MPH	5 mg *d,l*-MPH	5 mg *d*-MPH	10 mg *d,l*-MPH	10 mg *d*-MPH	20 mg *d,l*-MPH
C_{max} (ng/mL)	66.7 ± 22.7 (n=30)	63.5 ± 21.2 (n=29)	107.2 ± 38.5 (n=30)	101.4 ± 29.6 (n=30)	175.3 ± 51.2 (n=30)	169.3 ± 46.7 (n=30)
t_{max} (h)	2.2 ± 1.1 (n=30)	2.3 ± 1.2 (n=29)	2.2 ± 1.0 (n=30)	2.5 ± 1.2 (n=30)	2.3 ± 1.1 (n=30)	2.8 ± 1.1 (n=30)
$AUC_{0\text{-}inf}$ (ng.h/mL)	650 ± 262 (n=25)	681 ± 307 (n=27)	1110 ± 334 (n=30)	1049 ± 298 (n=29)	1984 ± 626 (n=27)	1810 ± 493 (n=28)
t½ (h)	5.8 ± 1.4 (n=25)	5.9 ± 1.3 (n=27)	6.1 ± 1.4 (n=30)	5.9 ± 1.7 (n=29)	6.8 ± 2.0 (n=27)	6.0 ± 1.5 (n=28)

The pharmacokinetics of *d*-MPH were linear within the studied dose range, after administration of either *d*-MPH or *d,l*-MPH, as shown in Figure 1-3. Figure 1-3 depicts dose-normalized values of C_{max} and $AUC_{0\text{-}inf}$ after the single doses of either racemate or the *d*-enantiomer.

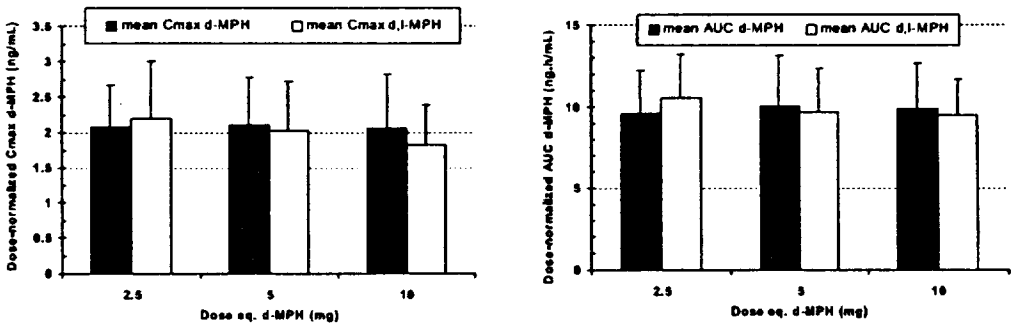

FIGURE 1-3. Dose normalized (mean + SD) C_{max} (left panel) and $AUC_{0\text{-}inf}$ (right panel) values of d-MPH after administration of the isomer, *d*-MPH (solid bars), and the racemate, *d,l*-MPH (unfilled bars). The *d,l*-MPH doses (5, 10, and 20 mg) are expressed as *d*-MPH equivalents.

The plasma concentrations of *l*-MPH were below the limit of quantitation for all but one subject after *d*-MPH administration (0.5 ng/mL after 10 mg *d*-MPH), and negligible after racemic MPH administration (5 mg: n=1; 10 mg: n=2; and 20 mg: n=3, max Cp= 2.5 ng/mL).

The pharmacokinetics of the *l*-isomer of the metabolite RA were also determined. As expected, there was a dose-proportional increase in the AUC after the single dose administrations of the racemate, but not after *d*-MPH dosing, as shown in Figure 2-3. The relatively constant levels of *l*-RA observed after *d*-MPH administration are most likely attributed to the previous day's intake of the children's regular medication of *d,l*-MPH. In this study the t½ of *l*-RA was about 3 h after *d,l*-MPH dosing and 6-9 h after *d*-MPH administration. The longer t½ is probably a more accurate estimate, since plasma samples were only collected up to 10 h post-dose, and the true elimination t½ was not captured after *d,l*-MPH dosing (*l*-RA t_{max} 1.8-2 h after *d,l*-MPH dosing).

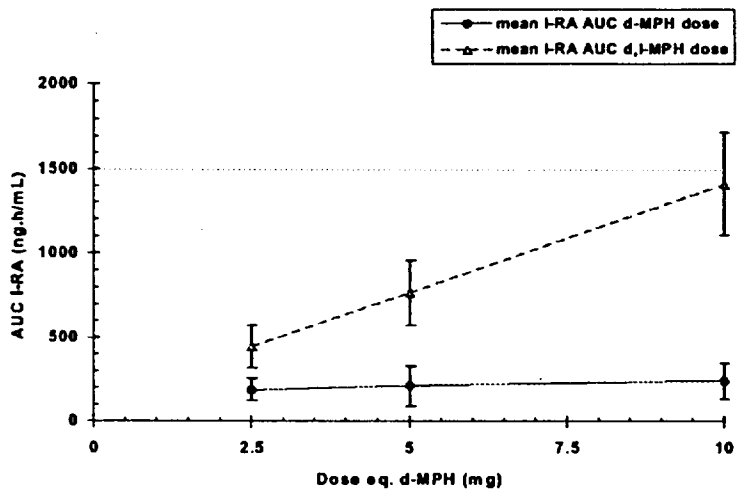

FIGURE 2-3. $AUC_{0\text{-}inf}$ (mean ± SD) of the metabolite *l*-RA after single dose administration of the isomer, *d*-MPH (solid line; n=10-14), and the racemate, *d,l*-MPH (dashed line; n=27-30). The *d,l*-MPH doses (5, 10, and 20 mg) are expressed as *d*-MPH equivalents.

There were indications of minor interconversion between the isomers, where four subjects had low *l*-RA plasma concentrations on five occasions after *d*-MPH dosing, but no measurable *l*-RA plasma concentrations in their pre-dose samples (1 patient after 2.5 mg; 1 patient after 5 mg; 3 patients after 10 mg *d*-MPH). The limit of quantitation (LOQ) for the analytical method for *l*-RA was 10 ng/mL, and the highest observed *l*-RA concentration was 12.1 ng/mL (10 mg *d*-MPH).

Pharmacodynamics:
The statistical analysis included an analysis of variance to determine potential influence of treatment regimen sequence, subject within sequence, visit and treatment (base-line Visit 1, excluded). No significant effects or carryover effects (CLAM or math tests) were observed. All subjects were included in the pharmacodynamic analyses *vs.* time (n=32). Placebo data from the single blind Visit 1 (baseline), as well as the placebo administered during the double-blind period were combined for the pharmacodynamic evaluation.

Overall, a linear dose-response relationship was observed for both the math test and the CLAM ratings, where MPH treatment showed a significant improvement in the test results compared to placebo treatment. The single isomer *d*-MPH was twice as potent as the racemate on a milligram-

basis. The drugs were equipotent (with regard to *d*-MPH content) and had similar duration of effects.

As shown in Figure 3-3, *d*-MPH and *d,l*-MPH treatment gave a similar improvement in the math test scores, where the high doses (10 or 20 mg) showed improved performance up to 6 h after dose intake.

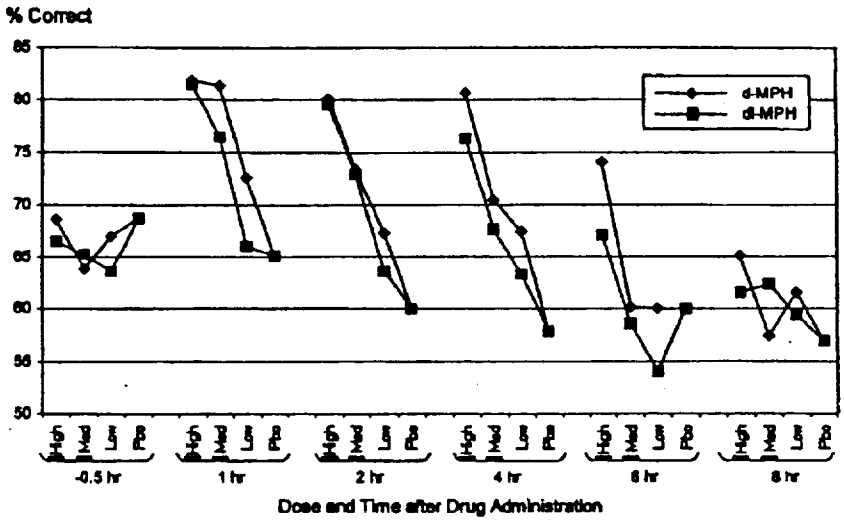

FIGURE 3-3. Means of math test results (% correct) *vs.* dose and time after drug administration. High dose: 10 mg *d*-MPH or 20 mg *d,l*-MPH; Medium dose: 5 mg *d*-MPH or 10 mg *d,l*-MPH; Low dose: 2.5 mg *d*-MPH or 5 mg *d,l*-MPH; Pbo: placebo

The CLAM rating scale, which is a more subjective measure of behavior that assesses inattention/ over-activity and aggression/defiance, showed a similar linear dose-response as the math test, as shown in Figure 4-3. The CLAM ratings were performed less often than the math test (3 vs. 6 occasions post-dose). Conners rating scale, a subset of the CLAM ratings (10 of the 16 items used in the CLAM ratings) gave almost identical results as the CLAM (data not shown in review).

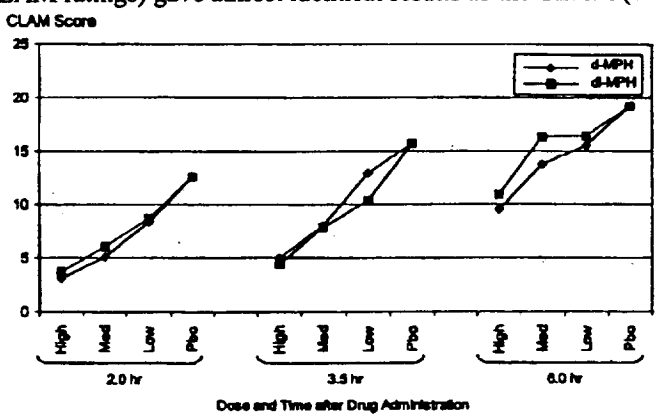

FIGURE 4-3. Means of the CLAM score results *vs.* dose and time after drug intake. High dose: 10 mg *d*-MPH or 20 mg *d,l*-MPH; Medium dose: 5 mg *d*-MPH or 10 mg *d,l*-MPH; Low dose: 2.5 mg *d*-MPH or 5 mg *d,l*-MPH; Pbo: placebo. A lower score indicates improvement.

The pharmacodynamic response followed the *d*-MPH plasma concentration-time profiles (see Figure 5-3), where the maximal pharmacodynamic response was observed when peak levels of *d*-MPH were reached (t_{max} about 1.5-2 h for all doses). Only patients with plasma concentration-time profiles available (and corresponding math test results) are included in Figure 5-3.

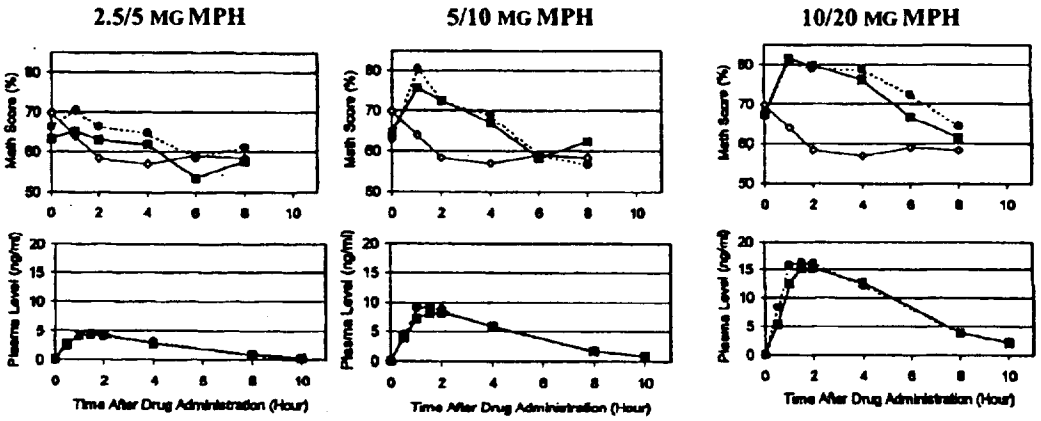

FIGURE 5-3. Upper panels: Means of math test results (% correct) *vs.* time after dose intake. Lower panels: Mean *d*-MPH plasma concentrations *vs.* time after dose intake. Left panels: low doses; Middle panels: medium doses: Right panels: high doses. *d*-MPH = dashed line with filled circles; *d,l*-MPH = solid line with filled squares; Placebo = solid line with unfilled circles

Safety:
A dose-related increase in heart rate was observed around 2 h (C_{max}) after dose-intake after both *d*-MPH and *d,l*-MPH. At the highest dose the mean increase from base-line was 7.7 bpm for *d*-MPH (10 mg) and 9.1 bpm for *d,l*-MPH (20 mg). No clear trends were observed in systolic and diastolic blood pressure or respiratory rate after dose intake (minor average differences compared to pre-dose values).

Food consumption, i.e. the weight of food eaten at lunchtime, was measured on the investigational days. There was a clear dose-dependent appetite suppressing effect of MPH compared to placebo, as shown in Figure 6-3. The appetite suppressant effect was similar after *d*-MPH and *d,l*-MPH dose intake.

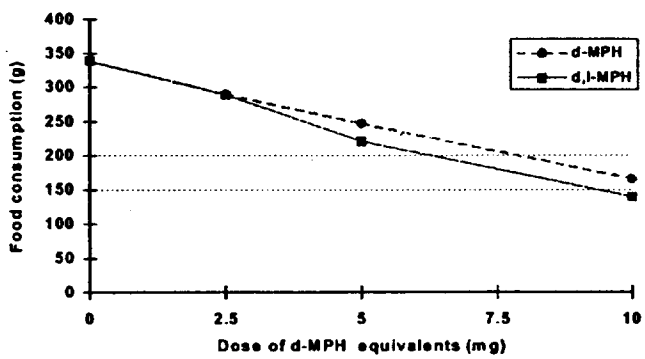

FIGURE 6-3. Food consumption (lunch) *vs.* dose of *d*-MPH or *d,l*-MPH expressed as *d*-MPH equivalents (Approximate times for dose intake was 8.30 a.m., and lunch intake at 12 noon)

The most common spontaneously reported AEs after any treatment were abdominal pain, headache, rhinitis, urinary frequency and dizziness. There were no early discontinuations due to AEs.

Comments:
The primary aims of this double-blind, randomized, placebo-controlled, multi-center, cross-over study in 31 boys diagnosed with ADHD was to compare the pharmacokinetics of the isomers of methylphenidate (MPH) and its major metabolites, and potential inter-conversion of the isomers after single doses of MPH administered as *d*- or *d,l*-MPH. The patients received study medication on 7-8 occasions during the double-blind period of the study (*d*-MPH: 2.5, 5, 10 mg; *d,l*-MPH: 5,10, 20 mg; placebo once; and in some instances a replicate dose of one of the active drugs).

The secondary aims of the study were to compare the pharmacodynamics/activity, as well as the safety profile, of single doses of *d*-MPH to that of *d,l*-MPH and placebo.

The study results showed that:

1. The pharmacokinetics of *d*-MPH and the metabolite, *d*-RA, were similar after a single doses of either *d*-MPH or *d,l*-MPH, indicating that the pharmacokinetics were not altered when MPH is administered as the single isomer, compared to the racemate.

2. Almost identical C_{max} and AUC values were achieved after the 50% lower doses (mg-basis) of *d*-MPH compared to the doses of the racemate (*d,l*-MPH), e.g. a 10 mg *d*-MPH dose gives plasma levels that corresponds to those observed after 20 mg *d,l*-MPH dose.

3. Dose-proportional increases in C_{max} and AUC were attained after 2.5 mg, 5 mg and 10 mg doses of *d*-MPH, indicating linear pharmacokinetics over the studied dose range of *d*-MPH. Dose-proportional increases in C_{max} and AUC were also observed after 5-20 mg of *d,l*-MPH.

4. Minor *in vivo* inter-conversion of *d*-MPH (or *d*-RA) to *l*-RA may occur, since it was observed that 4 of the 31 patients had low *l*-RA plasma concentrations on five occasions after *d*-MPH dosing, although no measurable *l*-RA plasma concentrations were present in their pre-dose samples.

5. The dose-response relationships (math test, CLAM rating scale) were linear, parallel (e.g. equipotent with regard to *d*-MPH) and had a similar duration of effect after corresponding doses of *d*-MPH and *d,l*-MPH.

6. There was a dose-related anorectic effect, where a higher degree of appetite suppression was observed at the highest dose of MPH (similar effects observed between *d*- and *d,l*-MPH).

It should be noted that a pilot-formulation, i.e. a capsule formulation, was used in this study.

Study # 4. Report *d*-MPH-PK-99-001: The determination of the human pharmacokinetics of a single dose and multiple doses of *d-threo*-methylphenidate hydrochloride (*d*-MPH) in children aged 6-16 years.

NDA Volume 1.35-1.37

Study Objective:

- To determine and compare the pharmacokinetics of *d-threo*-methylphenidate (*d*-MPH) after single (10 mg) and repeated doses (10 mg b.i.d.) of the to-be-marketed *d*-MPH HCl IR tablet in children diagnosed with ADHD.

Study Methods:

This was a two-period, combined single- and multiple dose study. Only patients with prior stimulant medication (4-week treatment with other stimulant or MPH, minimum MPH dose of 20 mg/day) were enrolled in the study. A total of 12 children and adolescents (8 M/4 F) diagnosed with ADHD were enrolled and completed the study. The mean ± SD (range) age was 10.8±2.7 (7-16) years, the mean ± SD (range) weight was 39.5±11.3 (23-57) kg and the mean ± SD (range) height was 147±16 (122-174) cm. The majority of the subjects were Caucasian (n=8; 1 Black, 2 Filipino American, 1 Hispanic).

All subjects received a single 10 mg *d*-MPH dose on Day 1, followed by twice daily dose-intake for 6½ days (10 mg at 8.00 a.m. and 12.00 noon) on Days 2-8 (Day 8, only a.m. dose intake). A washout period of about 44 h preceded the 1st dose intake. Drug intake on Days 1 and 8 was preceded by an overnight fast, and was followed by a standardized breakfast. No special dietary instructions were given during the outpatient period (Days 2-7). Blood samples for plasma analysis were collected frequently up to 12 h post-dose (10 samples/day) on Days 1 and 8. Safety assessments (physical examination, ECG and clinical laboratory tests) were performed pre-dose and at the end of the study. Adverse events and vital signs (BP, HR) were monitored throughout the investigational period. No pharmacodynamic measurements were performed in this study.

The plasma samples were analyzed for *d*- and *l*-MPH, and the inactive metabolites *d*-ritalinic acid (RA) and *l*-RA. For details regarding the bioanalysis, see Section #5 of Appendix 2. The pharmacokinetic (PK) parameters (AUC, C_{max}, t_{max}, $t_{½}$) were calculated (non-compartmental methods), and statistical comparisons were performed (90% confidence intervals, ANOVA).

Results:

Pharmacokinetics:

All 12 subjects were included in the safety analysis. Eleven of the 12 subjects were included in the PK analysis for the inactive metabolite *d*-RA, where one subject was excluded due to high pre-dose concentrations of *d*-RA (33% of C_{max}). Only 9 subjects were included in the PK evaluation of *d*-MPH, due to a failed bioanalytical run, where the quality control samples were out of range. No additional plasma was available for a re-analysis of these samples.

Measurable *d*-MPH and *d*-RA plasma concentrations were obtained after dose intake, but *l*-MPH and *l*-RA concentrations were not measurable after the single dose or the 6½ days of repeated dosing, indicating that no *in vivo* inter-conversion between enantiomers took place, in most subjects. However, after repeated dosing of *d*-MPH, the plasma samples from one subject, Subject no. 7 (Caucasian male, 11 years old), had measurable concentrations of *l*-MPH in 2 samples (C_{max} 0.1 ng/mL in pre-dose sample Day 8), and measurable *l*-RA concentrations (C_{max} 27.1 ng/mL in pre-dose sample Day 8) during the whole dosing interval.

Plasma concentration (Cp) -time profiles of *d*-MPH after the single (10 mg) and repeated doses (10 mg b.i.d.) are shown in Figure 1-4.

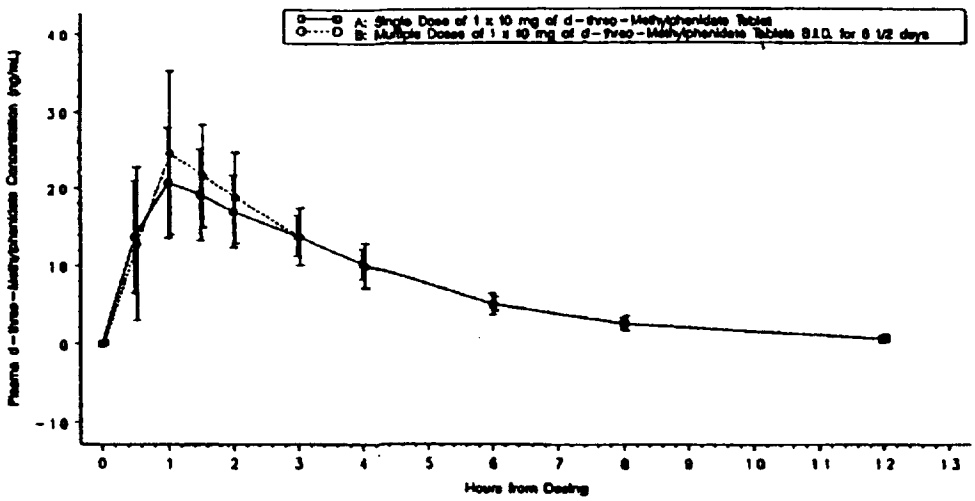

FIGURE 1-4. Mean ± SD Cp-time profiles of *d*-MPH in children and adolescents (n=9) 7-15 years of age. The solid line depicts a single dose of 10 mg (1x10 mg IR tablet) *d*-MPH HCl, and the dashed line depicts steady state conditions, after the last a.m. dose of *d*-MPH HCl (10 mg IR tablet b.i.d. for 6½ days, dosing 8 a.m. and 12 noon; 20 mg/day).

The pharmacokinetic parameters for *d*-MPH after administration of single and multiple doses are shown in Table 1-4.

TABLE 1-4. Pharmacokinetic parameters (mean ± SD) of *d*-MPH in 9 children (age 7-15 years) after a single dose of 1x10 mg and repeated doses (1x10 mg on Day 8) *d*-MPH HCl. Mean ratios (%) and 90% confidence intervals (CI) for ln AUC and ln C_{max} are also depicted.

Parameter	10 mg *d*-MPH (n=9)		Multiple *vs.* Single Dosing	
	Single Dose	Repeated Doses	90% CI	%Mean Ratio
C_{max} (ng/mL)	21.4 ± 6.5	25.1 ± 10.1	98.4 – 131.3	113.7
t_{max} (h)	1.1 ± 0.4	1.2 ± 0.4		
AUC_{0-12h} (ng.h/mL)	82.4 ± 20.6	90.4 ± 24.2	101.2 – 117.8	109.2
AUC_{0-inf} (ng.h/mL)	88.6 ± 20.2	93.5 ± 24.3	95.6 – 114.8	104.8
t½ (h)	2.3 ± 0.4	2.2 ± 0.4		

The pharmacokinetics of *d*-MPH were similar between the girls and boys after a single and repeated doses of 10 mg, as shown in Table 2-4.

TABLE 2-4. *Demographics* and pharmacokinetic parameters (mean ± SD) of *d*-MPH in girls and boys after a single dose of 1x10 mg and repeated doses (1x10 mg on Day 8) of *d*-MPH HCl.

Parameter	Single Dose		Repeated Doses	
	Girls (n=4)	Boys (n=5)	Girls (n=4)	Boys (n=5)
Age (years)	*9.5 ± 2.1*	*10.4 ± 2.9*	*9.5 ± 2.1*	*10.4 ± 2.9*
Height (cm)	*138.3 ± 9.8*	*146.6 ± 19.4*	*138.3 ± 9.8*	*146.6 ± 19.4*
Weight (kg)	*32.8 ± 6.5*	*40.6 ± 13.8*	*32.8 ± 6.5*	*40.6 ± 13.8*
C_{max} (ng/mL)	22.7 ± 7.8	20.4 ± 5.6	25.9 ± 10.6	24.4 ± 10.9
t_{max} (h)	1.0 ± 0.4	1.3 ± 0.4	1.2 ± 0.5	1.2 ± 0.3
AUC_{0-12h} (ng.h/mL)	85.2 ± 25.5	80.1 ± 18.6	90.8 ± 29.2	90.1 ± 23.1
AUC_{0-inf} (ng.h/mL)	89.1 ± 26.6	88.1 ± 17.0	93.4 ± 29.3	93.6 ± 23.1
t½ (h)	2.0 ± 0.3	2.5 ± 0.4	2.1 ± 0.4	2.2 ± 0.3

The pharmacokinetic parameters for the inactive metabolite, *d*-RA after administration of single and multiple doses are shown in Table 3-4.

TABLE 3-4. Pharmacokinetic parameters (mean ± SD) of *d*-RA in 11 children (age 7-16 years) after a single dose of 10 mg (1x10 mg) and repeated doses (1x10 mg on Day 8) *d*-MPH HCl. Mean ratios (%) and 90% confidence intervals (CI) for ln AUC and ln C_{max} are also depicted.

Parameter	*d*-RA (n=11)		Multiple *vs.* Single Dosing	
	Single Dose	Repeated Doses	90% CI	%Mean Ratio
C_{max} (ng/mL)	199.3 ± 61.1	230.7 ±68.9	108.1 – 124.5	116.0
t_{max} (h)	1.6 ± 0.7	1.5 ± 0.8		
AUC_{0-12h} (ng.h/mL)	1370 ± 411.4	1659 ± 399.2	116.7 – 128.9	122.5
AUC_{0-inf} (ng.h/mL)	1890 ± 561	2304 ± 579.4	117.6 – 128.5	123.0
$t_{½}$ (h)	6.1 ± 0.8	6.2 ± 0.7		

There was a marginal indication of drug accumulation on average after repeated dosing of *d*-MPH HCl on both AUC and C_{max} for the active *d*-MPH (about 10%), and inactive metabolite *d*-RA (10-20%) compared to a single dose administration (see Tables 1-4 and 3-4).

Safety:
Heart rate, systolic (SBP) and diastolic (DBP) blood pressure showed increases 0-4 h after dose intake, which correlated with the plasma concentration (Cp)-time profiles, as shown in Figure 2-4 (mean values). As shown in Figure 2-4, there was no change in magnitude of the parameters between single and repeated doses of *d*-MPH HCl.

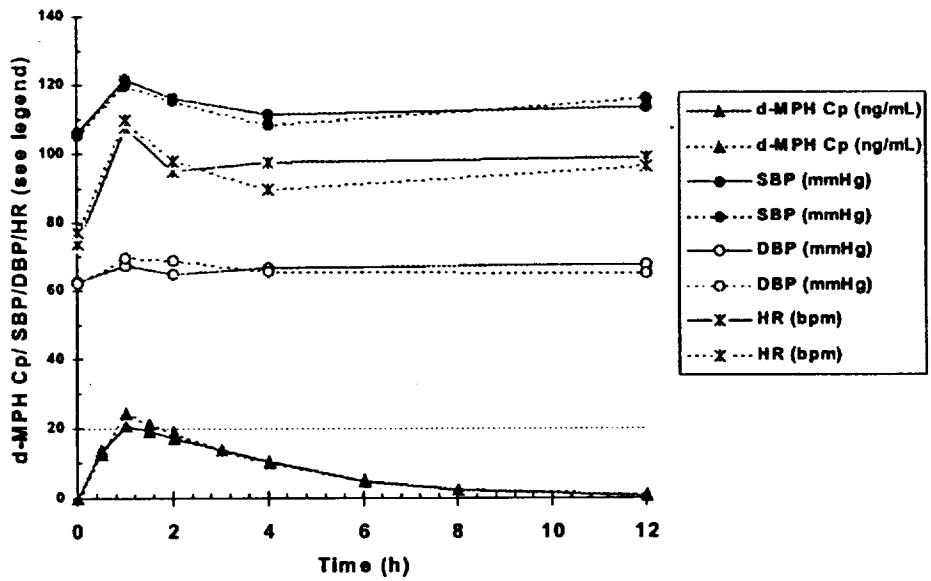

FIGURE 2-4. Mean profiles of vital signs (n=12) and Cp (n=9) *vs.* time in children and adolescents 7-16 years of age. The solid lines depict the variables after a single dose of 1x10 mg *d*-MPH HCl, and the dashed lines depict the variables during steady state conditions, after the last a.m. dose of 1x10 mg *d*-MPH HCl (Day 8). The curves show mean values of SBP, HR, DBP and Cp, respectively (from top to bottom of the graph).

Since only one dose level was investigated in the study, and no more than 3-4 measurements of the BP and HR in conjunction with measurable Cps of *d*-MPH were made in each subject, the data does not support an adequate PK/PD analysis. Respiration rate and body temperature were measured at the same time as BP and HR, and remained unchanged over the two observational periods.

One subject (#12, female Caucasian, 9 years old) exhibited several elevated systolic blood pressure readings on Day 8 (SBP/DBP; pre-dose 117/55 mmHg; 1 h: 142/73 & 159/78 mmHg; 4 h: 144/66 mmHg; 12 h: 145/67 mmHg), which were classified as AEs. She also had substantial elevations after the 1st dose (Day 1 pre-dose: 108/48 mmHg, highest BP increase at 1 h: 139/67 mmHg). However, the BP changes on Day 1 were not classified as AEs.

A total of 13 treatment emergent, mild and moderate, AEs were reported by 6 (50%) of the 12 subjects. The most common AEs were abdominal pain, headache, and dizziness. There were no early discontinuations due to AEs.

Comments:
The aim of the study was determine and compare the pharmacokinetics of *d*-MPH after single and repeated doses of the to-be-marketed *d*-MPH HCl tablet in 12 children (7-16 years old) diagnosed with ADHD. The highest dose strength 10 mg of the to-be-marketed IR tablet (10 mg as a single dose and after repeated b.i.d. doses for 6½ days) was used in the study.

The study results showed that:

1. The pharmacokinetics (C_{max} and AUC) of *d*-MPH and the metabolite, *d*-RA, were similar after a single dose and after the last dose intake after 6 days of repeated administration. After repeated dosing, slightly higher mean values of C_{max} (14%) and AUC_{∞} (5%) for *d*-MPH were observed than after a single dose, indicating some degree of accumulation. The corresponding increases for *d*-RA were 16% and 23%, respectively. This slight degree of accumulation is not considered to be of importance, since most subjects did not have quantifiable Cps of *d*-MPH (see Fig. 1-4) before dose-intake on the last day of repeated dosing.

2. The pharmacokinetics of *d*-MPH were similar between boys (n=5) and girls (n=4).

3. There was no indication of *in vivo* inter-conversion of *d*-MPH or *d*-RA to their respective *l*-isomers. One subject had measurable concentrations of *l*-MPH and *l*-RA during the last dosing interval, however those concentrations were highest in the plasma sample collected prior to dose intake. This may indicate that this patient took a tablet containing racemic MPH on the previous day (out-patient setting). The *d*-MPH concentrations for this subject are not reported (part of the failed bioanalytical runs of *d*-MPH for 3 subjects).

4. There was an increase in systolic BP (max average +20 mmHg) and HR (max average +30 bpm) 0-4 h after dose intake that corresponded to the *d*-MPH plasma concentration – time profiles (Fig 2-4). Similar increases in BP and heart rate to the observed increases in BP and HR in this study have been described in the literature where oral doses of racemic MPH were administered.

5. Effect of age: Results from this study were compared to data from the food effect study in adults (fasting arm, Study #2), as shown in Table 3-5 (next page). The results indicate that the C_{max} was similar, however children (6-12 years of age) showed somewhat lower AUCs compared to the adults.

TABLE 3-5. Comparison C_{max} and AUC values of *d*-MPH across different age groups.

			d-MPH	
Age	**N**	**Dose (mg/kg)**	**C_{max} (ng/mL)**	**AUC (ng.h/mL)**
< 12 years*	7	0.31 ± 0.09	26.04 ± 10.79	94.51 ± 26.0
≥ 12 years*	2	0.23 ± 0.07	21.68 ± 12.76	90.0 ± 20.2
Adults†	15	0.29 ± 0.05	23.72 ± 9.91	120.9 ± 55.3
			d-RA	
< 12 years	6		256.69 ± 75.61	2600 ± 634.6
≥ 12 years	2		194.7 ± 67.42	1884 ± 36.8
Adults	15		255.4 ± 57.33	2628 ± 430.5

*Children with ADHD following 10 mg *d*-MPH b.i.d. by age (Study #5; PK-99-001)
†Adults (healthy volunteers) following 2x10 mg *d*-MPH as a single dose in the fasted state (Study #2, PK-00-001).

Due to the very limited data in adolescents (n=2), no comparison between adolescents and adults can be made.

APPEARS THIS WAY
ON ORIGINAL

Section # 5. Bioanalytical Methods

Two different bioanalytical methods were used to determine the plasma concentrations of *d*- and *l*-MPH, and the metabolites, *d*-ritalinic acid (RA) and *l*-RA, in plasma. One method utilized gas chromatography - mass spectrometry (GC-MS), and the other method utilized liquid chromatography - tandem mass spectrometry (LC/MS-MS). The limits of quantitation (LOQ) and range of linearity of the calibration curves for the analytes used in the different assay methods are given in Table 1-5.

TABLE 1-5. Limits of quantitation (LOQ) and range of linearity of the calibration curves for the analytes of the GC-MS and LC-MS/MS assay methods used for the studies in NDA 21-278.

Study	Method	Analyte	LOQ (ng/mL)	Linearity (ng/mL)
#3				
#2 & #4				

LC/MS method (Study #3)

The plasma samples from Study #3 were analyzed by a validated enantiospecific LC/MS method that was developed and performed by the [redacted] The assay was tested for specificity, accuracy, stability, efficiency and potential racemization. The analytes were extracted into t-methyl butyl ether from alkalized plasma and back extracted into acid. The extraction into t-methyl butyl ether was repeated. A polar solvent and a salt was added to the aqueous portion to enable extraction of ritalinic acid, and the samples were evaporated (vacuum centrifuge). The samples were reconstituted, propylated, and internal standard was added (deuteriated isopropylphenidate and deuteriated MPH). A chiral derivatizing agent (HPC) was added. All analytes were determined by [redacted]

The influence of plasma sample volume and stability of frozen samples (three freeze-thaw cycles, -70°C) was investigated (*d*- and *l*-MPH; *d*- and *l*-RA). The stability of *d*- and *l*-MPH was found to be significantly altered (-41%-+24%) after three freeze-thaw cycles compared to one cycle. The *d*-RA and *l*-RA were not significantly altered by repeated freezing and thawing of samples. Samples thawed more than twice would not be deemed suitable for assay. One shipment of samples arrived thawed to the analytical facility, these samples were not assayed. The patients repeated the treatment and the new samples were assayed and used in the pharmacokinetic analysis. The long-term stability of frozen plasma samples was not investigated. The precision (inter- and intra-day) for the *d*-MPH analyses are shown in Table 2-5. The data for the other 3 analytes (*l*-MPH, *d*- and *l*-RA) were within the same range.

TABLE 2-5. Precision (CV%) of the GC-MS method, where upper and lower values of the quality control (QC) samples are given (1.2, 6.0 & 12.0 ng/mL). Only data for *d*-MPH are displayed.

Study	LOQ (ng/mL)	Inter-day CV%	Intra-day CV%
[redacted]			

LOQ = Limit of quantitation; CV = coefficient of variation; N/A = not applicable;

An estimate of the accuracy (RE%) of the method was not included in the report, however, the method is judged to be adequately documented.

LC/MS-MS method (Studies #2 and #4)

The plasma samples from Studies #2 and #4 were analyzed by a validated enantiospecific LC/MS-MS method that was developed and performed by [redacted] The analytes and internal standards were extracted into n-pentane from alkalized plasma, and the organic phase was evaporated (N_2). A salt was added to the aqueous portion to enable extraction of ritalinic acid into the polar solvent. The reconstituted samples (solutions of organic solvents) were injected onto a chiral column [redacted] LC/MS-MS; positive ions monitored in the MRM mode). Deuterium-moieties of the analytes were used as internal standards.

The influence of time on re-injection and bench-top stability and stability under refrigerated (+2-8°C) and frozen conditions (-20°C) was investigated (*d*- and *l*-MPH; *d*- and *l*-RA). The stability of *d*-MPH under re-injection, bench-top (room temperature), and refrigerated conditions was shown to be adequate up to 118, 24, and 73 hours, respectively. The stability of *d*-MPH was found to be 98-99% after three freeze-thaw cycles compared to one cycle. The long-term stability of frozen plasma samples was ensured up to 46 weeks for *d*-MPH, and up to 54 weeks for the other 3 analytes (*l*-MPH, *d*- and *l*-RA). The precision and accuracy (inter- and intra-day) for *d*-MPH are shown in Table 3-5. The data for the other 3 analytes (*l*-MPH, *d*- and *l*-RA) were within the same range.

TABLE 3-5. The precision (CV%) and accuracy (RE%) of the LC-MS/MS method. Upper and lower values of the quality control (QC) samples based on the standards (Inter-day: 1.56, 8.32, 39.0 & 45.0 ng/mL; Intra-day: 1.56, 8.32 & 39.0 ng/mL). Only data for *d*-MPH are displayed.

Study	LOQ (ng/mL)	Inter-day		Intra-day	
		CV%	RE%	CV%	RE%
LC-MS/MS Method	0.5	2.41 - 5.56	-0.24 - +15.66	1.92 - 2.72	-0.89 - +4.63
QC:					
Study #2*	0.5	6.60 - 6.86	-3.55 - +7.12	N/A	N/A
Study #4*	0.5	5.32 - 8.65	-0.76 - +8.63	N/A	N/A

LOQ = Limit of quantitation; CV = coefficient of variation; RE = relative error; N/A = not applicable; * QC: 1.5, 8.0 and 37.5 ng/mL)

Comment

The bioanalytical assays used for the different studies are adequately validated.

10 page(s) of revised draft labeling has been redacted from this portion of the review.

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION

NDA 21-278
SPONSOR: Celgene Corporation
Date Submitted: October 25, 2001
User Fee Date: August 25, 2001

DRUG NAME

Generic Name: dexmethylphenidate hydrochloride
Proposed Trade Name: [redacted]

DRUG CATEGORIZATION

Pharmacological Class: Psychostimulant
Proposed Indication: Attention Deficit Disorder
Dosage Forms: 2.5 mg, 5 mg, and 10 mg tablets

REVIEWER INFORMATION

Medical Officer: Roberta L. Glass, M.D.
Review Completion Date: July 26, 2001