Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-303 SE5-009
Generic Name:	Mixed Salts of a single entity amphetamine product
Trade Name:	Adderall XR™
Dosage Strengths:	5, 10, 15, 20, 25, 30 mg
Sponsor:	Shire
Indication:	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Adolescents (13- 17 years)
OND Clinical Division:	DNDP (HFD-120)
OCPB Division:	DPE1 (HFD-860)
Submission Type:	Priority - Response to Pediatric Written Request
Submission Date:	9/17/04
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader (Acting):	Sally Yasuda, Pharm. D.

1. Executive Summary

1.1. Recommendations

Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-303 SE5-009, the information provided to support the approval of Adderall XR for treatment of ADHD in adolescents is acceptable. OCPB supports a recommendation of approval for use of Adderall XR in adolescents (13 – 17 years) with ADHD.

1.2. Phase 4 Commitments

The reviewer is not recommending any Phase IV commitments

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Adderall XR capsules have been approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (6- 12 years) and adults. A pediatric Written Request (WR) was issued for adolescents (13 –17 years) with ADHD. The WR for pediatric information included requests for pharmacokinetic data for adolescents ADHD patients (ages 13 – 17 years) and a comparison of those data with pediatric patients (ages 6 to 12 years). The WR specified that pharmacokinetic assessments must be made with respect to dextro (d)- and levo (l)-amphetamine. With respect to the analysis of the data, the WR indicated that the data analysis must address the effect of factors such as age, body weight and gender on pharmacokinetic parameters. The pharmacokinetic parameters derived from the adolescent population was to be compared to historical values from adults and children ages 6 to 12 years.

The pharmacokinetics of d- and l- amphetamine after administration of Adderall XR are linear over single oral doses ranging from 10 mg to 40 mg in adolescent ADHD patients weighing ≤ 75 kg/165 lbs. The pharmacokinetics of d- and l-amphetamine are linear over doses ranging from 20 to 60 mg in adolescent (13 – 17 years) ADHD patients weighing > 75 kg/165lbs. In adolescents, the range of dose normalized Cmax, dose-normalized AUC∞, Cl/F and Vz/F was similar in males and females for both d- and l-amphetamine. In the adolescents, exposure measured by AUC∞ was not affected by age. However, there was a decrease in Cmax for both d- and l- amphetamine with age and a decrease in Cmax and AUC with increasing body weight.

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of Adderall XR in pediatric (6-12 years) and adolescent (13 –17) ADHD patients and healthy adults (22 – 46 years) indicates that body weight was the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across age range. Systemic exposure measured by AUC∞ and Cmax decreased with increases in body weight. Contrasts between age groups showed that all of the significant differences in pharmacokinetics occurred between the pediatric population and the adolescent and/or adult populations. There were no significant differences between adolescents and adults.

Table 1: Statistical comparison of pharmacokinetic parameters for d- and l-amphetamine between age groups after oral administration of Adderall XR

Parameter	p-value[1]		
	Pediatric vs Adolescent	Pediatric vs Adult	Adolescent vs Adult
d-amphetamine	Pediatric vs Adolescent	Pediatric vs Adult	Adolescent vs Adult
AUC∞	0.0337	0.0117	0.4491
Cl/F	0.0807	0.0321	0.4923
Vz/F	<0.0001	<0.0001	0.3740
T ½	<0.0001	0.0080	0.0723
Cmax	<0.0001	0.0001	0.8997
Tmax	0.5964	0.6976	0.9478
l-amphetamine			
AUC∞	0.7137	0.2794	0.4235
Cl/F	0.8785	0.5533	0.6310
Vz/F	<0.0001	0.0002	0.4623
T ½	<0.0001	0.0073	0.1468
Cmax	<0.0001	0.0008	0.8780
Tmax	0.6381	0.8981	0.7817

[1]p-value for t-test between age groups

Table 2: Multivariate statistical evaluation of the effect of gender, age, and body weight on the pharmacokinetic parameters for d- and l-amphetamine after oral administration of Adderall XR

Parameter	p-value[1]					
	d-amphetamine			l- amphetamine		
	Gender	Age	Weight	Gender	Age	Weight
AUC∞ (h*ng/mL)	0.5662	0.5638	0.0184	0.3283	0.6405	0.1240
CL/F (mL/min)	0.6505	0.1306	0.0651	0.3073	0.4709	0.0821
Vz/F (L)	0.8955	0.6208	<0.0001	0.4613	0.3712	<0.0001
T ½ (h)	0.8379	0.0686	0.0034	0.6680	0.1788	0.0222
C max (ng/mL)	0.1132	0.0931	<0.0001	0.1013	0.0703	<0.0001

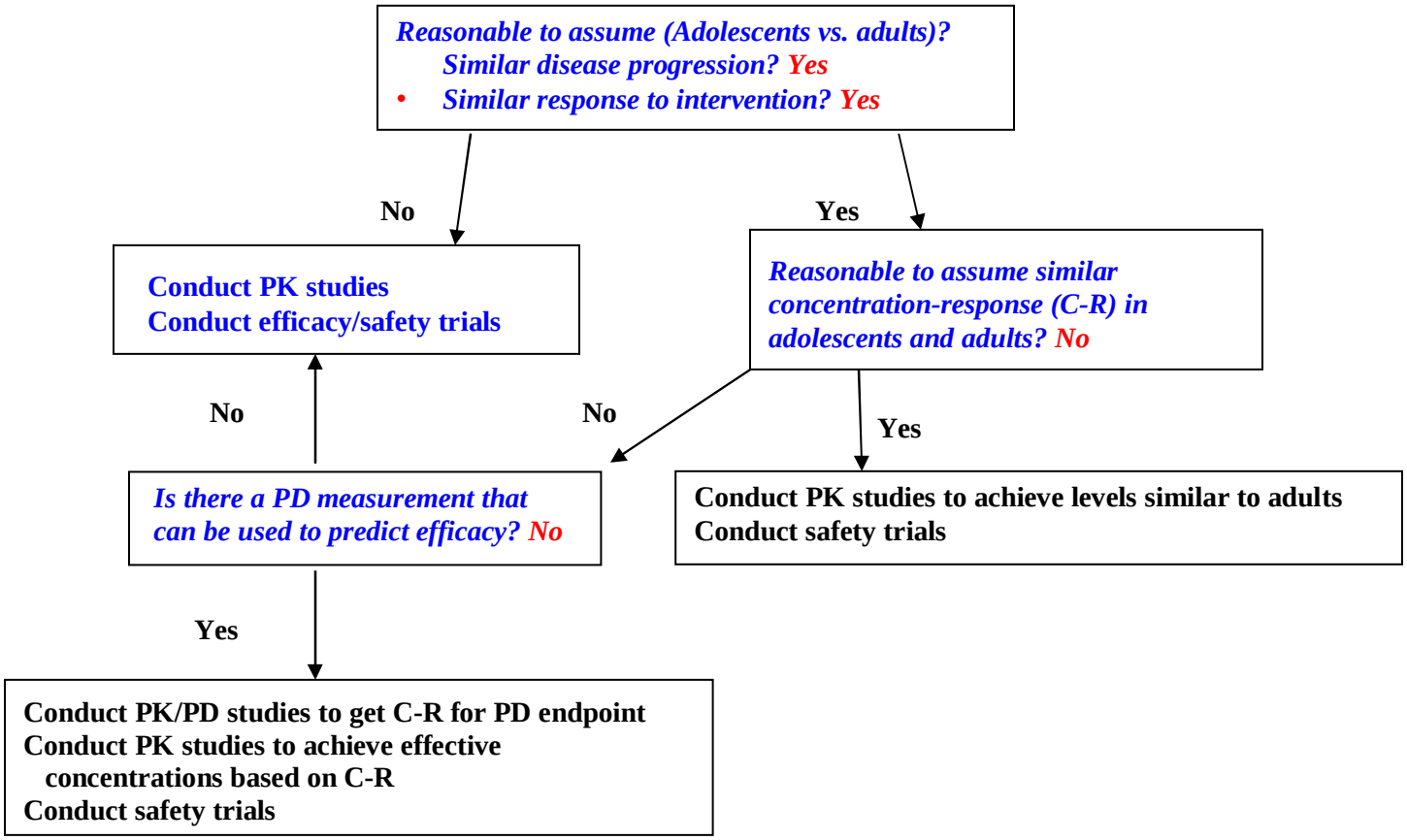
[1]p-value for the indicated effect from an analysis of variance

In addition to the pharmacokinetic study (SLI381.110), safety and efficacy studies were conducted in support of the dosing and use of Adderall XR for treating ADHD in adolescents. The pivotal safety and efficacy study was a randomized, double-blind, placebo-controlled trial designed to determine the safety and effectiveness of Adderall XR in adolescents with ADHD (SLI381.314 Part A). The safety of Adderall XR was also assessed in an uncontrolled, open-label study (SLI381.314 Part B) in which subjects were treated for up to 6 months. These studies will be reviewed by the medical officer.

The Pediatric Decision Tree is provided on the following page. Based on the decision tree and discussion with the reviewing medical officer, a pharmacokinetic and a safety study only in

adolescent patients may not have been sufficient. A medical decision was made at the time of issuing the WR to conduct clinical safety and efficacy studies in addition to the pharmacokinetic study. Discussions with the medical reviewer and medical Team Leader suggested that theoretically the disease progression and response to intervention should be similar. But it may not be reasonable to assume that concentration-response in adolescents and adults are the same. There are no known pharmacodynamic (PD) measures that can be used to predict efficacy.

Fig 1


Reasonable to assume (Adolescents vs. adults)?
Similar disease progression? Yes
Similar response to intervention? Yes
No
Yes
Conduct PK studies
Conduct efficacy/safety trials
Reasonable to assume similar concentration-response (C-R) in adolescents and adults? No
No
No
Yes
Is there a PD measurement that can be used to predict efficacy? No
Conduct PK studies to achieve levels similar to adults
Conduct safety trials
Yes
Conduct PK/PD studies to get C-R for PD endpoint
Conduct PK studies to achieve effective concentrations based on C-R
Conduct safety trials

Kofi A. Kumi, Ph.D._____

RD/FT Initialed by Sally Yasuda, Pharm.D._____

CPD Briefing: 2/28/05, Attendees: HFD-120 (P. Andreason, R. Taylor), HFD-860 (M. Mehta, A. Rahman, S. Yasuda, K. Kumi), HFD-870 (J. Hunt), HFD-880 (J. Lazor)

CC: NDA-21-303SE5-009, HFD-120, HFD-860 (Mehta, Rahman, Baweja, Yasuda, KumiK), CDR (Biopharm)

2 Question Based Review (QBR)

2.1 What are the general attributes?

Adderall XR capsules have been approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (6- 12 years) and adults. Subsequent to the approval of Adderall XR, a pediatric Written Request (WR) was issued. The WR for pediatric information included requests for pharmacokinetic data for adolescent ADHD patients (ages 13 – 17 years). The WR specified that pharmacokinetic assessments must be made with respect to dextro and levo-amphetamine. For each of dextro- and levo-amphetamine, the data collected must provide adequate estimates of important pharmacokinetic parameters, e.g. AUC, half-life, Cmax, Tmax and apparent volume of distribution and oral clearance in pediatric patients in the relevant age range. With respect to the analysis of the data, the WR indicated that the data analysis must address the effect of covariates such as age, body weight and gender on pharmacokinetic parameters such as apparent volume of distribution and half-life. The pharmacokinetic parameters derived from the adolescent population should be compared to historical values from adults and children ages 6 to 12 years.

2.1.1 What are the highlights of the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Adderall XR is a modified release formulation of an approved immediate release (IR) formulation, Adderall. Adderall XR was developed to facilitate once a day dosing for treatment of ADHD. Both Adderall IR and Adderall XR contain d-amphetamine and l-amphetamine salts (b) (4) The components and composition of Adderall XR capsules have not changed from those in the original submission approved in October, 2001. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Oral administration of Adderall XR delivers a dose of mixed amphetamine salts via a two pulse release. (b) (4)

2.1.2. What is the mechanism of action and therapeutic indication?

The mode of therapeutic action in ADHD is not known. Amphetamines are thought to block the re-uptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Adderall XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder.

2.1.3. What are the proposed dosage and route of administration?

(b) (4)

(b) (4) It is recommended that treatment for the first time or switching from another medication, patients should start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 10 mg at weekly intervals.

2.2. General clinical pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims

Three clinical studies were conducted in support of the dosing and use of Adderall XR for treating ADHD in adolescents. The pharmacokinetic study (SLI381.110) was an open-label, single dose, 3-treatment, 3-period, randomized, crossover, study. The primary cohort of this study included 17 healthy adolescents (aged 13 –17 years) with ADHD, weighing less than or equal to 75 kg/165 lbs. Each of the subjects were randomly assigned to 3 treatments groups. Each of the groups received a single oral dose of 10, 20 or 40 mg Adderall XR after an overnight fast during the 1st period and then was crossed over to the alternate periods with a 7-day washout period. The secondary cohort included 6 healthy adolescent subjects with ADHD, weighing greater than 75 kg/165 lbs. Each of the subjects were randomly assigned to one of 3 dosing sequences. Each of the groups received a single oral dose of 20, 40 and 60 mg after an overnight fast during the 1st period and then were crossed over to the alternate treatments during subsequent periods. The study assessed the pharmacokinetics of d- and l-amphetamine in adolescents aged 13 – 17 years old. The effect of age, gender and body weight on the pharmacokinetics of d- and l-amphetamine after administration of Adderall XR was evaluated. An analysis was conducted to compare the pharmacokinetics with historical values from pediatric patients aged 6 –12 years and adults.

The efficacy and safety study (SLI381-314) was a multicenter, randomized, double-blind, parallel-group trial. The study evaluated the safety and efficacy of Adderall XR in adolescents (13 –17 years) with ADHD at doses of 10 mg to 40 mg (for those weighing ≤ 75 kg/165 lbs) in addition to doses of 50 mg and 60 mg (for those weighing greater than 75 kg/165 lbs). The study had up to 4 weeks of double blind exposure, which permitted acceptable inferences of treatment group differences on acute safety, tolerance and efficacy and clinical manifestations of ADHD in adolescents. Additionally, the study incorporated a 6-month open-label extension phase testing the long term safety of once a day administration of Adderall XR in the treatment of adolescents with ADHD at doses of 10 to 60 mg depending on the clinical investigator's judgement of each subjects' optimal dose.

2.2.2. What is the primary measurement of efficacy

The primary measurement of efficacy was the ADHD-RS-IV. ADHD-RS-IV is a standard instrument for assessing attention deficit and hyperactivity. Hyperactivity/impulsivity and inattentiveness subscales, are the two components of the ADHD-RS-IV.

2.2.3. Are the active moieties in the plasma appropriately identified and measured?

Yes, the active moieties (d- and l- amphetamine) are appropriately measured and identified. The identification of active moieties and validation of analytical methods were determined in previous submissions and have not changed. The analytical methods are acceptable.

2.2.4. Exposure- Response Relationship

2.2.4.1. What are the characteristics of the exposure-response relationships for efficacy?

Concentration response was not evaluated in the efficacy studies. According to the sponsor, at study endpoint (defined as last post-baseline measurement), improvements in the primary cohort ITT population were statistically significant greater in all four primary cohort active treatment groups (Adderall XR 10, 20, 30 and 40 mg) compared with the placebo group. According to the sponsor, analysis of the time course of the primary efficacy variable demonstrated statistically significant differences in improvement between placebo group and all active treatment groups for all post-baseline assessments. According to the sponsor total scores were due to improvements in both the hyperactivity/impulsivity and inattentiveness subscales, which are the two components of the ADHD-RS-IV total score. Refer to the medical review for the Agency's assessment of the pivotal safety and efficacy studies.

2.2.4.2. What are the characteristics of the exposure-response relationships for safety?

Concentration response was not evaluated in the safety studies. According to the sponsor, the incidence of adverse events was generally lowest in subjects treated with Adderall XR 10 mg. According to the sponsor, there was no apparent relationship to dose in the overall incidence of adverse events from 20 to 60 mg. With the exception of anorexia and weight loss, according to the sponsor, there were not apparent relationships to dose observed for individual adverse events. According to the sponsor, anorexia and weight loss tended to increase with increasing dose up to 30 mg during the short term study. According to the sponsor, there were no differences in overall adverse event incidence between the lower dose groups (10-40 mg) and the higher dose groups (50 – 60 mg). According to the sponsor, overall the incidence of adverse events was higher in the subjects treated with Adderall XR compared with the subjects who received placebo. According to the sponsor, the most frequently reported treatment-emergent adverse events and with a higher incidence in Adderall-XR were anorexia, insomnia, abdominal pain, weight loss, nervousness and dizziness. According to the sponsor, systolic and diastolic blood pressure were increased by an average of 1.1 mmHg and 1.9 mmHg, respectively in subjects who were exposed to Adderall XR for at least 6 months. The sponsor stated that these increases were not clinically significant. According to the sponsor, there were no deaths reported in any of the studies. Refer to the medical review for the Agency's evaluation of safety.

2.2.4.3. Does this drug prolong the QT or QTc interval?

According to the sponsor, no subject who was exposed to Adderall XR for at least 6 months had a QT, QTcB or QTcF > 500 msec at month 6. Therefore, there was no evidence of significant QT interval prolongation after 6 months exposure to Adderall XR. QT prolongation is not described in the currently approved label for pediatric (6-12 years) and adults.

2.2.4.4. What is the dosing regimen recommended for adolescents and is this consistent with dose –response relationship observed?

The sponsor is recommending a dose (b) (4) for adolescents (b) (4) The pharmacokinetics of d and l-amphetamine after administration of 10 to 40 mg/day of Adderall XR to adolescents is similar to adults and supports the dosing recommendation. The dosing recommendation is consistent with the dose- response (efficacy and safety) reported by the sponsor in the pivotal safety and efficacy.

2.2.5. What are the Pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1. Are the pharmacokinetics of dextro and levo-amphetamine linear after administration Adderall XR to adolescents (age 13 – 17 years)?

The pharmacokinetics of d- and l- amphetamine are linear over doses ranging from 10 mg to 40 mg in adolescent ADHD patients weighing ≤ 75 kg/165 lbs. The pharmacokinetics of d- and l-amphetamine are linear over doses ranging from 20 to 60 mg in pediatric ADHD patients weighing > 75 kg/165lbs. Log-log plots of Cmax and AUC were linear with slopes approximately equal to 1, indicating linear pharmacokinetics.

An open-label, single-dose, 3-treatment, 3-period, randomized, crossover study was conducted to assess the pharmacokinetics of single 10 to 60 mg doses of Adderall XR in adolescents with Attention- Deficit/Hyperactivity Disorder (ADHD). Seventeen healthy, adolescent subjects aged 13 – 17 years and weighing less than or equal to 75 kg/165lbs with ADHD comprised the primary cohort. Each subject was assigned to one of three treatment sequences according to a randomization schedule with a target of 4 subjects per treatment sequence. Each subject received their assigned treatment of a single oral dose of 10 mg, 20 mg, or 40 mg of Adderall XR after an overnight fast for at least 10 hours during all study periods. Subjects were crossed over to the remaining treatments per the randomization schedule with a 7-day washout period between treatments. The secondary cohort included a target of 6 healthy adolescents with ADHD, weighing more than 75 kg/165 lbs. Each subject received their assigned treatment of a single oral dose of 20 mg, 40 mg or 60 mg of Adderall XR after an overnight fast during the first study period. Subjects were crossed over to the alternate treatments for subsequent study period with a 7 day washout period between treatments. The following tables contain the results. Data shown are the mean ± SD except for Tmax.

Table 3: Summary of Pharmacokinetic Parameters for d-amphetamine after Oral administration of 10 mg, 20 mg and 40 mg of Adderall XR to Adolescent subjects weighing ≤ 75 kg/165 lbs (Mean ±SD)

Parameter	10 mg	20 mg	40 mg
Cmax (ng/mL)	18.4 ± 2.96	34.1 ± 7.80	69.6 ± 15.17
Tmax (h) (median)	3.93	4.99	5.00
AUC (0-t)(h*ng/mL)	333 ± 60.8	667 ± 119	1372 ± 243
AUC∞ (h*ng/mL)	351 ± 56.9	689 ± 128	1426 ± 285
T ½ (h)	10.8 ± 2.65	11.0 ± 2.28	11.4 ± 2.93
Cl/F (mL/min)	366 ± 65.3	377 ± 87.7	364 ± 73.2
Vz/F (L)	337 ± 67.4	352 ± 67.6	351 ± 68.3

Table 4: Summary of Pharmacokinetic Parameters for l-amphetamine after Oral administration of 10 mg, 20 mg and 40 mg of Adderall XR to Adolescent subjects weighing ≤ 75 kg/165 lbs (Mean ± SD)

Parameter	10 mg	20 mg	40 mg
Cmax (ng/mL)	5.80 ± 0.86	11.3 ± 2.45	22.7 ± 4.84
Tmax (h) (median)	4.00	5.01	5.00
AUC (0-t)(h*ng/mL)	111 ± 25.7	246 ± 57.0	511 ± 102.8
AUC∞ (h*ng/mL)	129 ± 28.6	267 ± 62.7	554 ± 145.7
T ½ (h)	12.9 ± 4.54	13.5 ± 3.62	14.2 ± 4.82
Cl/F (mL/min)	337 ± 71.2	331 ± 94.4	319 ± 77.9
Vz/F (L)	358 ± 74.9	369 ± 70.9	372 ± 73.8

Table 5: Summary of Pharmacokinetic Parameters for d-amphetamine after Oral administration of 20 mg, 40 mg and 60 mg of Adderall XR to Adolescent subjects weighing > 75 kg/165 lbs (Mean ± SD)

Parameter	20 mg	40 mg	60 mg
Cmax (ng/mL)	29.4 ± 2.70	60.7 ± 5.91	81.6 ± 9.16
Tmax (h) (median)	5.0	4.49	7.48
AUC (0-t)(h*ng/mL)	563 ± 69.4	1133 ± 183.3	1893 ± 306.9
AUC∞ (h*ng/mL)	589 ± 84.2	1177 ± 2.4.0	2001 ± 366.2
T ½ (h)	12.4 ± 2.05	12.0 ± 1.75	13.2 ± 2.45
Cl/F (mL/min)	432 ± 61.7	436 ± 77.3	388 ± 86.2
Vz/F (L)	457 ± 42.4	443 ± 46.4	431 ± 53.2

Table 6: Summary of Pharmacokinetic Parameters for l-amphetamine after Oral administration of 20 mg, 40 mg and 60 mg of Adderall XR to Adolescent subjects weighing > 75 kg/165 lbs (Mean ± SD)

Parameter	20 mg	40 mg	60 mg
Cmax (ng/mL)	9.60 ± 0.97	19.5 ± 1.78	26.4 ± 1.97
Tmax (h) (median)	4.98	4.49	7.48
AUC (0-t)(h*ng/mL)	205 ± 30.6	414 ± 76.5	684 ± 129
AUC∞ (h*ng/mL)	225 ± 39.1	445 ± 93.0	758 ± 173
T ½ (h)	15.0 ± 2.78	14.7 ± 2.71	16.4 ± 3.95
Cl/F (mL/min)	380 ± 65.1	389 ± 83.8	347 ± 91.4
Vz/F (L)	485 ± 58.6	480 ± 48.0	475 ± 73.5

Figure 6: Relationships between Cmax and AUC_∞ and dose of l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb.

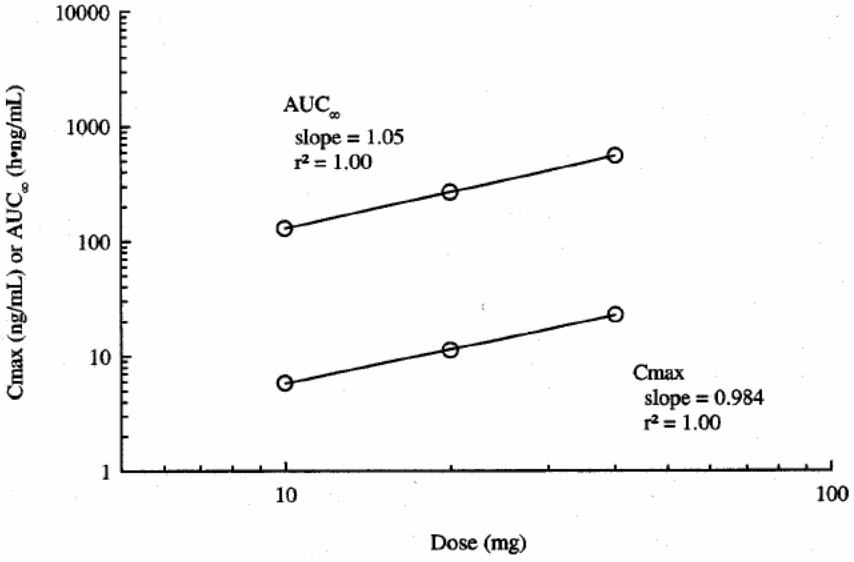


Figure 2 (above)

Figure 5: Relationships between Cmax and AUC_∞ and dose of d-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb.

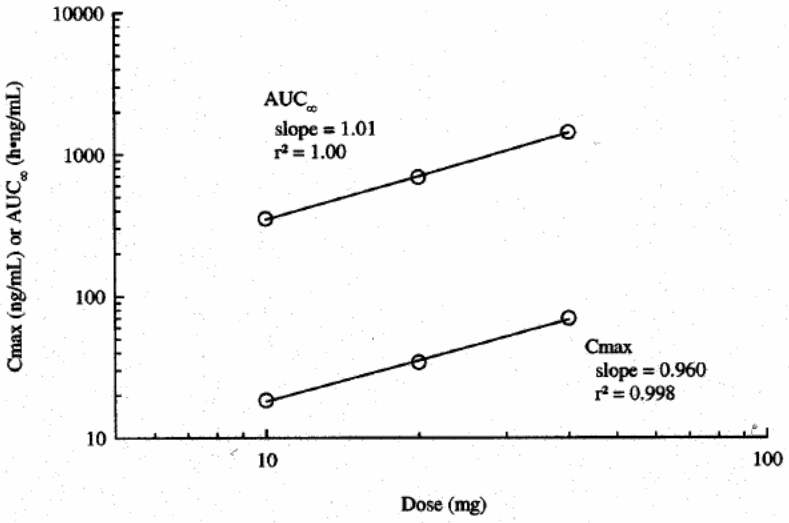


Figure 3

2.3. Intrinsic Factors

2.3.1. How do the pharmacokinetics of d and l- amphetamine compare between pediatric patients (6 –12 years), adolescents (13 –17 years) and adults?

A comparison of means among age groups demonstrated statistically significant differences for all d-amphetamine parameters except Tmax and Vz/F, T ½ and Cmax for l-amphetamine. Contrasts between the age groups showed that all of the significant differences occurred between the pediatric ADHD population and the adolescent ADHD and/or healthy adult populations with no significant differences between adolescents and adults. The range of individual patient or subject values was essentially the same in the 6 to 12 and 13 to 17 year ADHD groups and in healthy adults (22 – 46 years). Although Vz/F did not appear to vary between adolescents and adults, pediatric patients tended to have lower values. Pediatric patients had lower values for t ½ and higher values for Cmax than the other age groups.

Data were selected from 3 pharmacokinetic studies with Adderall XR. The pediatric and adult populations were historical controls. Study SLI381.107 was a two-period, two-sequence, two-treatment comparison of single doses of 1 x 40 mg capsules in pediatric patients (6 to 12 years of age) with Attention Deficit Hyperactivity Disorder (ADHD). Study SLI381.108 was a three period, three sequence, three treatment comparison of single doses of 20 mg, 40 mg and 60 mg in healthy adult subjects. Study SLI381.110 was a three period, six-sequence, three treatment comparison of single doses of 10 mg, 20 mg and 40 mg in adolescent patients (ages 13 –17 years) weighing ≤ 75 kg/165 lbs or 20 mg, 40 mg and 60 mg in adolescent ADHD patients (ages 13 –17 years) weighing > 75 kg/165 lbs. Mean values for Cmax, Tmax, AUC∞, t ½, CL/F and Vz/F were compared among age groups using an analysis of variance with age group (pediatric, adolescent, adult) as the classification variable. Comparisons between age groups were done using the least square means and a t-test. The results of the analysis are presented in the following tables.

Table 7: Summary of Pharmacokinetic Parameters

Isomer = d- amphetamine				
Parameter	Age Group	N	Mean ± SD	
Cl/F (mL/min)	6-12 13-17 Adult	17 21 12	337.20 ± 88.94 384.45 ± 79.75 404.77 ± 71.16	
Cl/F/kg (mL/min/kg)	6-12 13-17 Adult	17 21 12	8.28 ± 1.55 5.85 ± 1.16 5.49 ± 0.74	
Cmax (ng/mL)	6-12 13 – 17 Adult	17 21 12	98.61 ± 28.21 67.03 ± 13.66 67.94 ± 10.27	
Tmax (h)	6 – 12 13 – 17 Adult	20 21 12	5.35 ± 3.25 4.94 ± 2.11 5.00 ± 1.13	
Vz/F/kg (L/kg)	6 – 12 13 – 17 Adult	17 21 12	5.84 ± 0.92 5.66 ± 0.66 4.80 ± 0.39	
T ½ (h)	6-12 13 – 17 Adult	17 21 12	8.23 ± 1.07 11.58 ± 2.62 10.28 ± 1.50	
AUC (h*ng/mL)	6-12 13-17 Adult	17 21 12	1573.95 ± 377.52 1354.96 ± 283.69 1270.20 ± 220.83	

Table 8: Summary of Pharmacokinetic Parameters

Isomer = l- amphetamine				
Parameter	Age Group	N	Mean ± SD	
Cl/F (mL/min)	6-12 13-17 Adult	17 21 12	334.70 ± 102.05 339.02 ± 84.05 354.08 ± 71.16	
Cl/F/kg (mL/min/kg)	6-12 13-17 Adult	17 21 12	8.16 ± 1.62 5.15 ± 1.21 4.83 ± 0.79	
Cmax (ng/mL)	6-12 13 – 17 Adult	17 21 12	30.27 ± 8.57 21.79 ± 4.41 22.14 ± 3.81	
Tmax (h)	6 – 12 13 – 17 Adult	20 21 12	5.45 ± 3.21 5.08 ± 2.23 5.33 ± 0.89	
Vz/F/kg (L/kg)	6 – 12 13 – 17 Adult	17 21 12	6.54 ± 1.11 6.04 ± 0.71 5.18 ± 0.39	
T ½ (h)	6-12 13 – 17 Adult	17 21 12	9.40 ± 1.51 14.32 ± 4.26 12.67 ± 2.12	
AUC (h*ng/mL)	6-12 13-17 Adult	17 21 12	538.91 ± 148.34 522.92 ± 140 491.33 ± 28.37	

Table 9: Statistical comparison of pharmacokinetic parameters for d- and l-amphetamine between age groups after oral administration of Adderall XR

Parameter	p-value[1]		
	Pediatric vs Adolescent	Pediatric vs Adult	Adolescent vs Adult
d-amphetamine	Pediatric vs Adolescent	Pediatric vs Adult	Adolescent vs Adult
AUC∞	0.0337	0.0117	0.4491
Cl/F	0.0807	0.0321	0.4923
Vz/F	<0.0001	<0.0001	0.3740
T ½	<0.0001	0.0080	0.0723
Cmax	<0.0001	0.0001	0.8997
Tmax	0.5964	0.6976	0.9478
l-amphetamine			
AUC∞	0.7137	0.2794	0.4235
Cl/F	0.8785	0.5533	0.6310
Vz/F	<0.0001	0.0002	0.4623
T ½	<0.0001	0.0073	0.1468
Cmax	<0.0001	0.0008	0.8780
Tmax	0.6381	0.8981	0.7817

[1]p-value for t-test between age groups

2.3.2. What are the effects of weight and gender on the pharmacokinetics of Adderall XR across the different age groups?

Comparison of the pharmacokinetics of d- and l- amphetamine after oral administration of Adderall XR in pediatric (6 – 12 years) and adolescents (13 –17 years) ADHD patients and healthy adult volunteers (22 –46 years) indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. There were negative relationships between AUC∞, Cmax and body weight for d- and l-amphetamine across the 3 age groups that were significant. There were significant positive relationships between Cl/F and Vz/F and body weight for d- and l-amphetaminc. Body weight increased with age through adolescence and then became relatively constant through the adult years and this relationship appears to be independent of gender.

Although there were trends across age groups, there did not appear to be substantial differences within age groups between males and females in the range of values for either d- and l-amphetamine for AUC∞, t ½, Cmax or Tmax.

Data were selected from 3 pharmacokinetic studies with Adderall XR. Study SLI381.107 was a two-period, two-sequence, two-treatment comparison of single doses of 1 x 40 mg capsules in pediatric patients (6 to 12 years of age) with Attention Deficit Hyperactivity Disorder (ADHD). Study SLI381.108 was a three period, three sequence, three treatment comparison of single doses of 20 mg, 40 mg and 60 mg in healthy adult subjects. Study SLI381.110 was a three period, six-sequence, three treatment comparison of single doses of 10 mg, 20 mg and 40 mg in adolescent patients (ages 13 –17 years) weighing ≤ 75 kg/165 Ibs or 20 mg, 40 mg and 60 mg in adolescent ADHD patients (ages 13 –17 years) weighing > 75 kg/165 Ibs. Mean values for Cmax, Tmax, AUC∞, t ½, CL/F and Vz/F were compared among age groups using an analysis of variance with age group (pediatric, adolescent, adult) as the classification variable. Comparisons between age groups were done using the least square means and a t-test. Graphical presentations are presented below.

Fig 4

Figure 1: Relationship between AUC_∞ and weight for d-amphetamine after oral administration of ADDERALL XR®.

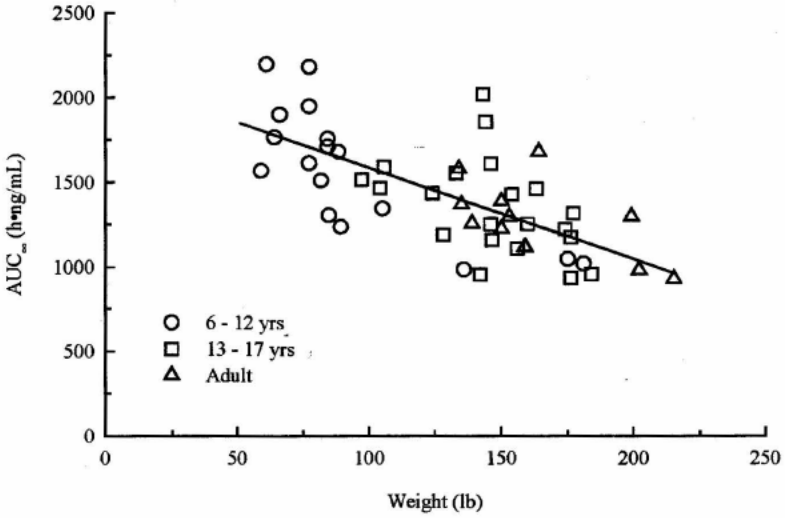


Figure 2: Relationship between AUC_∞ and weight for l-amphetamine after oral administration of ADDERALL XR®.

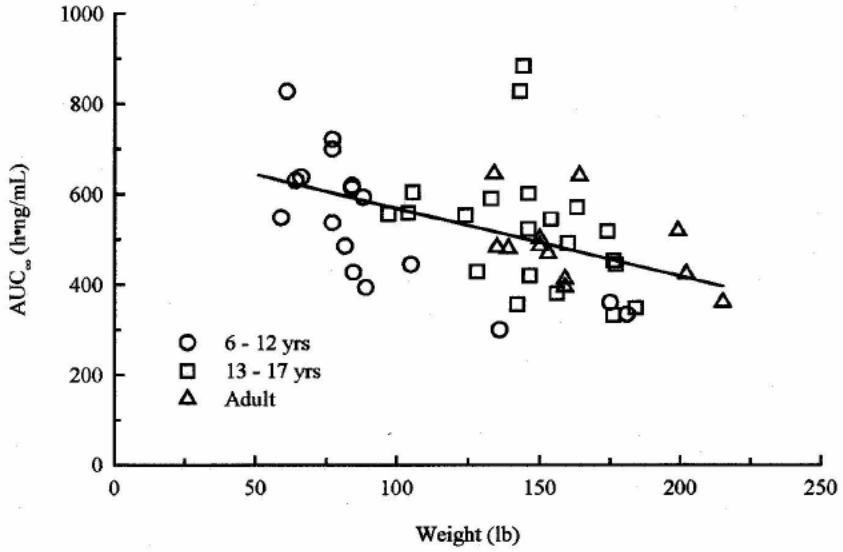
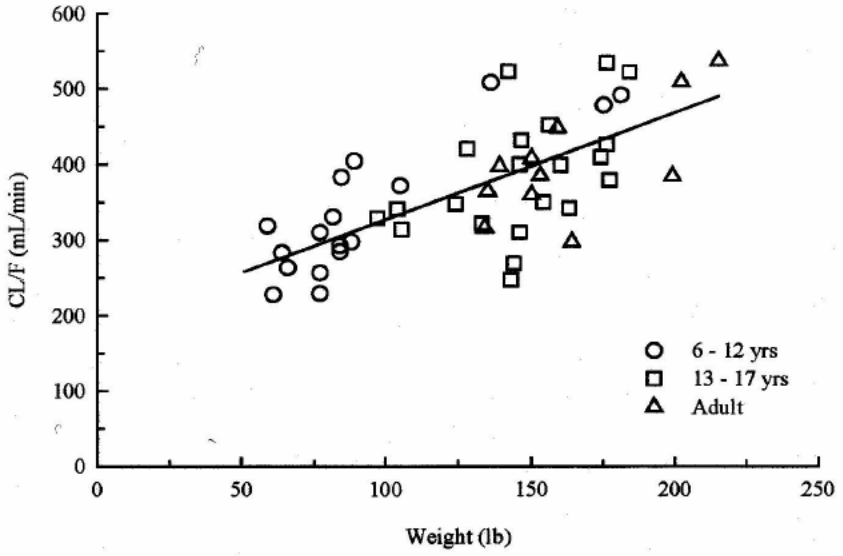


Figure 3: Relationship between CL/F and weight for d-amphetamine after oral administration of ADDERALL XR®.



Figs 5 (above) and 6 (below)

Figure 10: Relationship between Cmax and weight for l-amphetamine after oral administration of ADDERALL XR®.

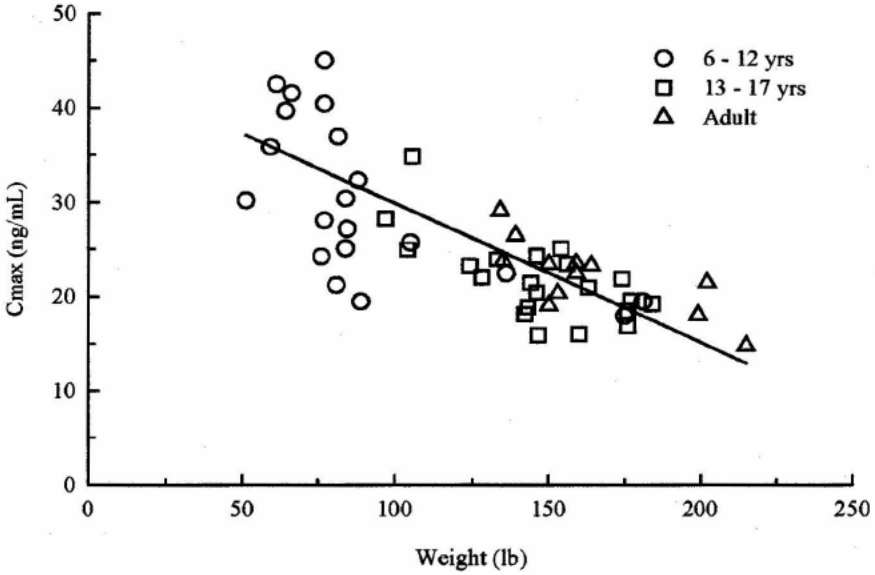
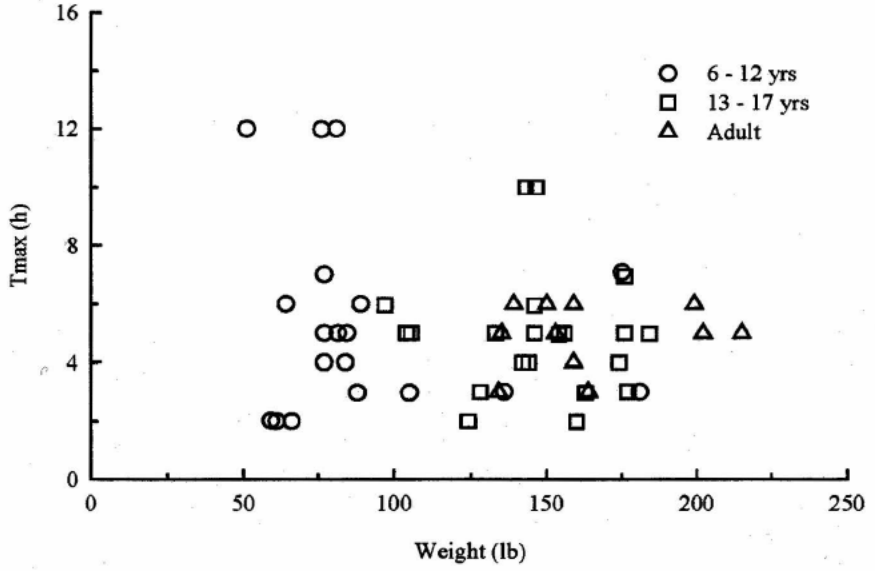


Figure 11: Relationship between Tmax and weight for d-amphetamine after oral administration of ADDERALL XR®.



Figs 7 (above) and 8 (below)

Figure 8: Relationship between t½ and weight for l-amphetamine after oral administration of ADDERALL XR®.

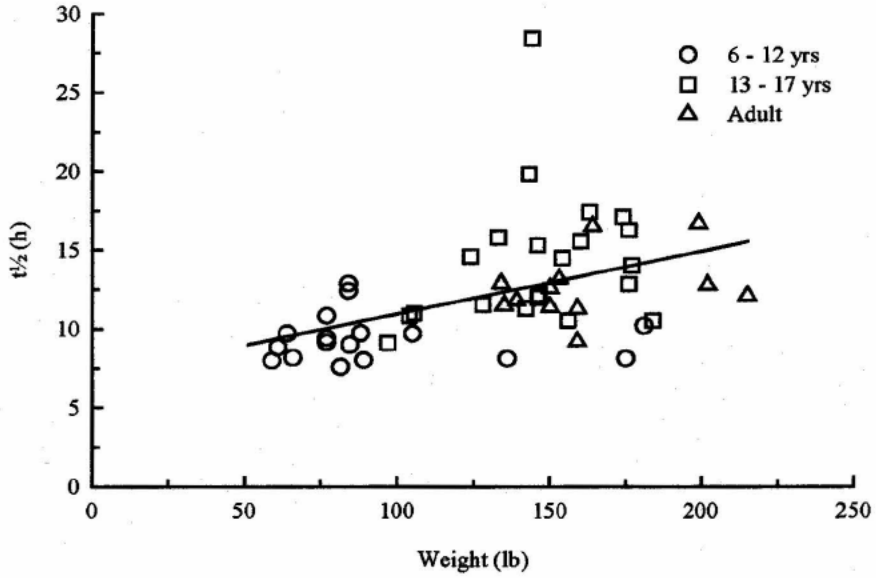
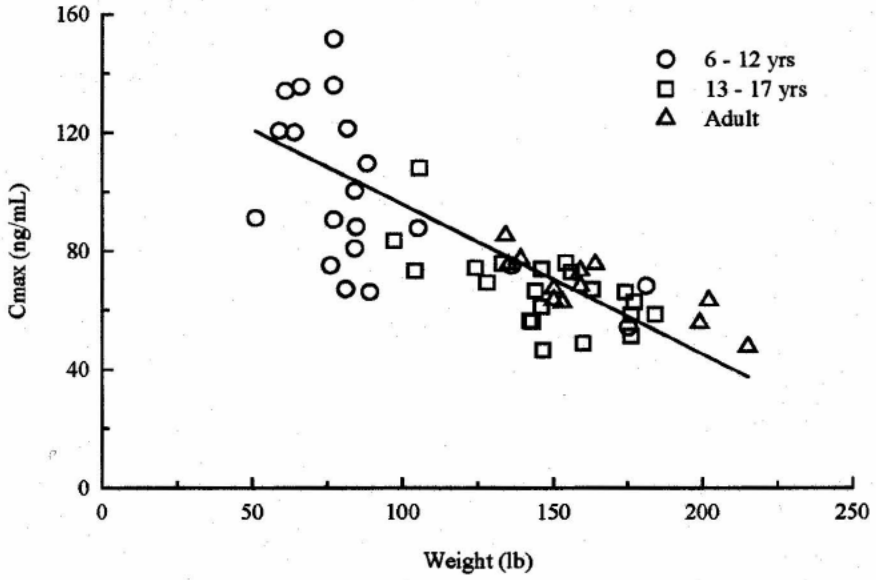


Figure 9: Relationship between Cmax and weight for d-amphetamine after oral administration of ADDERALL XR®.



Figs 9 (above) and 10 (below)

Figure 25: Relationship between AUC_∞ and gender for d-amphetamine after oral administration of ADDERALL XR®.

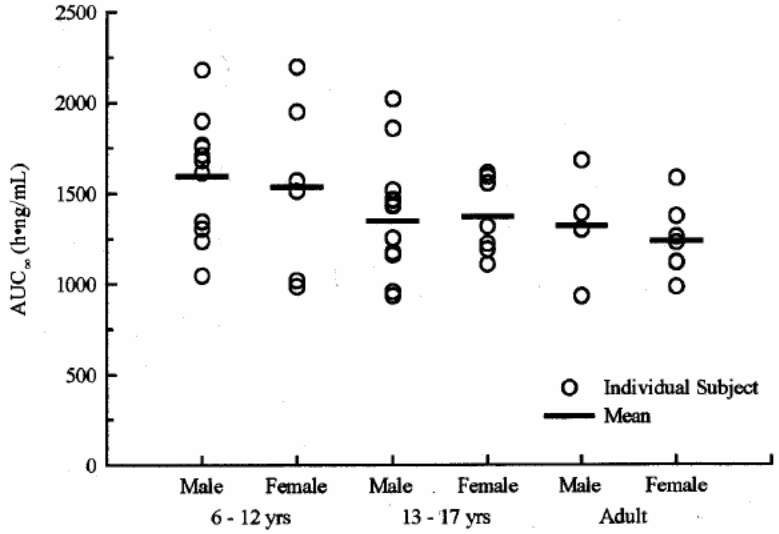
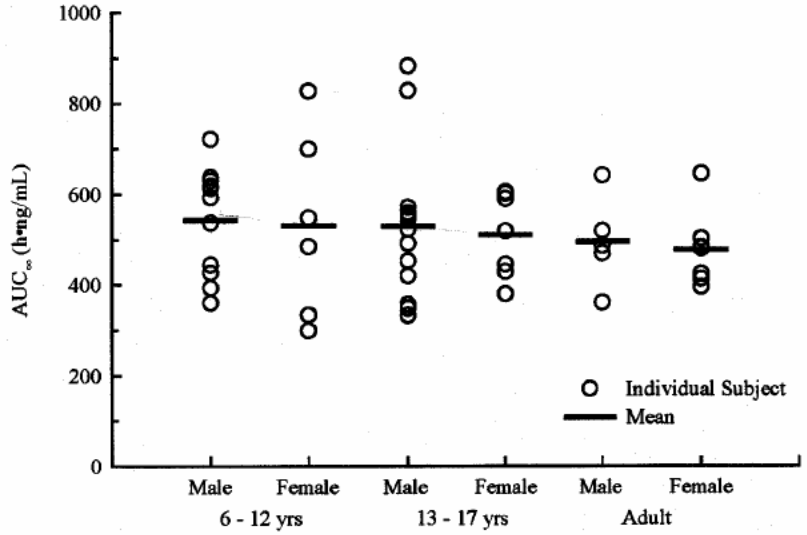


Figure 26: Relationship between AUC_∞ and gender for l-amphetamine after oral administration of ADDERALL XR®.



Figures 11 (above) and 12 (below)

Figure 33: Relationship between Cmax and gender for d-amphetamine after oral administration of ADDERALL XR®.

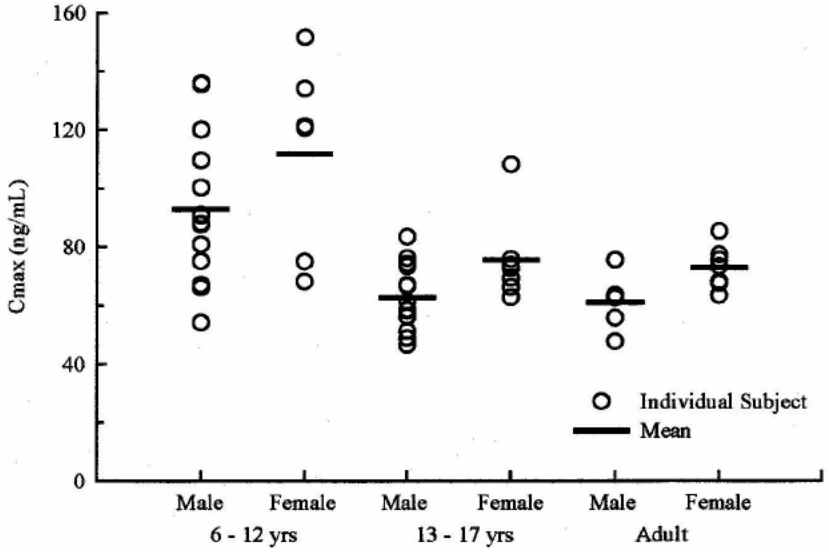
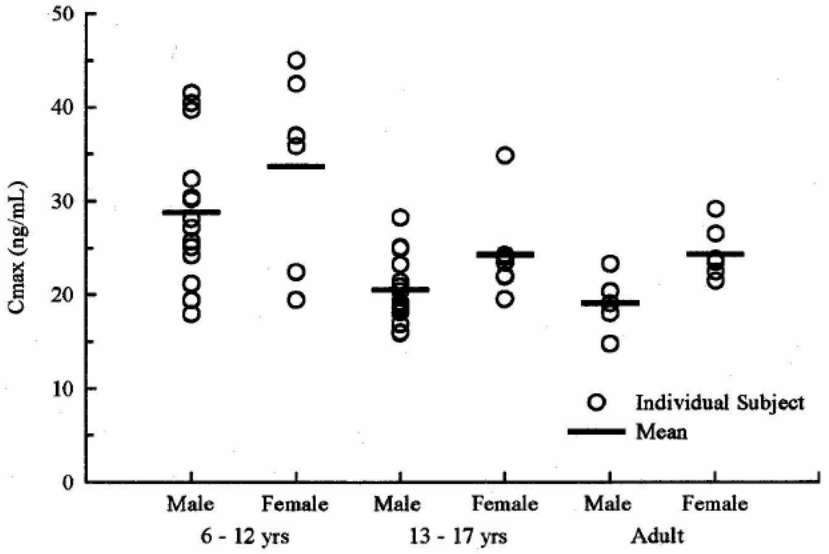


Figure 34: Relationship between Cmax and gender for l-amphetamine after oral administration of ADDERALL XR®.



Figures 13 (above) and 14 (below)

Table 10: Statistical evaluation of the effect of body weight on the pharmacokinetic parameters for d- and l- amphetamine after oral administration of Adderall XR

Parameter	p-value[1]	
	d-amphetamine	l-amphetamine
AUC∞ (h*ng/mL)	<0.0001	0.0006
CL/F (mL/min)	<0.0001	0.0003
Vz/F (L)	<0.0001	<0.0001
T ½ (h)	0.0006	0.0014
Cmax (ng/mL)	<0.0001	<0.0001

Table 11: Multivariate statistical evaluation of the effect of gender, age, and body weight on the pharmacokinetic parameters for d- and l-amphetamine after oral administration of Adderall XR

Parameter	p-value[1]					
	d-amphetamine			l- amphetamine		
	Gender	Age	Weight	Gender	Age	Weight
AUC∞ (h*ng/mL)	0.5662	0.5638	0.0184	0.3283	0.6405	0.1240
CL/F (mL/min)	0.6505	0.1306	0.0651	0.3073	0.4709	0.0821
Vz/F (L)	0.8955	0.6208	<0.0001	0.4613	0.3712	<0.0001
T ½ (h)	0.8379	0.0686	0.0034	0.6680	0.1788	0.0222
C max (ng/mL)	0.1132	0.0931	<0.0001	0.1013	0.0703	<0.0001

[1]p-value for the indicated effect from an analysis of variance

2.3.2.1. Are there any dose adjustments recommended for adolescents based on intrinsic factors?

No dose adjustments due to gender and age are recommended. There are no dose adjustments for patients weighing ≤ 75 kg/165 lbs.

2.4. Extrinsic Factors

The sponsor did not evaluate the effect of extrinsic factors (e.g. drugs, herbal products, diet, smoking, and alcohol use) in this patient population. It is expected that the effect of extrinsic factors will be similar to that reported and included in the label for adults.

2.5. General Biopharmaceutics

The dosage formulation and strengths to be used for this patient population are approved and commercially available. Adderall XR is approved in dosage strengths of 5, 10, 15, 20, 25 and 30 mg capsules. The pivotal clinical trials were conducted with commercially available 10, 20 and 30 mg Adderall XR capsules. Adderall XR 40, 50 and 60 mg capsules were submitted previously (NDA 21-303 SE5-005, SCS-006) and were approvable pending receipt of additional supportive clinical data. No new formulation are proposed for this application.

2.6. Analytical Method

2.6.1. What bioanalytical method is used to assess d- and l-amphetamine concentrations?

A validated LC/MS/MS was used to determine the concentrations of d- and l-amphetamine in plasma. The method is the same as that submitted and reviewed under the original application, NDA 21-303. The sensitivity of the assay is 0.5 ng/mL and the range is 0.5 to 75 ng/mL for both d- and l- amphetamine. For calibration standards, the mean percent accuracies ranged from 96 to 107.1% of the target concentrations and the precision ranged from 0.4 to 2.3% for both d-amphetamine and l-amphetamine. For the quality control samples (QC), the mean percent accuracies ranged from 98.3% to 100.1% and the precision ranged from 2.1% to 3.8% for both d- and l- amphetamine. The analytical method was found to be sensitive, specific, precise, accurate and reproducible for the quantitative determination of d- and l-amphetamine in human plasma. The calibration curves were acceptable. The analytical method used for determination of d- and l-amphetamine concentrations in the clinical studies submitted with this application is acceptable.

3. Detailed Labeling Recommendations

Clinical Pharmacology section

Double underline are reviewer modifications
~~Deletions are crossed out~~

Clinical Pharmacology: Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of ADDERALL XR® in pediatric (6-12 years) and adolescent (13-17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC_{∞}) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight. (Note to medical officer: (b) (4))

Pediatric Population

It is recommended the sponsor keeps the following paragraph in Pediatric Patients subsection of the approved label

(b) (4)

Gender: It is recommended the sponsor retains the statement in the approved label

(b) (4)

Systemic exposure to amphetamine was 20 to 30 % higher in women (N=20) than in men (N=20) due to higher dose administered to women on a mg/kg body weight basis. When the exposure (Cmax and AUC) were normalized by dose (mg/kg), these differences diminished.

Dosage and Administration:

The sponsor's recommendation is acceptable

4. Appendices

4.2. Package Insert

(b) (4)

15 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

4.2. Individual Study reviews

Title (Study No. SLI381-110): A Phase I Study to Assess the Pharmacokinetics of Single 10 mg to 60 mg Doses of Adderall XR in Adolescents Aged 13 – 17 with Attention-Deficit/Hyperactivity Disorder (ADHD)

Objectives: 1) To assess the pharmacokinetics of Adderall XR at doses of 10 to 40 mg in adolescents aged 13 – 17 with ADHD and weighing less than 75 kg/165 lbs 2) To assess the pharmacokinetics of Adderall XR at doses of 20 to 60 mg in adolescents aged 13 – 17 years weighing greater than 75 kg/165lbs. 3) To assess the effect of age, gender, and body weight on the pharmacokinetics of Adderall XR in adolescents aged 13 – 17 with ADHD

Study Design: This was an open-label, single-dose, 3-treatment, 3-period, randomized, crossover, Phase I study. Seventeen healthy, adolescent subjects aged 13 – 17 and weighing less than or equal to 75 kg/165 lbs with ADHD comprised the primary cohort (Cohort 1). The enrollment design required that at least 25% and not more than 75% were female. Each subject was assigned to one of three treatment sequences according to a randomization schedule with a target of 4 subjects per treatment sequence. Each subject received their assigned treatment of a single oral dose of 10 mg, 20 mg, or 40 mg of Adderall XR after an overnight fast for at least 10 hours during all study periods. Subjects were crossed over to the remaining treatments per the randomization schedule with a 7-day washout period between treatments.

The secondary cohort (cohort 2) included a target of 6 healthy adolescents (aged 13 –17) with ADHD, weighing more than 75 kg/165 lbs. There was no gender distribution requirement for the secondary cohort. Each was assigned to one of three treatment sequences. Each subject was randomly assigned to one of 3 treatments of a single oral dose of 20 mg, 40 mg and 60 mg of Adderall XR after an overnight fast. Subjects were crossed over to the subsequent treatments with a seven (7) day washout period between treatments. Blood was collected for plasma quantitation of d-amphetamine and l-amphetamine at 0 (pre-dose), 1, 2, 3, 4, 5, 6,7, 8, 9, 10, 11, 12, 14 and 24 hours post dose. For periods 1 through 3, additional blood collection for plasma quantitation of d-amphetamine and l-amphetamine was performed at 48 and 60 hours post dose.

Analytical Method: A validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method was used to quantitate plasma d-amphetamine and l-amphetamine concentrations for each sample. The validated lower limit of the assay (LOQ) was 0.5 ng/mL. The mean percent accuracies ranged from 96% to 107.1% of the target concentrations and the precision ranged from 0.4% to 2.3% for both d- and l-amphetamine.

Data Analysis: Pharmacokinetic parameters were calculated using non-compartmental methods. Statistical analyses were performed on pharmacokinetic parameters for all subjects. A parametric (normal-theory) general linear model was applied to the pharmacokinetic parameters to examine the differences among doses. Secondary, regression analysis was employed to estimate a change in a parameter as a function of increase or decrease in dose for AUC and Cmax based on a power model (i.e. P = a x Dose^b) to test dose proportionality. Log-Log plots of P vs Dose should be linear. Dose proportionality was concluded if parameter b was found to be approximately 1.

Results: Seventeen subjects enrolled into the study and 14 completed all 3 periods. Seventy one percent (12/17) of the subjects enrolled in Cohort 1 were male, 29% were female and 71% were Caucasian and 29% African- American. The mean age and weight were 14.8 ± 1.29 years and

132.29 ± 22.21 lbs, respectively. The mean plasma concentration time profiles for d- and l-amphetamine are provided in the attachments (Figures 1 - 4). The following table contains the pharmacokinetic parameters for d- and l- amphetamine

Summary of Pharmacokinetic Parameters for d-amphetamine after Oral administration of 10 mg, 20 mg and 40 mg of Adderall XR to Adolescent subjects weighing ≤ 75 kg/165 lbs

Parameter	10 mg	20 mg	40 mg
Cmax (ng/mL)	18.4 ± 2.96	34.1 ± 7.80	69.6 ± 15.17
Tmax (h)	3.93	4.99	5.00
AUC (0-t)(h*ng/mL)	333 ± 60.8	667 ± 119	1372 ± 243
AUC∞ (h*ng/mL)	351 ± 56.9	689 ± 128	1426 ± 285
T ½ (h)	10.8 ± 2.65	11.0 ± 2.28	11.4 ± 2.93
Cl/F (mL/min)	366 ± 65.3	377 ± 87.7	364 ± 73.2
Vz/F (L)	337 ± 67.4	352 ± 67.6	351 ± 68.3

Summary of Pharmacokinetic Parameters for l-amphetamine after Oral administration of 10 mg, 20 mg and 40 mg of Adderall XR to Adolescent subjects weighing ≤ 75 kg/165 lbs

Parameter	10 mg	20 mg	40 mg
Cmax (ng/mL)	5.80 ± 0.86	11.3 ± 2.45	22.7 ± 4.84
Tmax (h)	4.00	5.01	5.00
AUC (0-t)(h*ng/mL)	111 ± 25.7	246 ± 57.0	511 ± 102.8
AUC∞ (h*ng/mL)	129 ± 28.6	267 ± 62.7	554 ± 145.7
T ½ (h)	12.9 ± 4.54	13.5 ± 3.62	14.2 ± 4.82
Cl/F (mL/min)	337 ± 71.2	331 ± 94.4	319 ± 77.9
Vz/F (L)	358 ± 74.9	369 ± 70.9	372 ± 73.8

The pharmacokinetics of d- and l-amphetamine were dose proportional over the range of doses studied (Figure 5).

The mean plasma d- and l-amphetamine concentrations for subjects weighing > 75 kg/165 Ibs are provided in the attachments (Figures 7 – 10). Six subjects enrolled and 6 finished the study. The mean pharmacokinetic parameters are provided in the following tables

Summary of Pharmacokinetic Parameters for d-amphetamine after Oral administration of 20 mg, 40 mg and 60 mg of Adderall XR to Adolescent subjects weighing > 75 kg/165 lbs

Parameter	20 mg	40 mg	60 mg
Cmax (ng/mL)	29.4 ± 2.70	60.7 ± 5.91	81.6 ± 9.16
Tmax (h)	5.0	4.49	7.48
AUC (0-t)(h*ng/mL)	563 ± 69.4	1133 ± 183.3	1893 ± 306.9
AUC∞ (h*ng/mL)	589 ± 84.2	1177 ± 2.4.0	2001 ± 366.2
T ½ (h)	12.4 ± 2.05	12.0 ± 1.75	13.2 ± 2.45
Cl/F (mL/min)	432 ± 61.7	436 ± 77.3	388 ± 86.2
Vz/F (L)	457 ± 42.4	443 ± 46.4	431 ± 53.2

Summary of Pharmacokinetic Parameters for l-amphetamine after Oral administration of 20 mg, 40 mg and 60 mg of Adderall XR to Adolescent subjects weighing > 75 kg/165 lbs

Parameter	20 mg	40 mg	60 mg
Cmax (ng/mL)	9.60 ± 0.97	19.5 ± 1.78	26.4 ± 1.97
Tmax (h)	4.98	4.49	7.48
AUC (0-t)(h*ng/mL)	205 ± 30.6	414 ± 76.5	684 ± 129
AUC∞ (h*ng/mL)	225 ± 39.1	445 ± 93.0	758 ± 173
T ½ (h)	15.0 ± 2.78	14.7 ± 2.71	16.4 ± 3.95
Cl/F (mL/min)	380 ± 65.1	389 ± 83.8	347 ± 91.4
Vz/F (L)	485 ± 58.6	480 ± 48.0	475 ± 73.5

Plasma concentrations of both d- and l-amphetamine increased in a dose-proportional manner (Figure 12 and Table 5). Log-log plots of Cmax and AUC were linear with slopes approximately equal to 1, indicating linear pharmacokinetics.

The relationship between age, body weight or gender with the pharmacokinetics of d- and l-amphetamines is shown in Figures 13 – 27. There was a decrease in Cmax for both d- and l-amphetamine with increase in age. AUC∞ of d- and l- amphetamine was not affected by age. There was a trend towards an increase t ½ for both d- and l- amphetamine with increase age. Cmax and AUC∞ for both d- and l- amphetamine decreased with increased body weight. There was no statistically significant relationship observed between gender and any pharmacokinetic parameters (Figure 13 – 17 and Table 7).

Summary and Conclusions: The pharmacokinetics of d- and l- amphetamine are linear over doses ranging from 10 mg to 40 mg in pediatric ADHD patients weighing ≤ 75 kg/165 Ib. Log-log plots of Cmax and AUC∞ were linear with slopes approximately 1 and there were no significant differences among doses in CL/F, Vz/F or t ½. The pharmacokinetics of d- and l-amphetamine are linear over doses ranging from 20 to 60 mg in pediatric ADHD patients weighing > 75 kg/165 lbs. Log-Log plots of Cmax and AUC∞ were linear with slopes approximately 1. There was a statistically significant decrease in Cmax for both d- and l-amphetamine with age but AUC was not affected by age. There was a trend toward an increase in t ½ for both isomers with age which was statistically significant for both d- and l- amphetamine. Maximum exposure (Cmax) and AUC∞ for d- and l- amphetamine decreased as body weight increased. Both CL/F and Vz/F appeared to increase as body weight increased, resulting in no significant effect of weight on t ½.

Reviewer comments: The reviewer agrees with the sponsor's conclusions. The range of ages evaluated was narrow, hence caution should be exercised in making inferences to other patient populations.

Figure 1: Mean plasma concentrations of d-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb — linear axes.

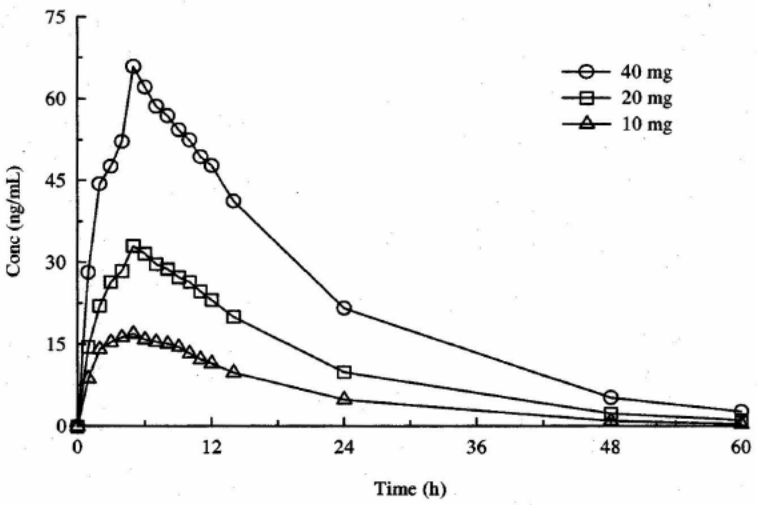


Figure 2: Mean plasma concentrations of d-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb — semi-logarithmic axes.

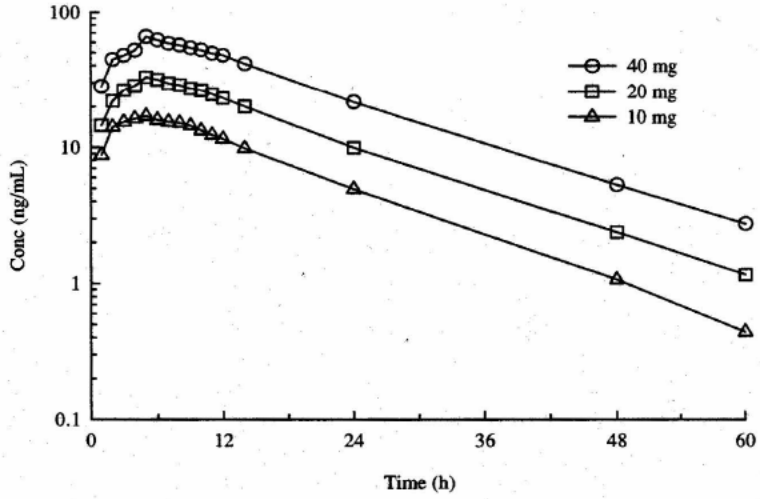


Figure 3: Mean plasma concentrations of l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb — linear axes.

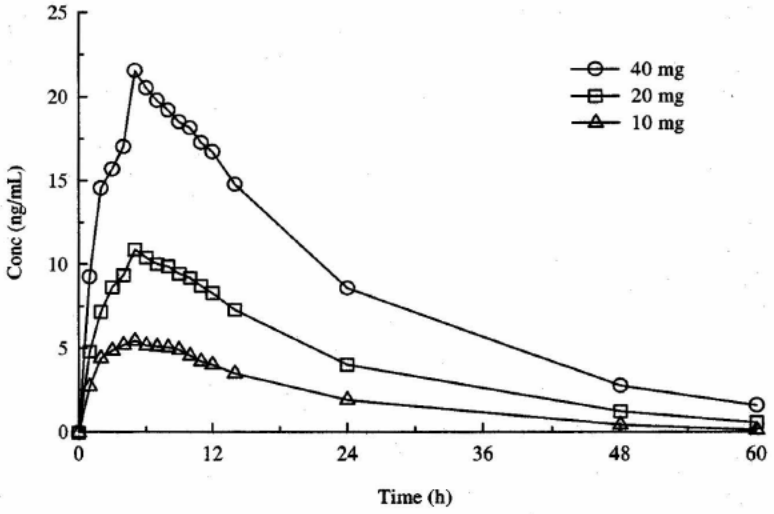


Figure 4: Mean plasma concentrations of l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb — semi-logarithmic axes.

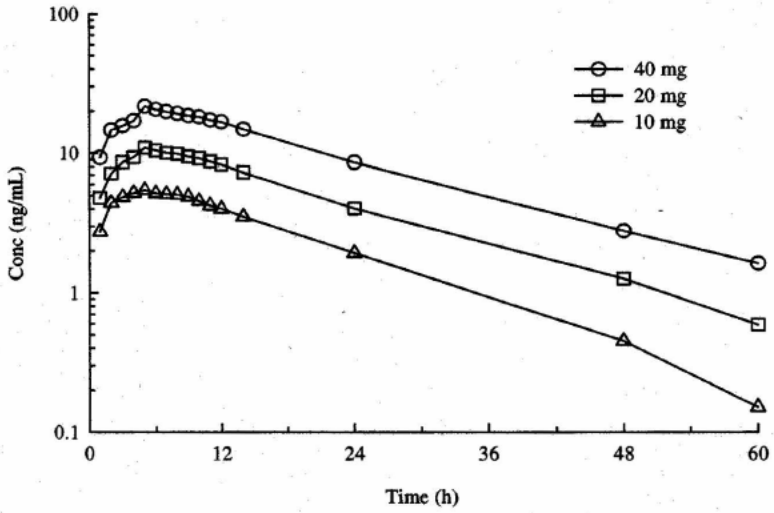


Table 3: Statistical comparison of Tmax and t½ for d- and l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb.

Parameter	p-value[1]
d-amphetamine	
Tmax	0.0148
t½	0.1450
CL/F	0.1821
Vz/F	0.2258
l-amphetamine	
Tmax	0.0457
t½	0.0659
CL/F	0.3051
Vz/F	0.4171

[1]Tmax: p-value from the Wilcoxon Rank Sum Test; t½: p-value for the treatment effect from an analysis of variance

Source: Appendix VI

Figure 5: Relationships between Cmax and AUC_∞ and dose of d-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb.

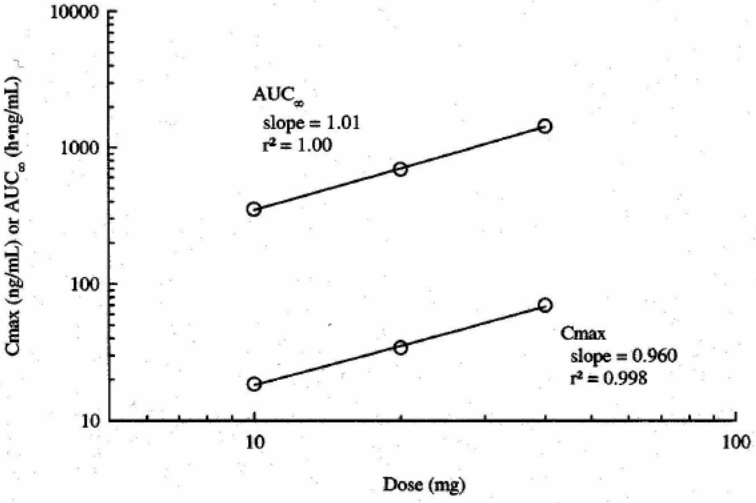


Figure 6: Relationships between Cmax and AUC_∞ and dose of l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb.

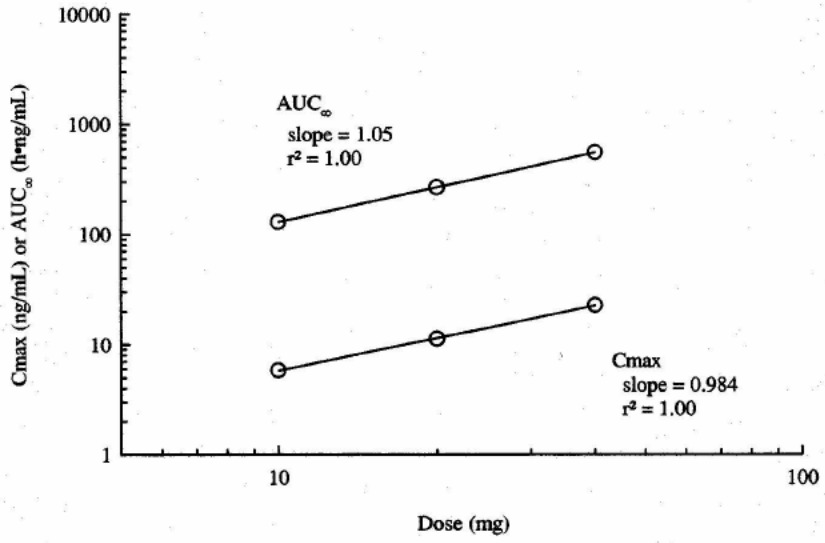


Figure 7: Mean plasma concentrations of d-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — linear axes.

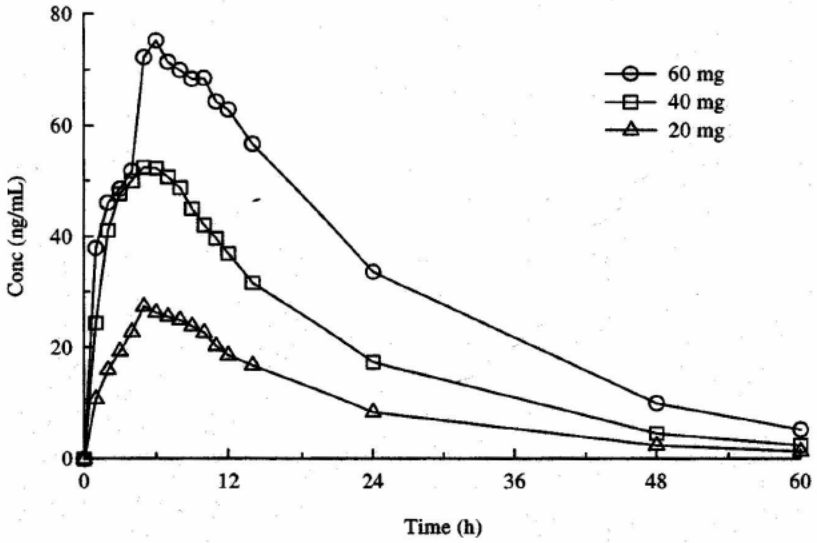


Figure 8: Mean plasma concentrations of d-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — semi-logarithmic axes.

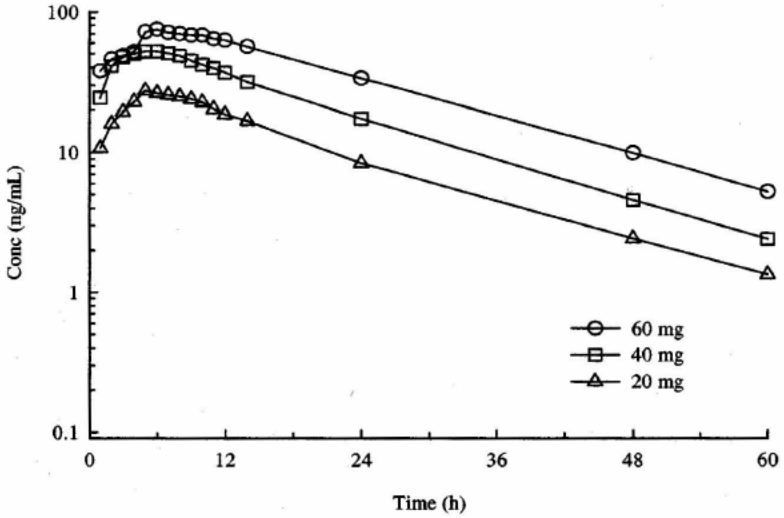


Figure 9: Mean plasma concentrations of l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — linear axes.

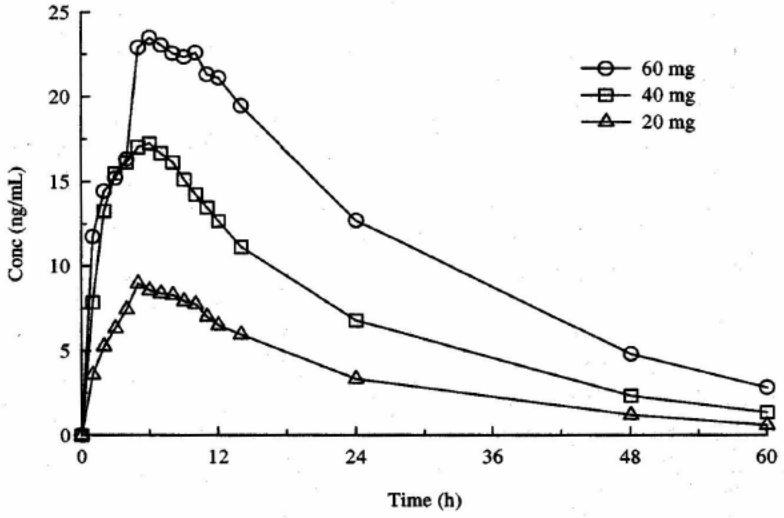


Figure 10: Mean plasma concentrations of l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — semi-logarithmic axes.

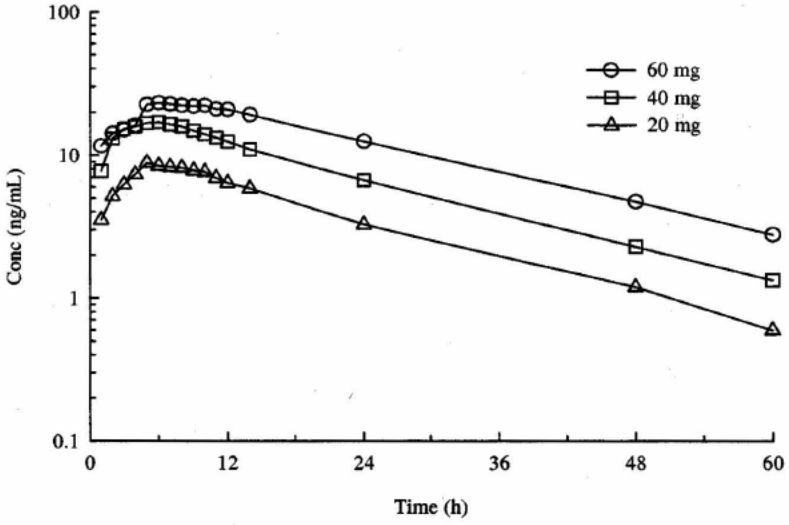


Table 4: Summary of pharmacokinetic parameters for d- and l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb.

Parameter[1]	20 mg	40 mg	60 mg
d-amphetamine			
Cmax (ng/mL)	29.4 ± 2.70	60.7 ± 5.91	81.6 ± 9.16
Tmax (h)	5.00	4.49	7.48
AUC_{0-t} (h•ng/mL)	563 ± 69.4	1133 ± 183.3	1893 ± 306.9
AUC_{∞} (h•ng/mL)	589 ± 84.2	1177 ± 204.0	2001 ± 366.2
t½ (h)	12.4 ± 2.05	12.0 ± 1.75	13.2 ± 2.45
CL/F (mL/min)	432 ± 61.7	436 ± 77.3	388 ± 86.2
Vz/F (L)	457 ± 42.4	443 ± 46.4	431 ± 53.2
l-amphetamine			
Cmax (ng/mL)	9.60 ± 0.97	19.5 ± 1.78	26.4 ± 1.97
Tmax (h)	4.98	4.49	7.48
AUC_{0-t} (h•ng/mL)	205 ± 30.6	414 ± 76.5	684 ± 129
AUC_{∞} (h•ng/mL)	225 ± 39.1	445 ± 93.0	758 ± 173
t½ (h)	15.0 ± 2.78	14.7 ± 2.71	16.4 ± 3.95
CL/F (mL/min)	380 ± 65.1	389 ± 83.8	347 ± 91.4
Vz/F (L)	485 ± 58.6	480 ± 48.0	475 ± 73.5

[1]Arithmetic mean ± standard deviation except for Tmax for which the median is reported.

Source: Appendix V

Table 5: Statistical comparison of pharmacokinetic parameters for d- and l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb.

Parameter[2]	Ratio (%)[1] Estimate	Confidence Interval		
d-amphetamine				
20 mg vs 40 mg				
Cmax	96.90	86.11	→	109.04
AUC_{0-t}	99.93	91.20	→	109.48
AUC_{∞}	100.54	91.66	→	110.28
60 mg vs 40 mg				
Cmax	89.54	79.57	→	100.76
AUC_{0-t}	111.21	101.50	→	121.84
AUC_{∞}	112.97	102.99	→	123.91
l-amphetamine				
20 mg vs 40 mg				
Cmax	98.46	89.18	→	108.70
AUC_{0-t}	99.71	90.08	→	110.37
AUC_{∞}	101.87	91.42	→	113.51
60 mg vs 40 mg				
Cmax	90.62	82.08	→	100.04
AUC_{0-t}	109.99	99.37	→	121.75
AUC_{∞}	113.06	101.47	→	125.98

[1]Geometric mean ratio. Based on analysis of natural log-transformed data.
[2]Parameters were normalized to the 20 mg dose prior to analysis.

Source: Appendix VII

Figure 12: Relationships between Cmax and AUC_∞ and dose of l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb.

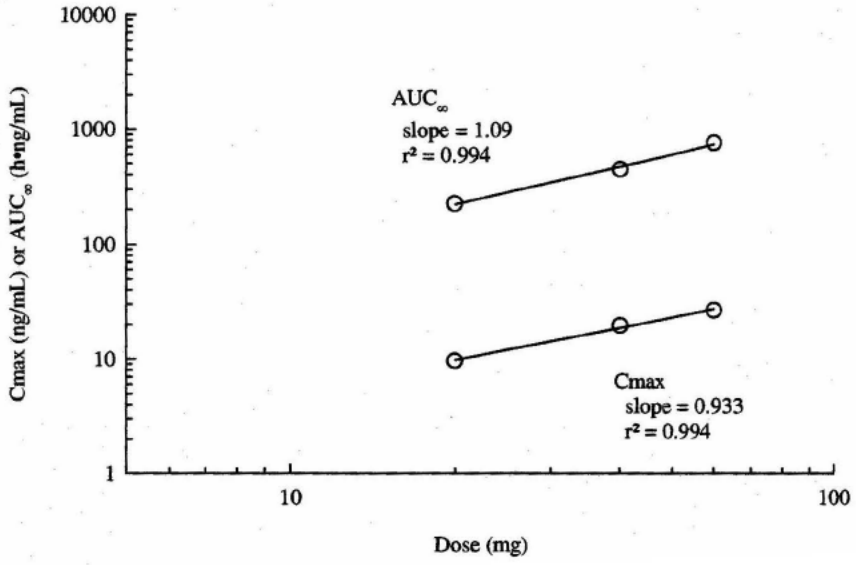


Figure 13: Relationship between dose-normalized Cmax and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

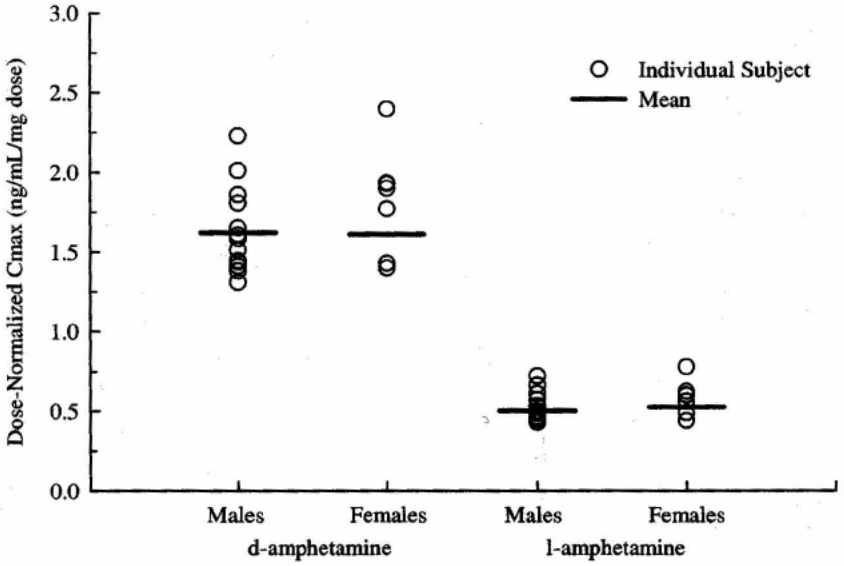


Figure 14: Relationship between dose-normalized AUC_∞ and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

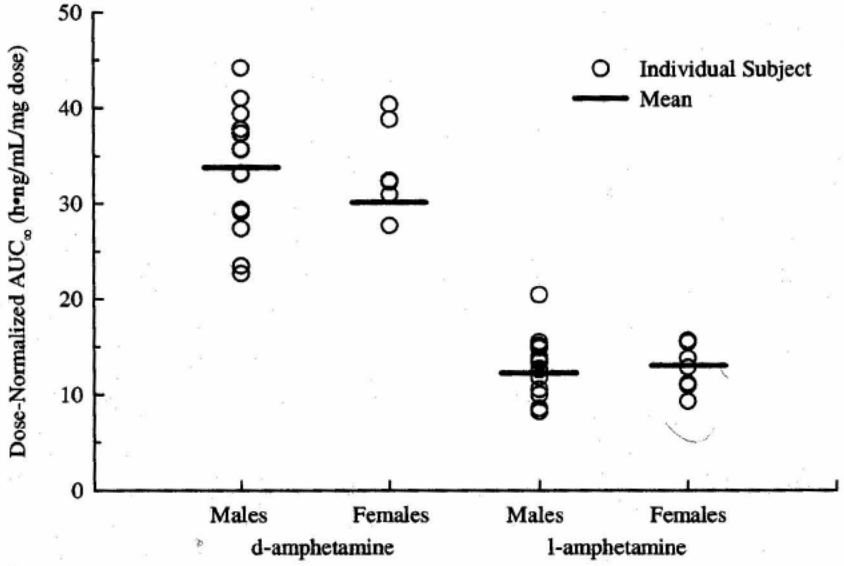


Figure 15: Relationship between t½ and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

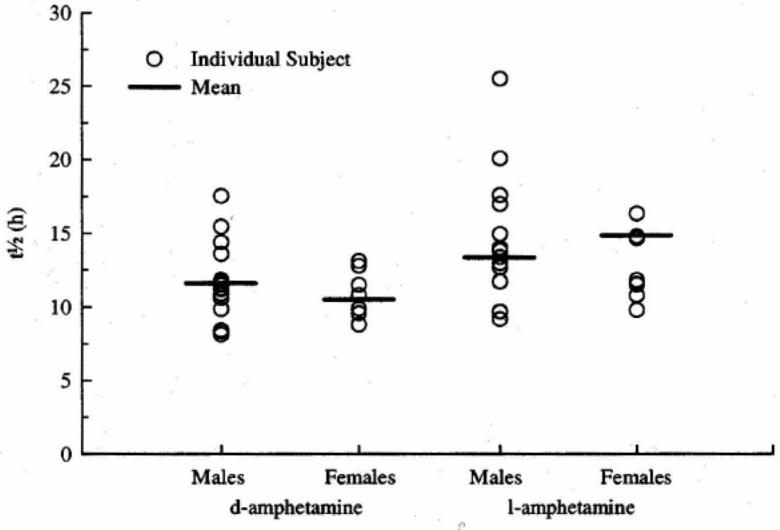


Figure 16: Relationship between CL/F and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

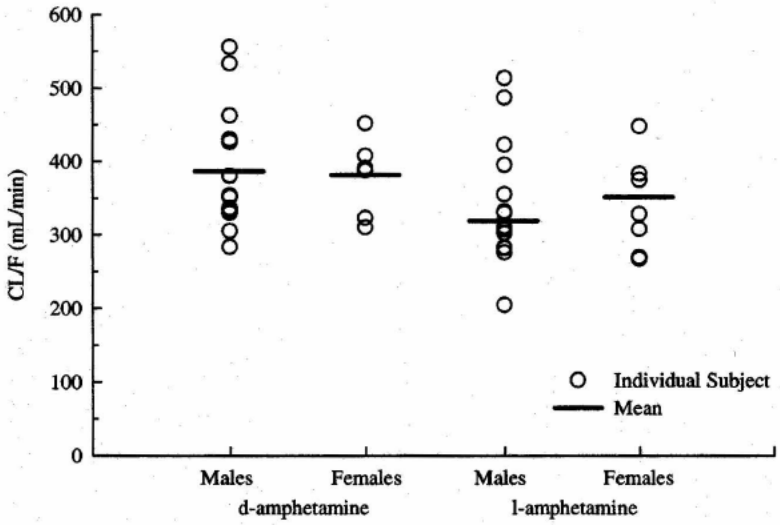


Figure 17: Relationship between Vz/F and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

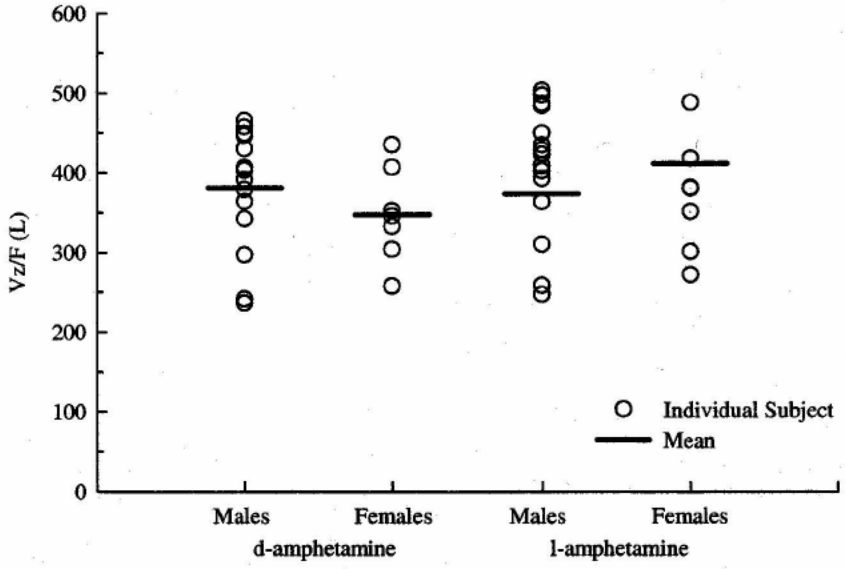


Table 7: Statistical comparison of Cmax, AUC_∞, t½, CL/F, and Vz/F for d- and l-amphetamine by gender after oral administration of ADDERALL XR® to adolescent subjects.

Parameter[2]	p-value[1]	
	d-amphetamine	l-amphetamine
Cmax	0.1344	0.1767
AUC_∞	0.7445	0.8410
t½	0.5245	0.3752
CL/F	0.6055	0.9871
Vz/F	0.3073	0.3325

[1]p-value from an analysis of variance with gender as the classification variable.
[2]Analysis of the mean parameter for the three doses for each subject. Cmax and AUC_∞ were normalized to dose before analysis.

Figure 18: Relationship between dose-normalized Cmax and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

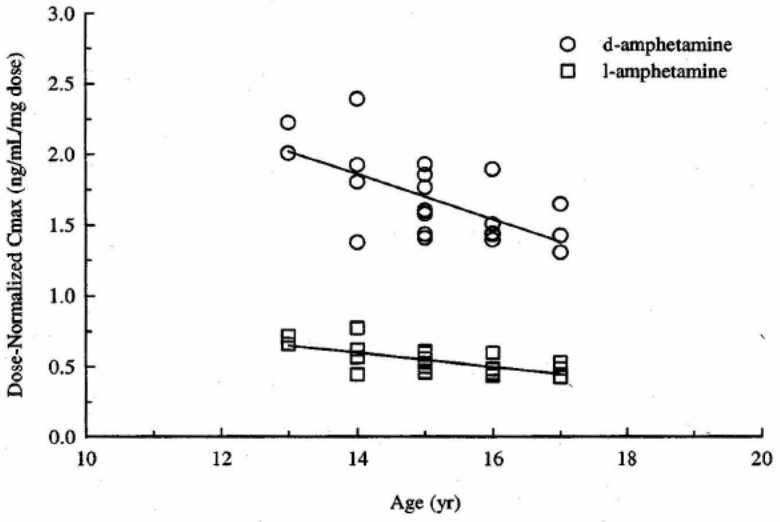


Table 8: Statistical comparison of Cmax, AUC_{∞}, t½, CL/F, and Vz/F for d- and l-amphetamine with age after oral administration of ADDERALL XR® to adolescent subjects.

Parameter[2]	p-value[1]	
	d-amphetamine	l-amphetamine
Cmax	0.0015	0.0017
AUC_{∞}	0.5348	0.9425
t½	0.0254	0.0443
CL/F	0.6924	0.9526
Vz/F	0.0038	0.0045

[1]p-value for the model from a regression against age.
[2]Analysis of the mean parameter for the three doses for each subject. Cmax and AUC_{∞} were normalized to dose before analysis.

Figure 19: Relationship between dose-normalized AUC_∞ and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

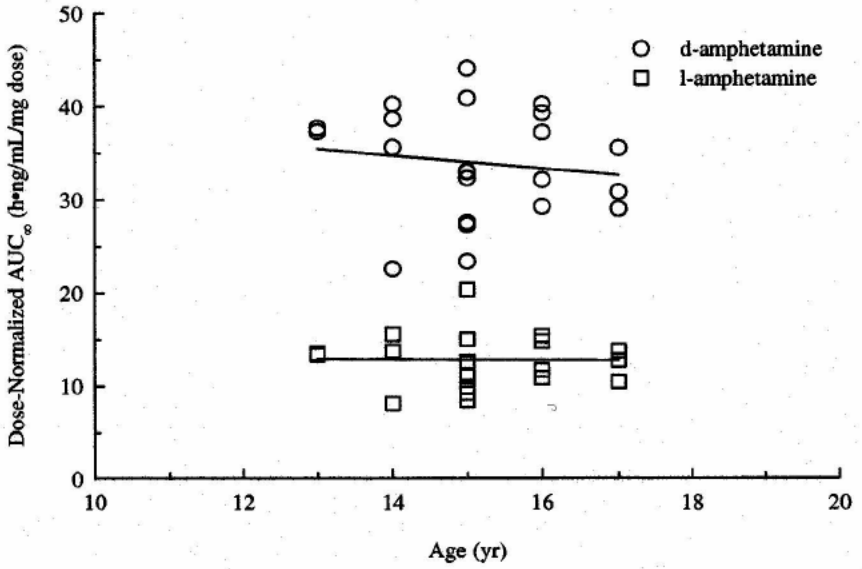


Figure 20: Relationship between t½ and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

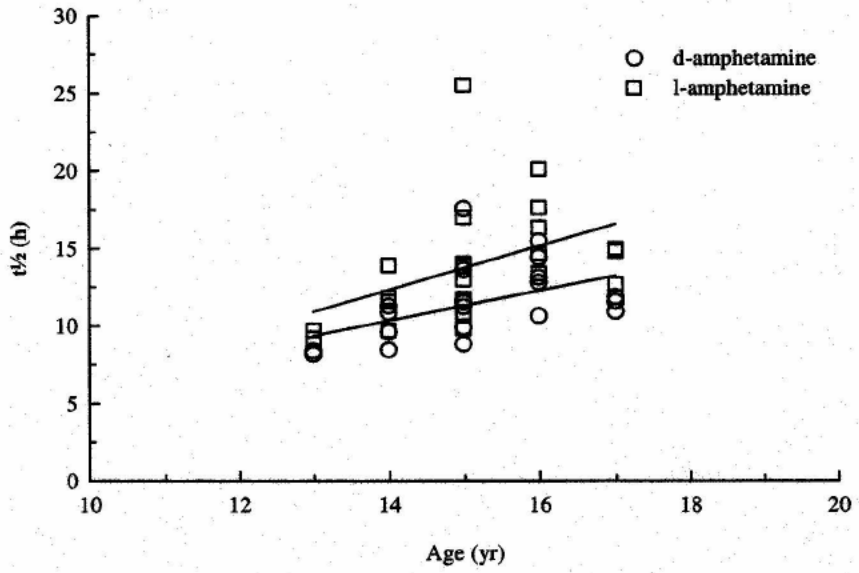


Figure 21: Relationship between CL/F and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

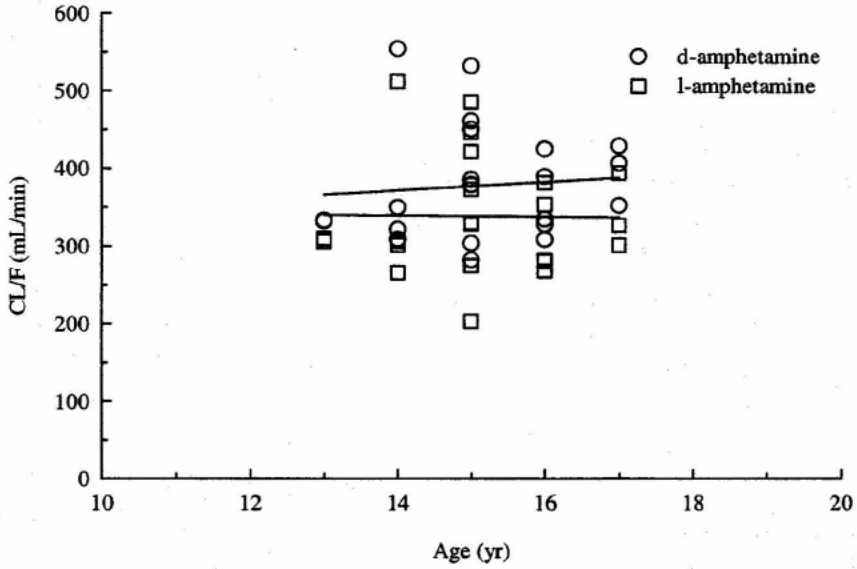


Figure 22: Relationship between Vz/F and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

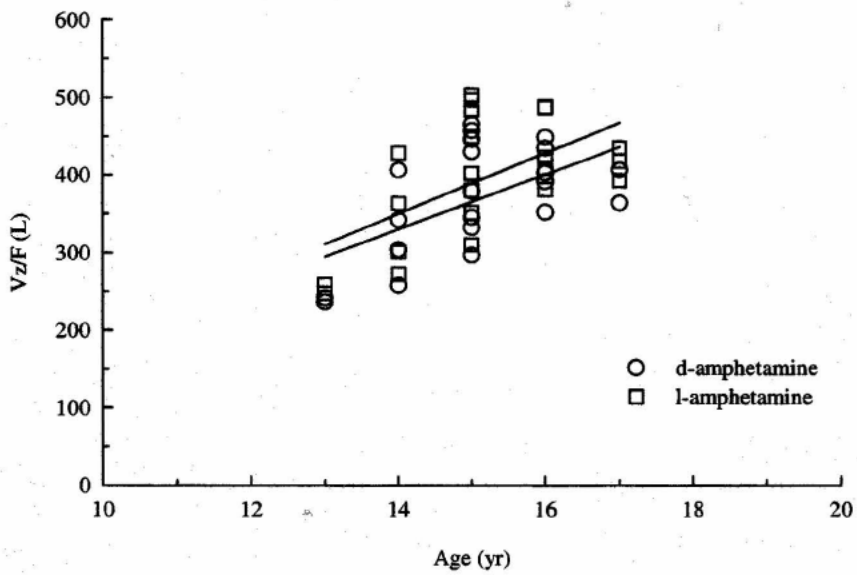


Figure 23: Relationship between dose-normalized Cmax and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

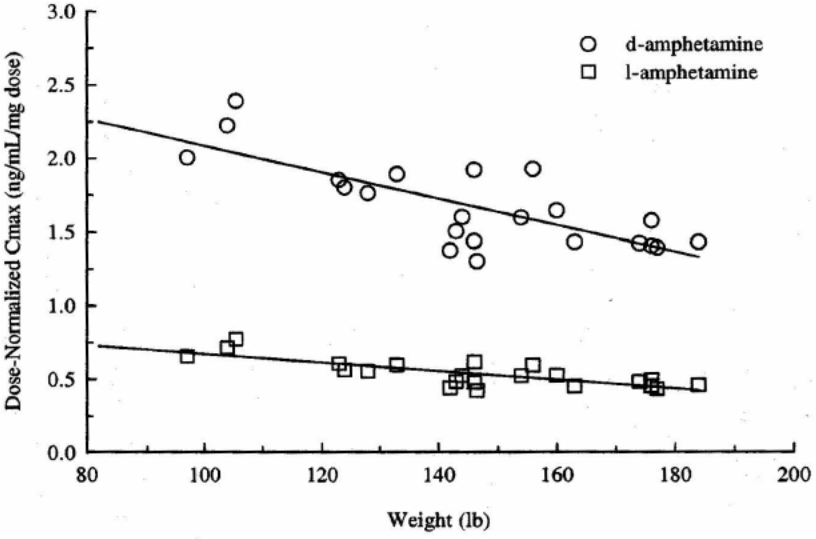


Figure 24: Relationship between dose-normalized AUC_∞ and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

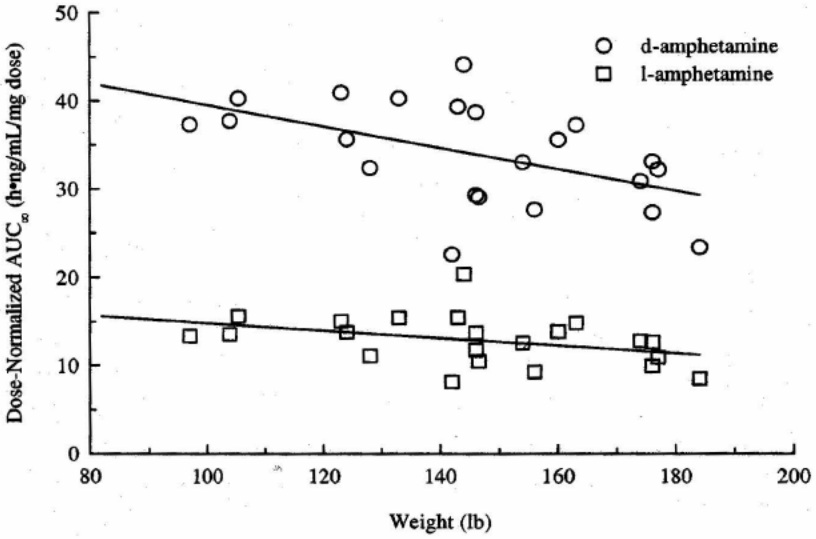


Figure 25: Relationship between t½ and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

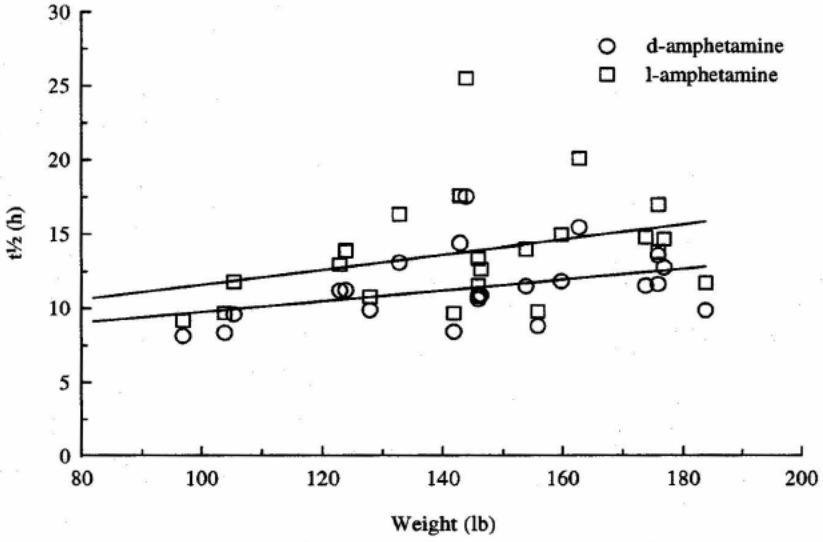


Figure 26: Relationship between CL/F and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

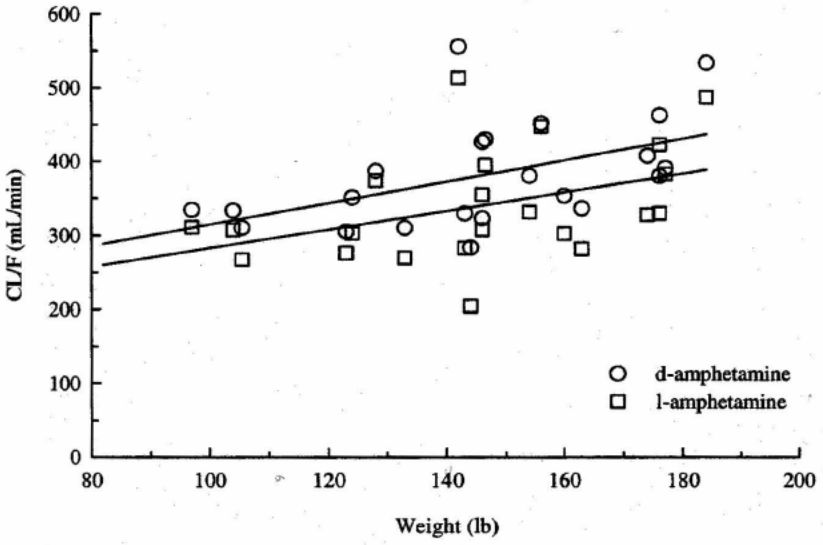


Figure 27: Relationship between Vz/F and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

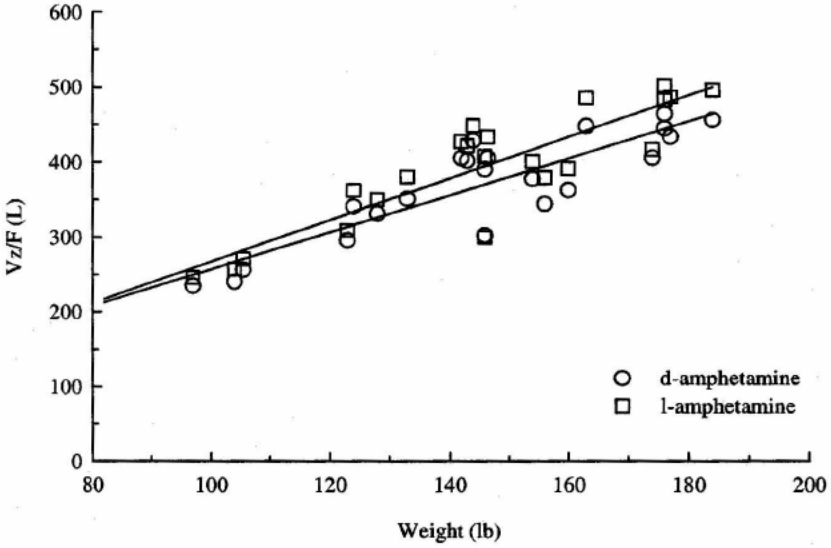


Table 9: Statistical comparison of Cmax, AUC_{∞}, t½, CL/F, and Vz/F for d- and l-amphetamine with weight after oral administration of ADDERALL XR® to adolescent subjects.

Parameter[2]	p-value[1]	
	d-amphetamine	l-amphetamine
Cmax	<0.0001	<0.0001
AUC_{∞}	0.0130	0.0835
t½	0.0768	0.1345
CL/F	0.0181	0.0576
Vz/F	<0.0001	<0.0001

[1]p-value for the model from a regression against weight.
[2]Analysis of the mean parameter for the three doses for each subject. Cmax and AUC_{∞} were normalized to dose before analysis.

Pharmacokinetic Parameters
Descriptive Statistics

Isomer	Parameter	Units	Age Group	N	Mean	Std Dev	Minimum	Median	Maximum
l-amphetamine	CL/F	mL/min	6 - 12	17	334.70	102.05	201.58	304.14	557.07
			13 - 17	21	339.02	84.05	188.82	318.99	500.68
			Adult	12	354.08	60.51	258.72	346.76	462.71
	CL/F/kg	mL/min/kg	6 - 12	17	8.16	1.62	5.83	7.87	11.34
			13 - 17	21	5.15	1.21	2.88	4.81	7.24
			Adult	12	4.83	0.79	3.49	4.96	5.85
	Cmax	ng/mL	6 - 12	20	30.27	8.57	17.93	29.11	45.00
			13 - 17	21	21.79	4.41	15.89	21.42	34.84
			Adult	12	22.14	3.81	14.76	22.86	29.11
	Tmax	h	6 - 12	20	5.45	3.21	2.00	4.50	12.00
			13 - 17	21	5.08	2.23	1.98	5.00	10.00
			Adult	12	5.33	0.89	3.00	5.50	6.00
	Vz/F	L	6 - 12	17	268.09	75.74	153.94	253.31	440.85
			13 - 17	21	402.68	83.26	236.20	417.96	556.54
			Adult	12	382.49	57.28	290.15	366.37	485.36
	Vz/F/kg	L/kg	6 - 12	17	6.54	1.11	4.09	6.39	7.94
			13 - 17	21	6.04	0.71	4.34	6.01	7.10
			Adult	12	5.18	0.39	4.68	5.06	5.85
	t½	h	6 - 12	17	9.40	1.51	7.59	9.13	12.88
			13 - 17	21	14.32	4.26	9.10	14.01	28.42
			Adult	12	12.67	2.12	9.20	12.35	16.70

Appendix II
Pharmacokinetic Parameters
Descriptive Statistics

Isomer	Parameter	Units	Age Group	N	Mean	Std Dev	Minimum	Median	Maximum
d-amphetamine	CL/F	mL/min	6 - 12	17	337.20	88.94	227.69	309.99	508.13
			13 - 17	21	384.45	79.75	247.69	379.94	535.04
			Adult	12	404.77	71.16	297.67	391.71	536.71
	CL/F/kg	mL/min/kg	6 - 12	17	8.28	1.55	5.97	8.21	11.89
			13 - 17	21	5.85	1.16	3.81	6.02	8.10
			Adult	12	5.49	0.74	3.99	5.55	6.29
	Cmax	ng/mL	6 - 12	20	98.61	28.21	54.16	90.78	151.54
			13 - 17	21	67.03	13.66	46.52	66.67	108.16
			Adult	12	67.94	10.27	47.69	67.79	85.25
	Tmax	h	6 - 12	20	5.35	3.25	2.00	4.50	12.00
			13 - 17	21	4.94	2.11	1.98	5.00	10.00
			Adult	12	5.00	1.13	3.00	5.00	6.00
	Vz/F	L	6 - 12	17	239.49	66.05	152.32	218.26	365.44
			13 - 17	21	377.07	74.95	220.02	395.30	510.43
			Adult	12	355.07	55.11	278.42	346.90	440.53
	Vz/F/kg	L/kg	6 - 12	17	5.84	0.92	4.06	5.72	7.08
			13 - 17	21	5.66	0.66	4.18	5.77	6.69
			Adult	12	4.80	0.39	4.26	4.74	5.43
	t½	h	6 - 12	17	8.23	1.07	6.29	8.08	10.65
			13 - 17	21	11.58	2.62	7.71	11.65	18.77
			Adult	12	10.28	1.50	8.10	9.95	13.20

An Analysis of the Effect of Age, Weight and Gender on the Pharmacokinetics of Adderall XR in Pediatric and Adolescent Patients with ADHD and Healthy Adults

Background: To meet the requirements of the Written Request, Shire conducted a study (SL1381.110), a three-period, six sequence, three treatment comparison of single doses of 10 mg, 20 mg and 40 mg in adolescent patients (ages 13 – 17 years) weighing ≤ 75 kg/165 lb or 20 mg, 40 mg and 60 mg in adolescents weighing > 75 kg/165 lb. The pharmacokinetic parameters were examined for effects of body weight, age, and gender and those data were then compared with historical data in pediatric ADHD patients (ages 6 – 12 years) and adults (22 – 46 years).

Objective: The objective of the analysis was to examine the effects of body weight, age and gender on the pharmacokinetics of d- and l-amphetamine after oral administration of Adderall XR

Study Design: Data were selected from 3 pharmacokinetic studies with Adderall XR. Study SLI381.107 was a two-period, two-sequence, two-treatment comparison of single doses of 1 x 40 mg capsules in pediatric patients (6 to 12 years of age) with Attention Deficit Hyperactivity Disorder (ADHD). Study SLI381.108 was a three period, three sequence, three treatment comparison of single doses of 20 mg (2 x 10 mg), 40 mg (2 x 20 mg) and 60 mg (2 x 30mg) in healthy adult subjects. Study SLI381.110 was a three period, six-sequence, three treatment comparison of single doses of 10 mg (1 x 10 mg), 20 mg (1 x 20 mg) and 40 mg (2 x 20 mg) in adolescent patients (ages 13 –17 years) weighing ≤ 75 kg/165 lbs or 20 mg (1 x 20 mg), 40 mg (2 x 20 mg) and 60 mg (2 x 30 mg) in adolescent ADHD patients (ages 13 –17 years) weighing > 75 kg/165 Ibs. For each of the subject in each study, age, gender and body weight were extracted from SAS datasets.

Data Analyses: Mean values for Cmax, Tmax, AUC∞, t ½, CL/F and Vz/F were compared among age groups using an analysis of variance with age group (pediatric, adolescent, adult) as the classification variable. Comparisons between age groups were done using the least squares means and a t-test. Relationships between pharmacokinetic parameters and body weight, age and gender were first examined graphically. If suggested by the graphical presentation, univariate and/or multivariate statistical analyses were conducted to determine either if significant relationship existed or to document that there was no relationship.

Results: The descriptive statistics for age and body weight are shown in the following table.

Age and Body Weight by Age Group (Mean ± SD)

Population	Age (year)	Weight (lb)
6 – 12 years	10.2 ± 1.63	89.9 ± 35.1
13 – 17 years	15.1 ± 1.20	147 ± 24.9
Adult (Healthy)	32.6 ± 8.24	163 ± 27.3

Descriptive statistics for pharmacokinetic parameters by age are shown in the Tables on page 60 – 61. There were significant differences among age groups for all d-amphetamine parameters except Tmax and Cl/F; for l-amphetamine, there were significant differences for Vz/F, t ½ and Cmax. Contrasts between the age groups showed that all of the significant differences occurred between the pediatric population and the adolescent and/or adult populations; there were no significant differences between adolescents and adults. To attempt to determine the source or

sources of the differences among age groups, univariate and multivariate analyses of the effects of body weight, age, and gender were performed.

There were negative relationships between AUC∞, Cmax and body weight for d- and l-amphetamine across the 3 age groups that were significant. There were significant positive relationships between Cl/F and Vz/F and body weight for d- and l-amphetaminc. These results are shown in Figures 1 – 12 and Table 5.

There was no apparent relationship between AUC∞ and age. The was no apparent relationship between Cl/F and age for either isomer of amphetamine. The range of individual patient or subject values was essentially the same in the 6 to 12 and 13 to 17 year ADHD groups and in healthy adults. Although Vz/F did not appear to vary between adolescents (13 to 17 years) and adults, pediatric patients tended to have lower values. Pediatric patients had lower values for t ½ and higher values for Cmax than the other age groups. Tmax for d- and l-amphetamine did not appear to be a function of the age of the patient. Although there were trends across age groups, there did not appear to be substantial differences within age groups between males and females in the range of values for either d- and l-amphetamine for AUC∞, t ½, Cmax or Tmax. Body weight increased with age through adolescence and then became relatively constant through the adult years and this relationship appears to be independent of gender.

Summary and Conclusion: A comparison of means among age groups demonstrated statistically significant differences for all d-amphetamine parameters except Tmax and for Vz/F, T ½ and Cmax for l-amphetamine. Contrasts between the age groups showed that all of the significant differences occurred between the pediatric ADHD population and the adolescent ADHD and/or healthy adult populations with no significant differences between adolescents and adults. Univariate and multivariate analyses of the effects of gender, age and body weight indicate that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine. After normalization for body weight, mean values of Vz/F were comparable although there was a trend toward a decrease in mean value as age increased. Significant relationships were apparent between AUC∞, CL/F and Vz./F and body weight for both isomers. Nevertheless, body weight is not independent of age, particularly for pediatric and younger adolescents, and may also be related to gender. The multivariate analyses demonstrated that when gender and age are included in the analyses, CL/F was not dependent on any of the demographic parameters. Body weight was the only significant determinant for Vz/F and thus t ½ and Cmax. Comparison of the pharmacokinetics of d- and l- amphetamine after oral administration of Adderall XR in pediatric (6 – 12 years) and adolescents (13 –17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by AUC∞ and Cmax decreased with increases in bodyweight, while Vz/F, Cl/F and t ½ increased with increases in bodyweight. Age and gender had no direct effect on the pharmacokinetics of d- and l-amphetamine.

Reviewer's conclusion: The reviewer agrees with the conclusion of sponsor that body weight is the primary determinant of differences in the pharmacokinetics of d and l-amphetamine. And, that the differences are observed primary between the pediatric and adolescents/adult populations. There appears to be no difference in pharmacokinetic parameters between adolescents and adult population. Since this analysis is based on data from different studies conducted at different times, caution should be exercised in the application of the conclusions of the analyses.

Figure 1: Relationship between AUC_∞ and weight for d-amphetamine after oral administration of ADDERALL XR®.

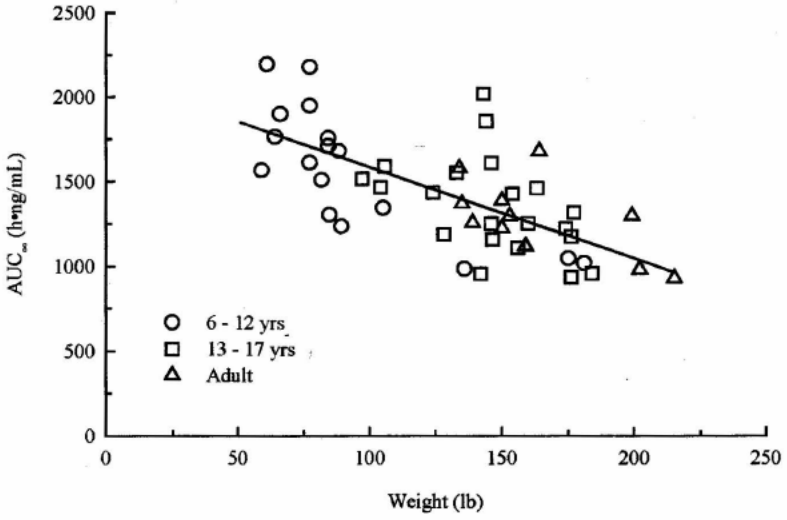


Figure 2: Relationship between AUC_∞ and weight for l-amphetamine after oral administration of ADDERALL XR®.

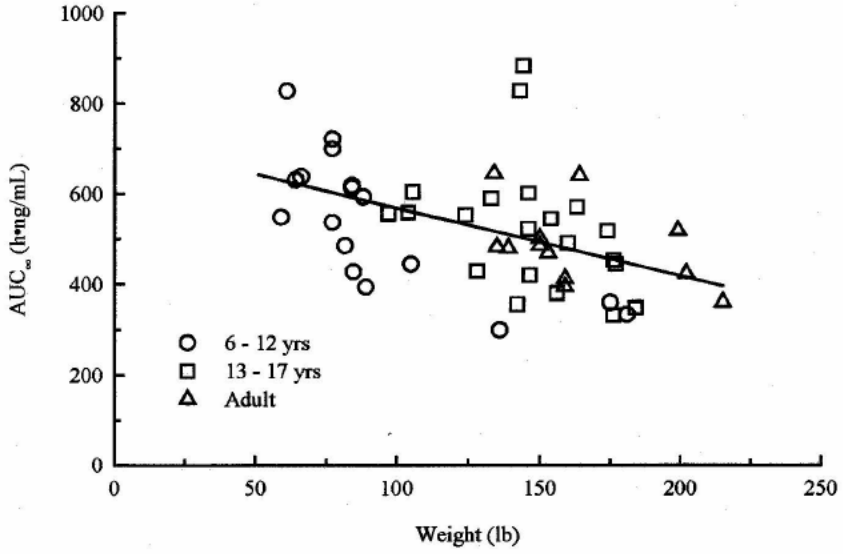


Figure 3: Relationship between CL/F and weight for d-amphetamine after oral administration of ADDERALL XR®.

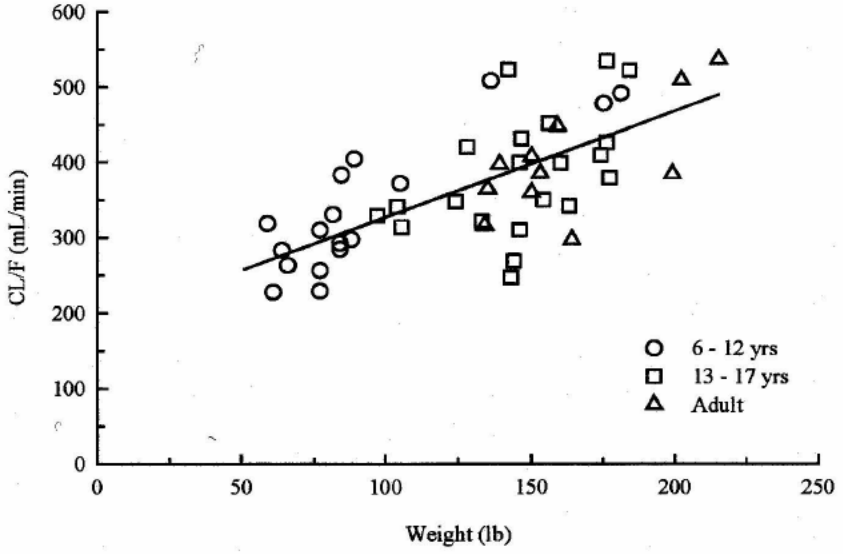


Figure 4: Relationship between CL/F and weight for l-amphetamine after oral administration of ADDERALL XR®.

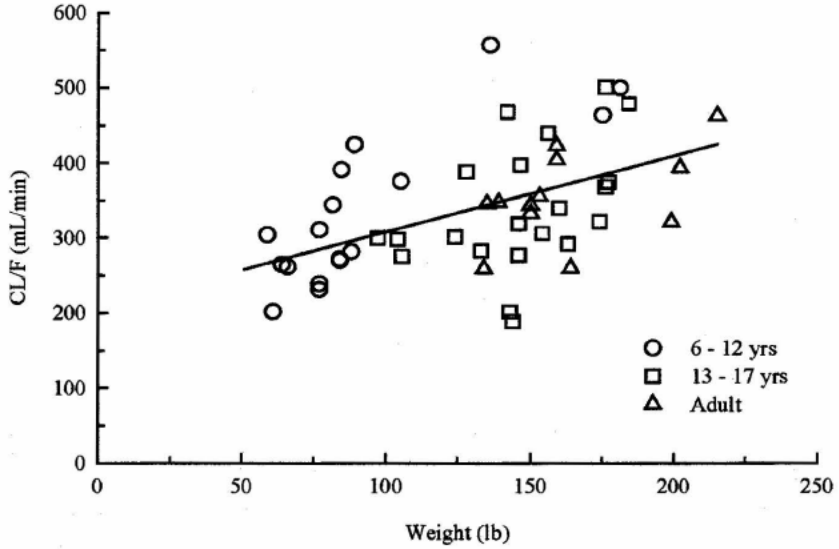


Figure 5: Relationship between Vz/F and weight for d-amphetamine after oral administration of ADDERALL XR®.

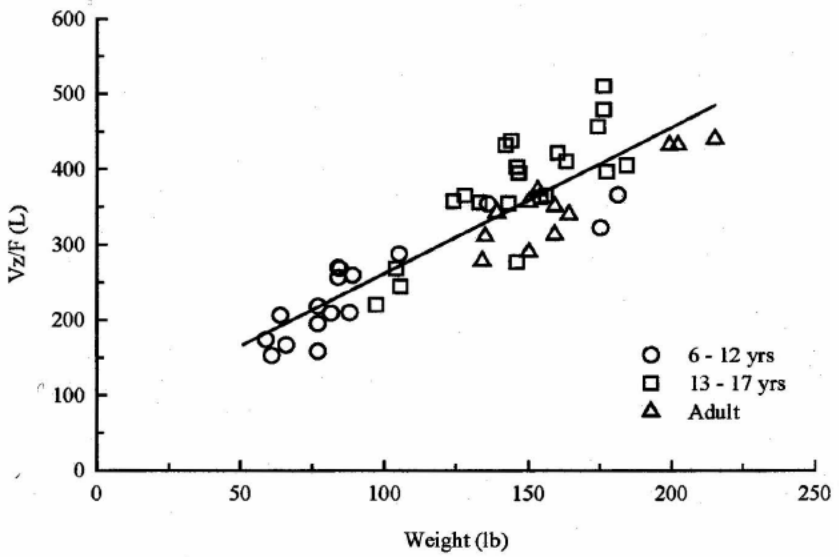


Figure 6: Relationship between Vz/F and weight for l-amphetamine after oral administration of ADDERALL XR®.

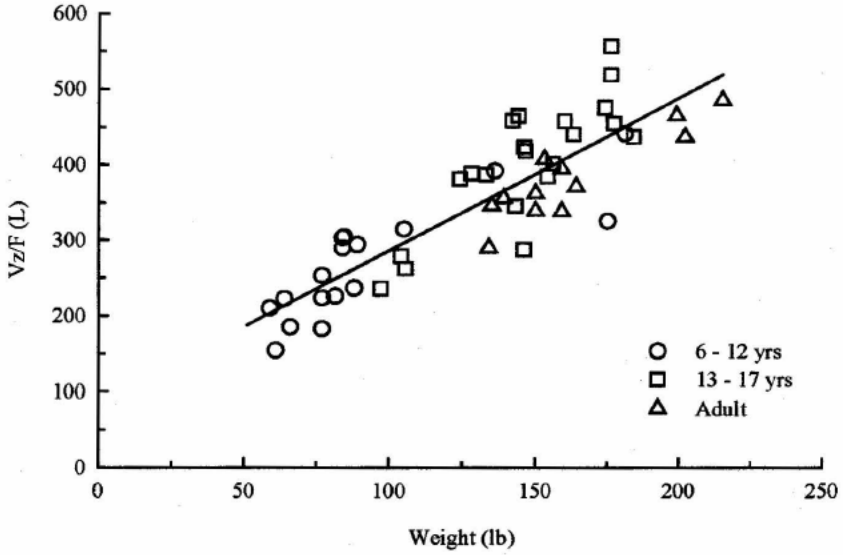


Figure 7: Relationship between t½ and weight for d-amphetamine after oral administration of ADDERALL XR®.

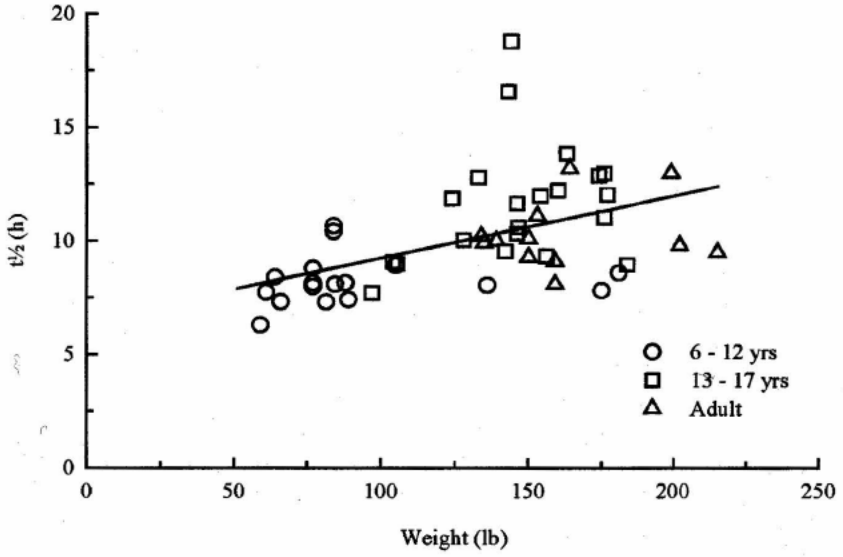


Figure 8: Relationship between t½ and weight for l-amphetamine after oral administration of ADDERALL XR®.

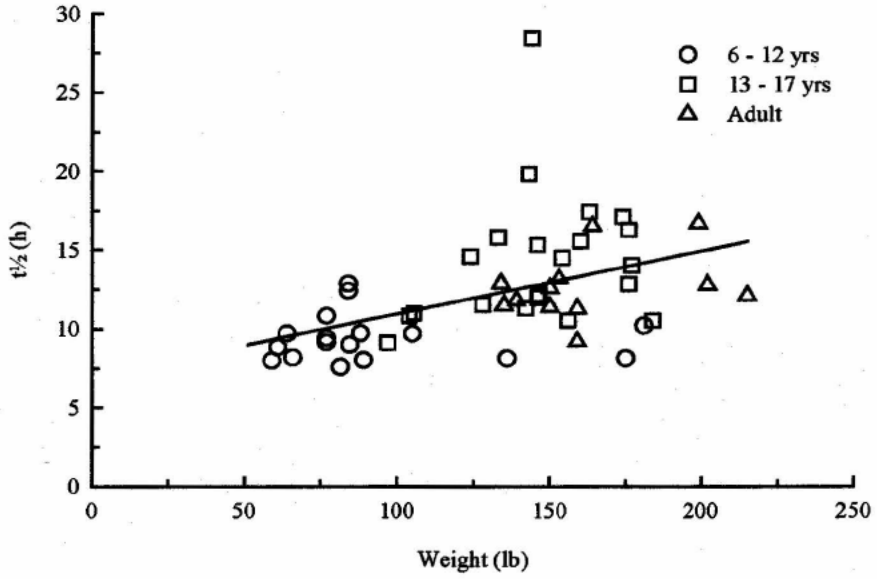


Figure 9: Relationship between Cmax and weight for d-amphetamine after oral administration of ADDERALL XR®.

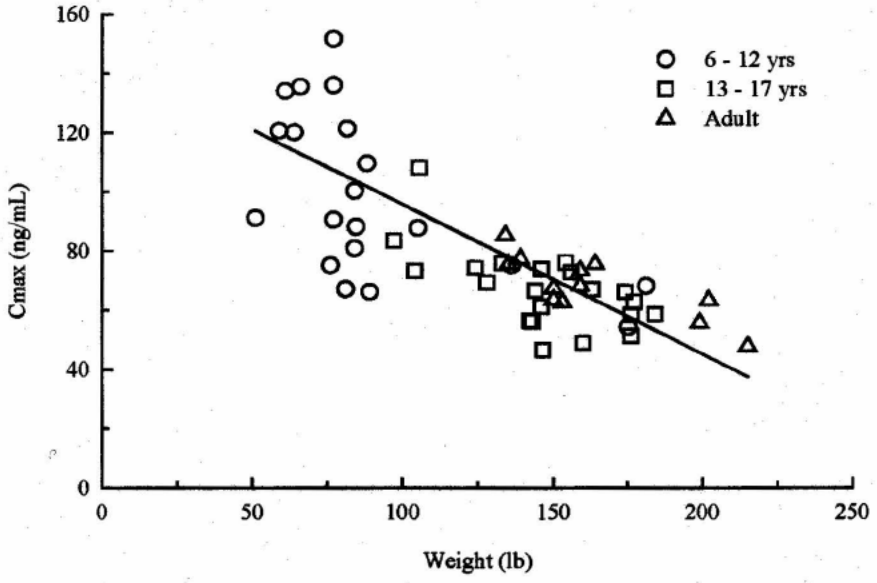


Figure 10: Relationship between Cmax and weight for l-amphetamine after oral administration of ADDERALL XR®.

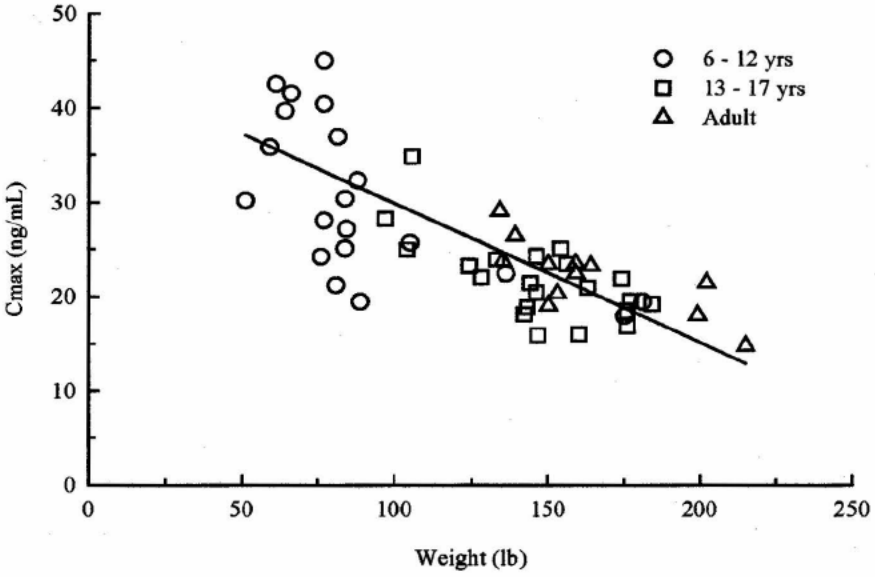


Figure 11: Relationship between Tmax and weight for d-amphetamine after oral administration of ADDERALL XR®.

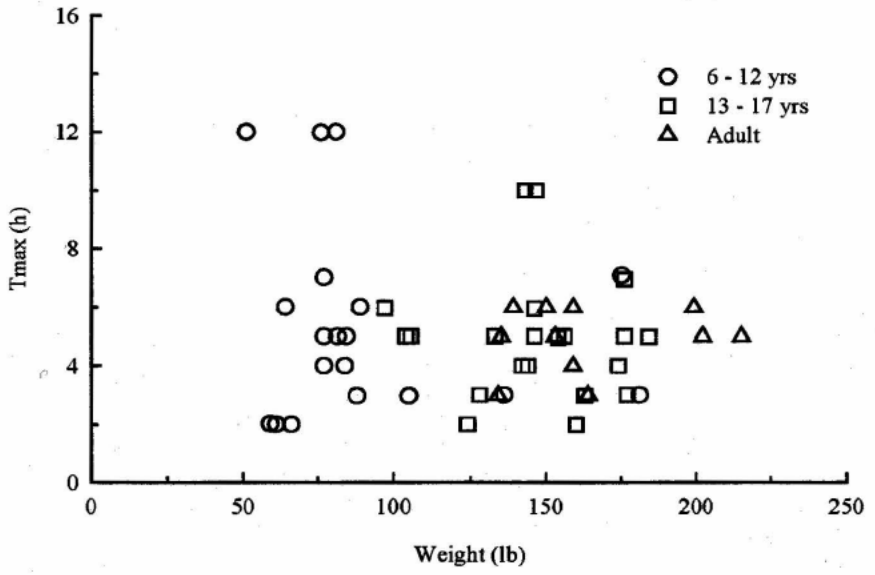


Figure 12: Relationship between Tmax and weight for l-amphetamine after oral administration of ADDERALL XR®.

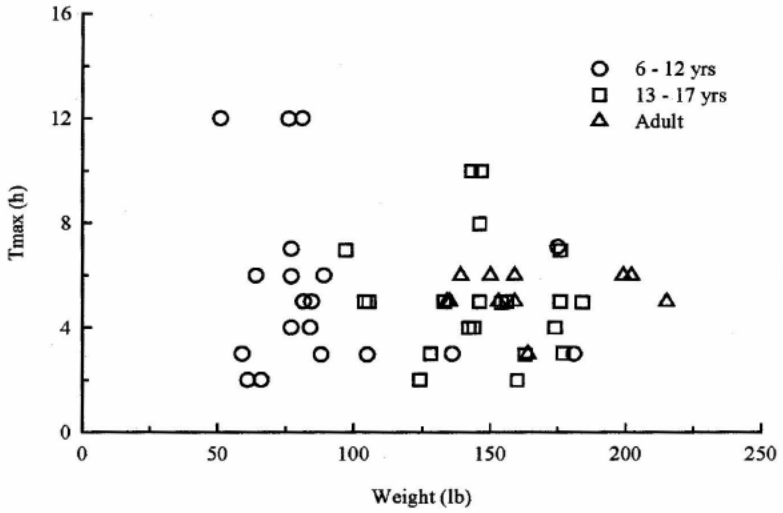


Table 5: Statistical evaluation of the effect of body weight on the pharmacokinetic parameters for d- and l-amphetamine after oral administration of ADDERALL XR®.

	p-value[1]	
Parameter	d-amphetamine	l-amphetamine
AUC_∞ (h•ng/mL)	<0.0001	0.0006
CL/F (mL/min)	<0.0001	0.0003
Vz/F (L)	<0.0001	<0.0001
t½ (h)	0.0006	0.0014
Cmax (ng/mL)	<0.0001	<0.0001

Figure 13: Relationship between AUC_∞ and age for d-amphetamine after oral administration of ADDERALL XR®.

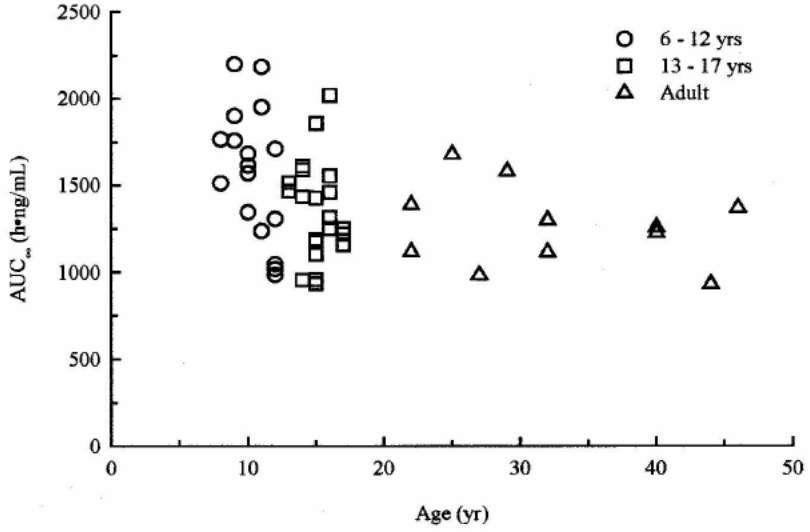


Figure 14: Relationship between AUC_∞ and age for l-amphetamine after oral administration of ADDERALL XR®.

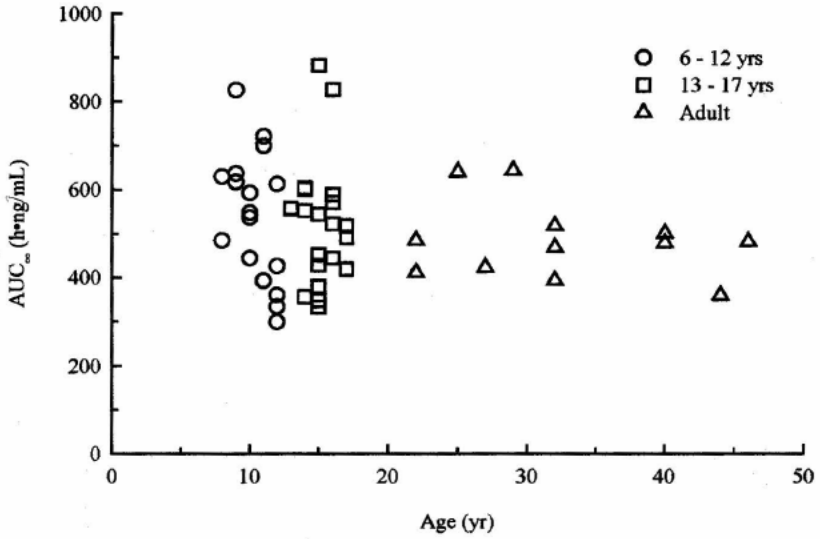


Figure 15: Relationship between CL/F and age for d-amphetamine after oral administration of ADDERALL XR®.

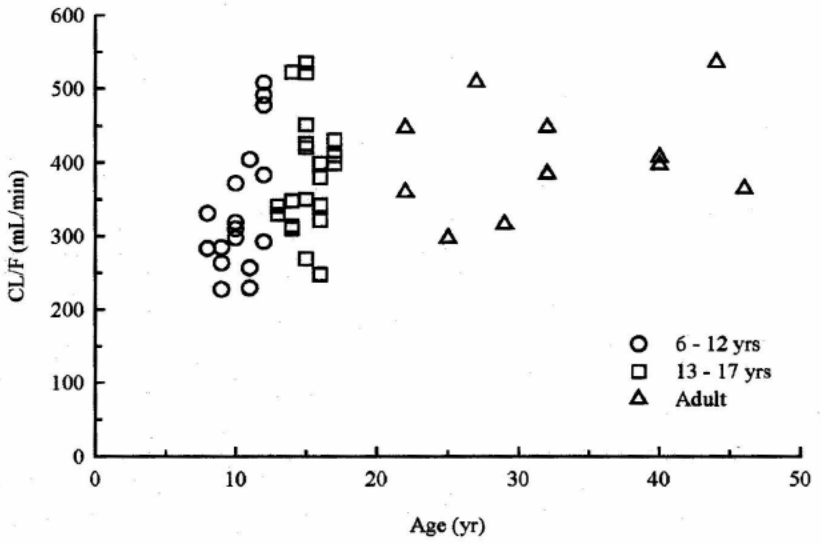


Figure 16: Relationship between CL/F and age for l-amphetamine after oral administration of ADDERALL XR®.

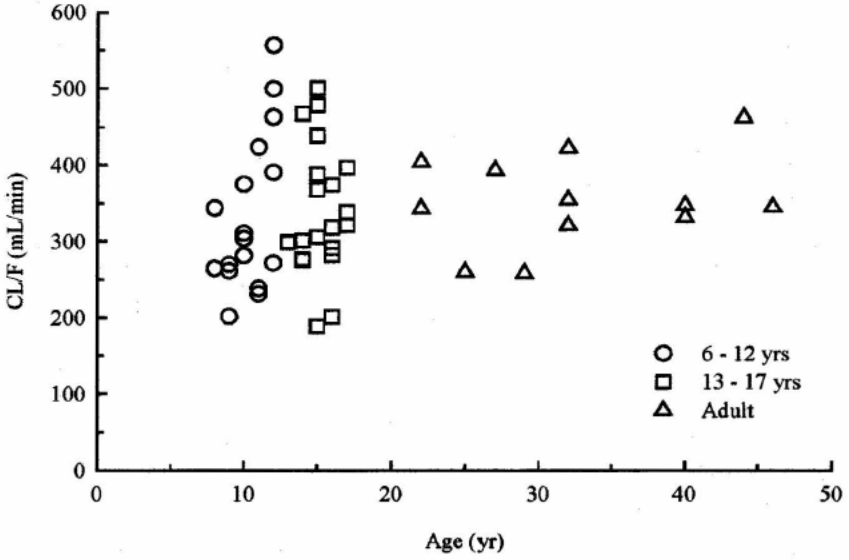


Figure 17: Relationship between Vz/F and age for d-amphetamine after oral administration of ADDERALL XR®.

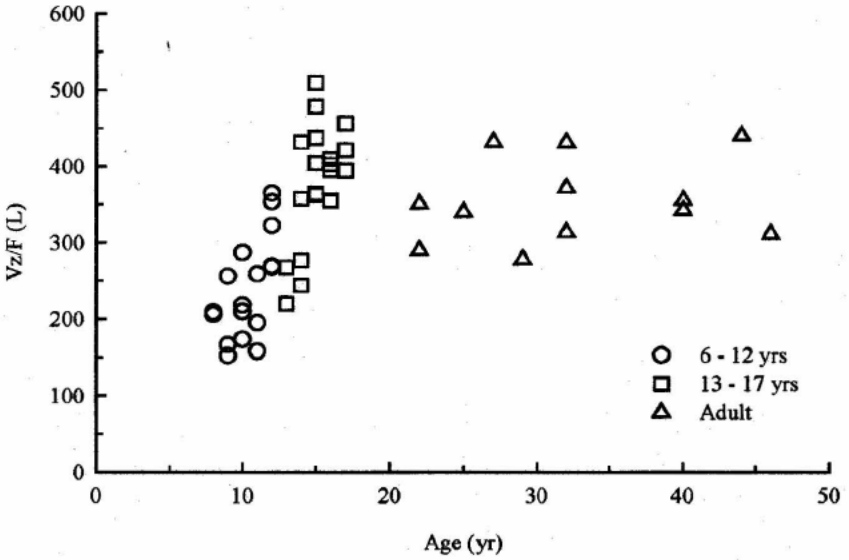


Figure 18: Relationship between Vz/F and age for l-amphetamine after oral administration of ADDERALL XR®.

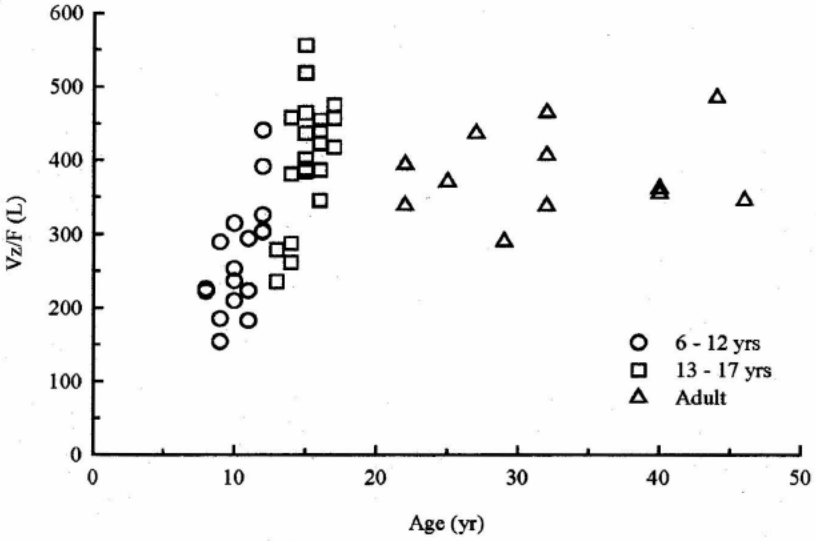


Figure 19: Relationship between t½ and age for d-amphetamine after oral administration of ADDERALL XR®.

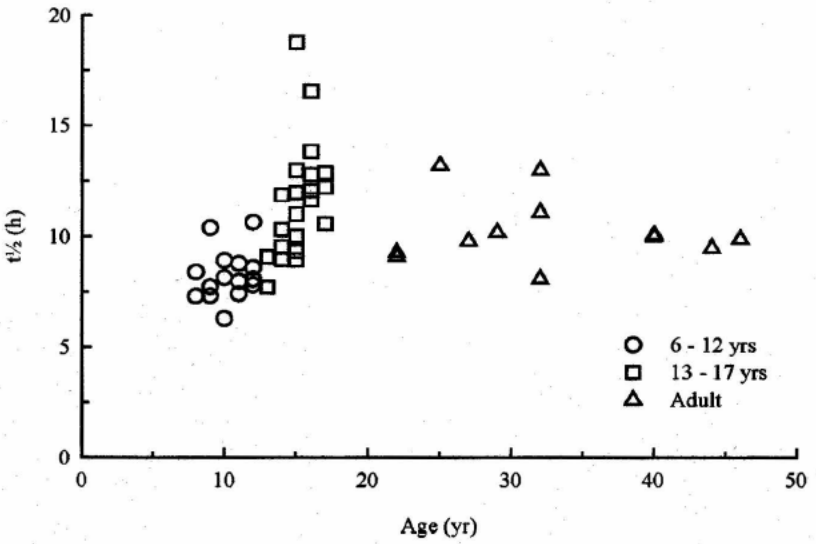


Figure 20: Relationship between t½ and age for l-amphetamine after oral administration of ADDERALL XR®.

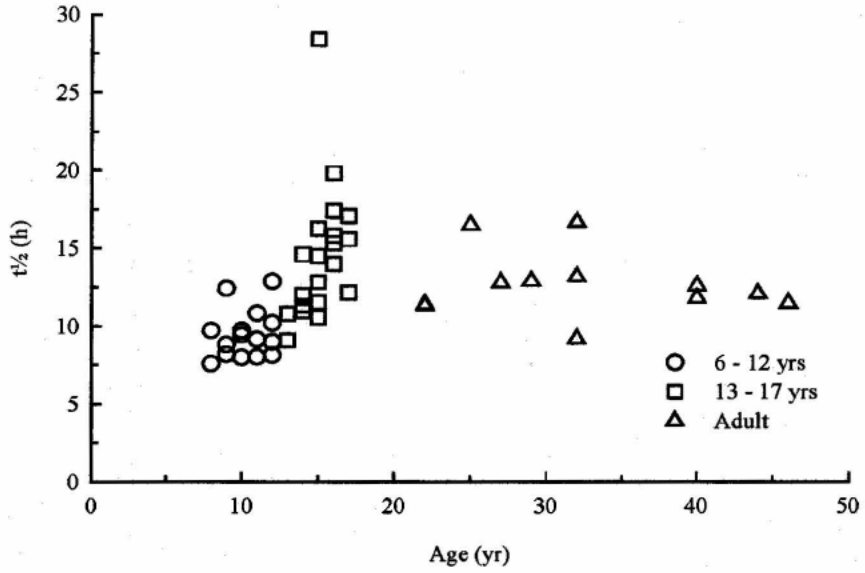


Figure 21: Relationship between Cmax and age for d-amphetamine after oral administration of ADDERALL XR®.

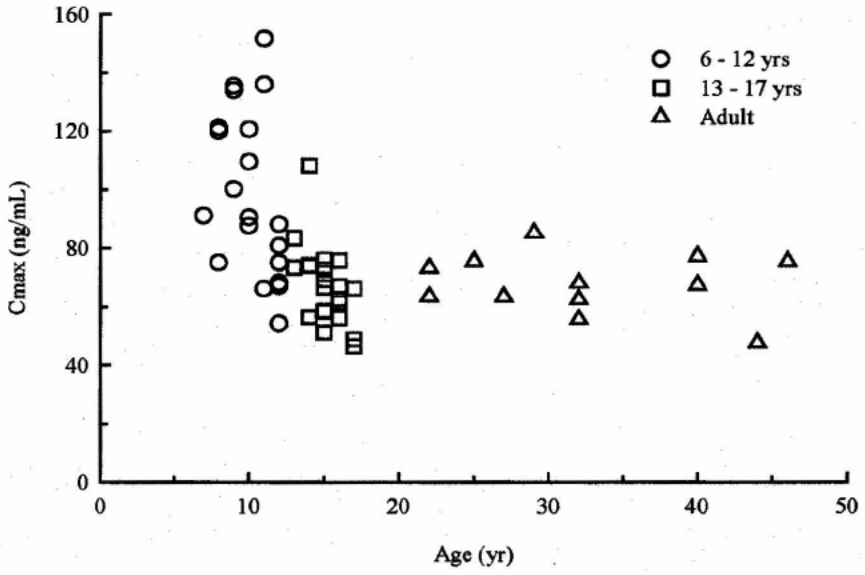


Figure 22: Relationship between Cmax and age for l-amphetamine after oral administration of ADDERALL XR®.

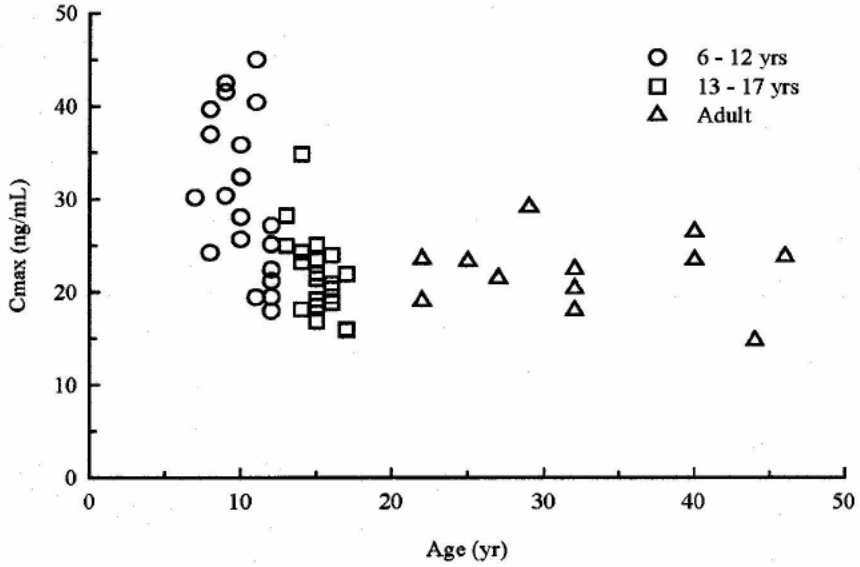


Figure 23: Relationship between Tmax and age for d-amphetamine after oral administration of ADDERALL XR®.

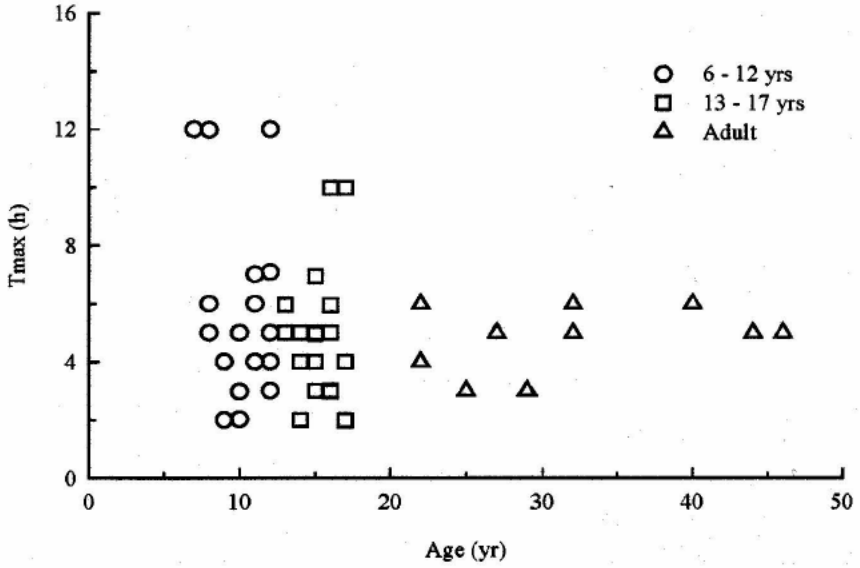


Figure 25: Relationship between AUC_∞ and gender for d-amphetamine after oral administration of ADDERALL XR®.

Figure 26: Relationship between AUC_∞ and gender for l-amphetamine after oral administration of ADDERALL XR®.

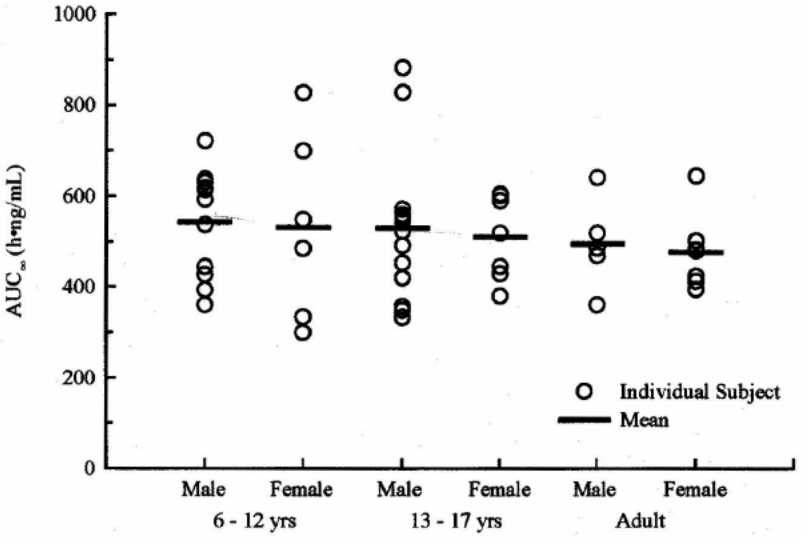


Figure 27: Relationship between CL/F and gender for d-amphetamine after oral administration of ADDERALL XR®.

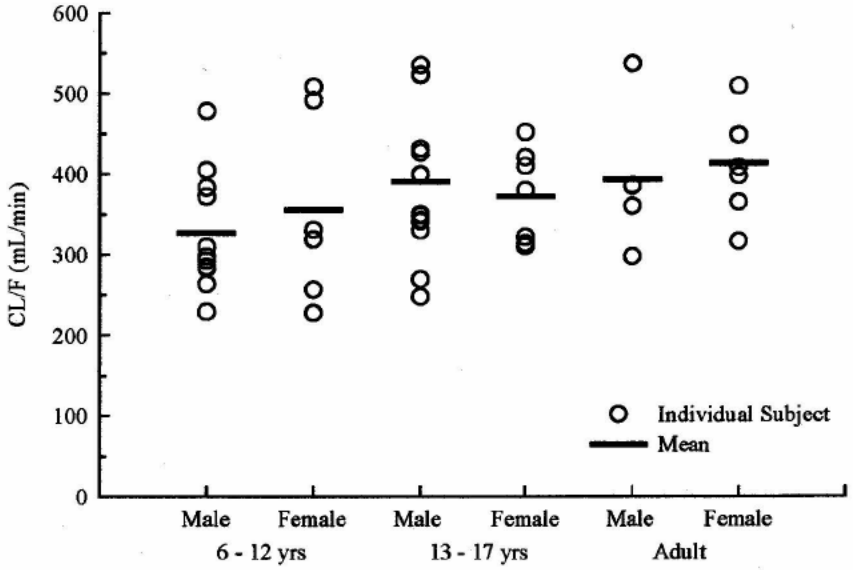


Figure 28: Relationship between CL/F and gender for l-amphetamine after oral administration of ADDERALL XR®.

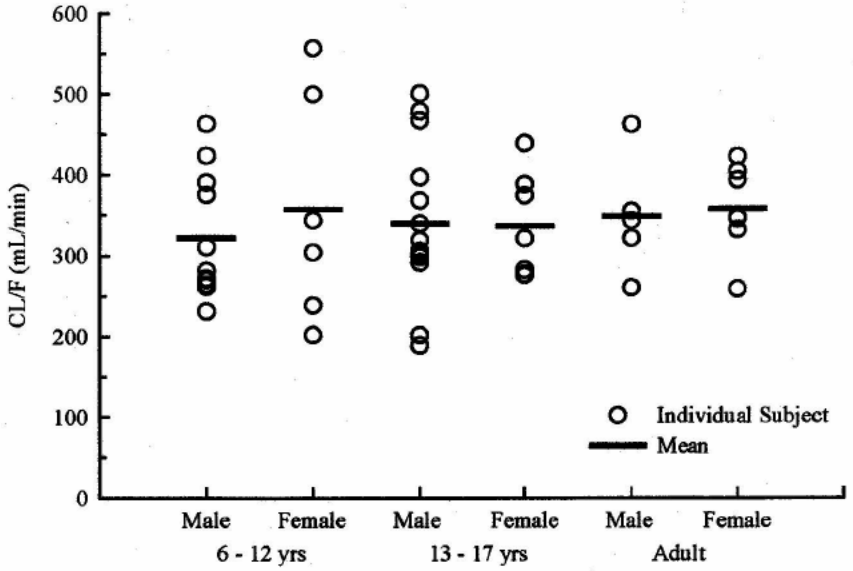


Figure 29: Relationship between Vz/F and gender for d-amphetamine after oral administration of ADDERALL XR®.

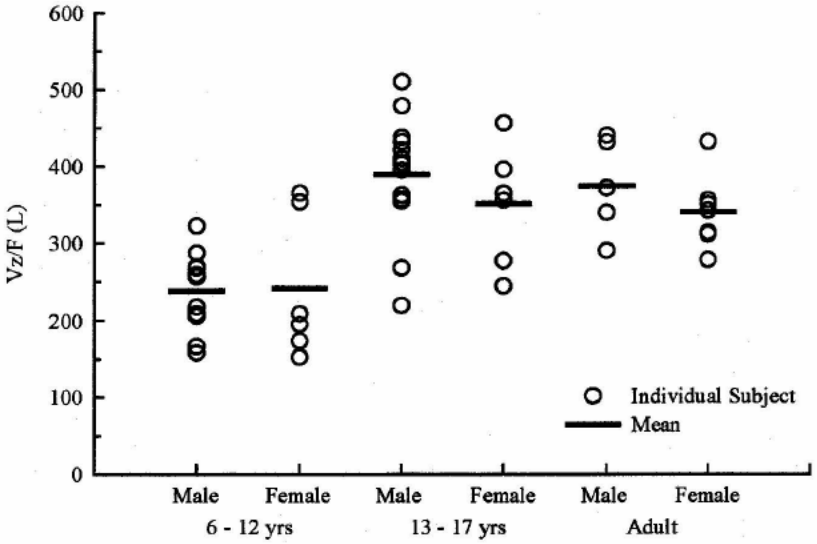


Figure 30: Relationship between Vz/F and gender for l-amphetamine after oral administration of ADDERALL XR®.

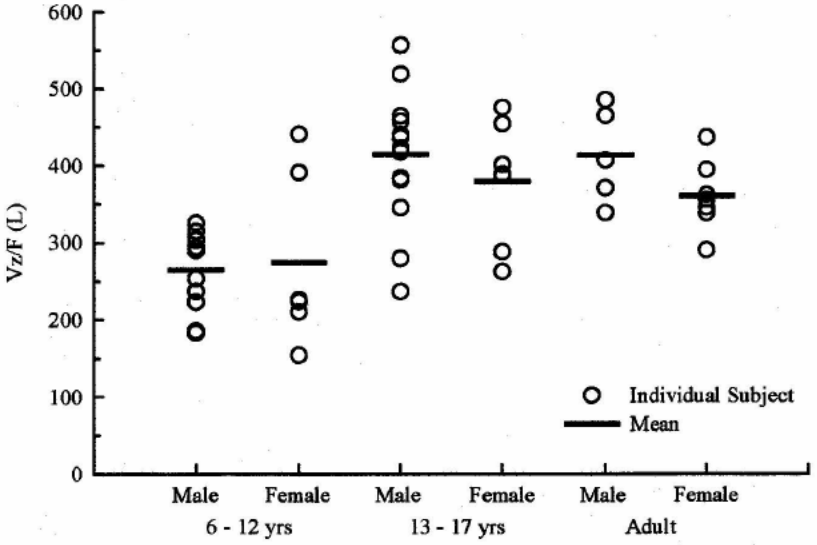


Figure 31: Relationship between t½ and gender for d-amphetamine after oral administration of ADDERALL XR®.

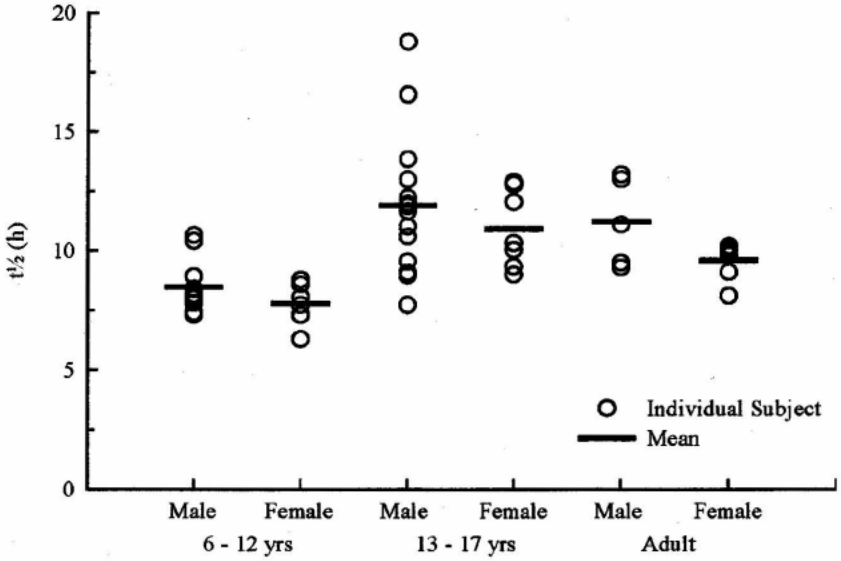


Figure 32: Relationship between t½ and gender for l-amphetamine after oral administration of ADDERALL XR®.

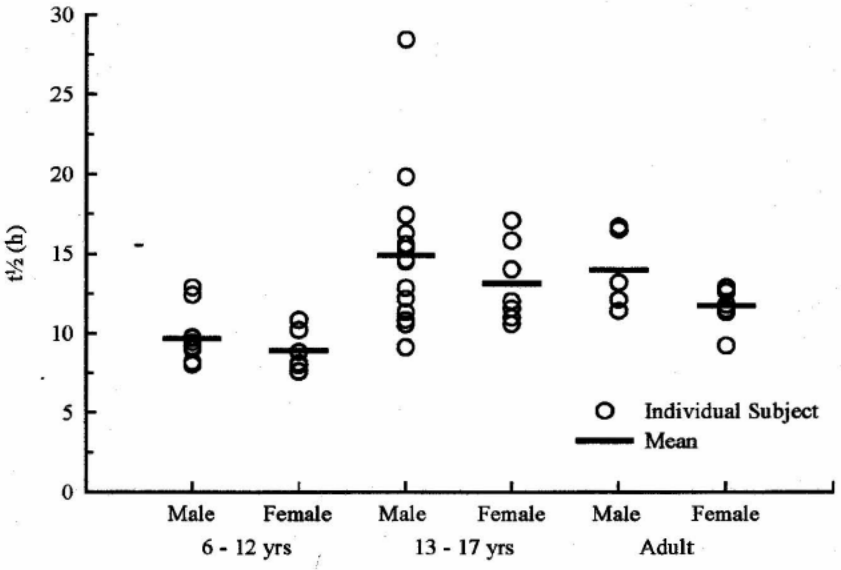


Figure 33: Relationship between Cmax and gender for d-amphetamine after oral administration of ADDERALL XR®.

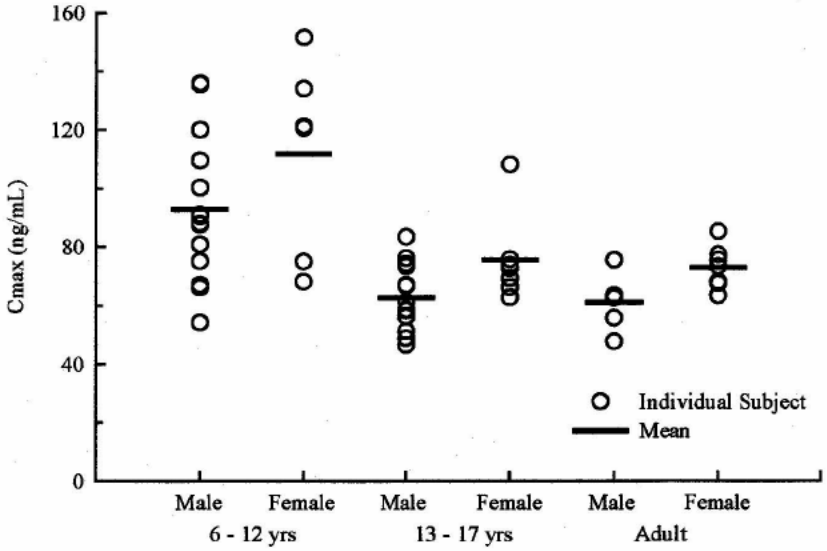


Figure 34: Relationship between Cmax and gender for l-amphetamine after oral administration of ADDERALL XR®.

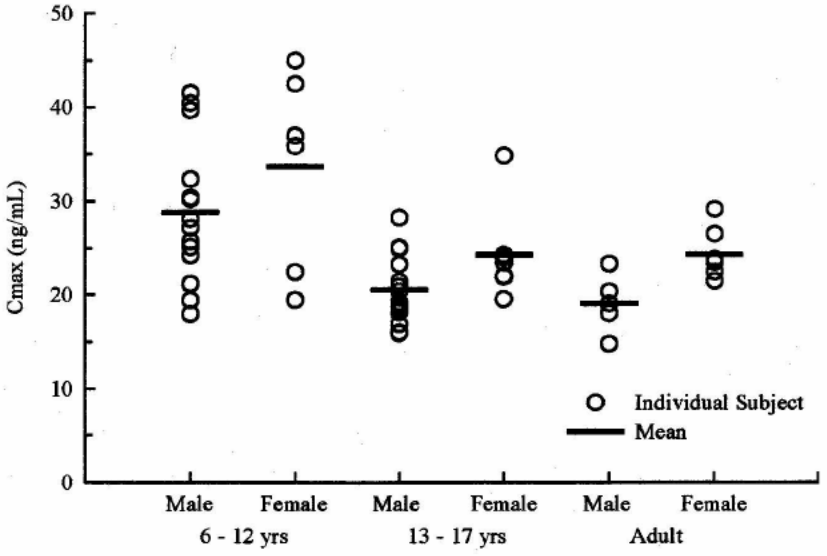


Figure 33: Relationship between Cmax and gender for d-amphetamine after oral administration of ADDERALL XR®.

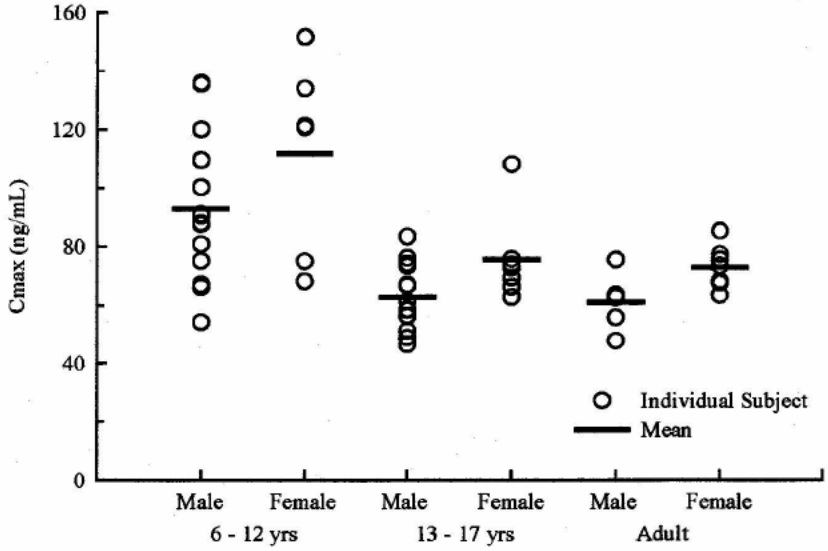


Figure 34: Relationship between Cmax and gender for l-amphetamine after oral administration of ADDERALL XR®.

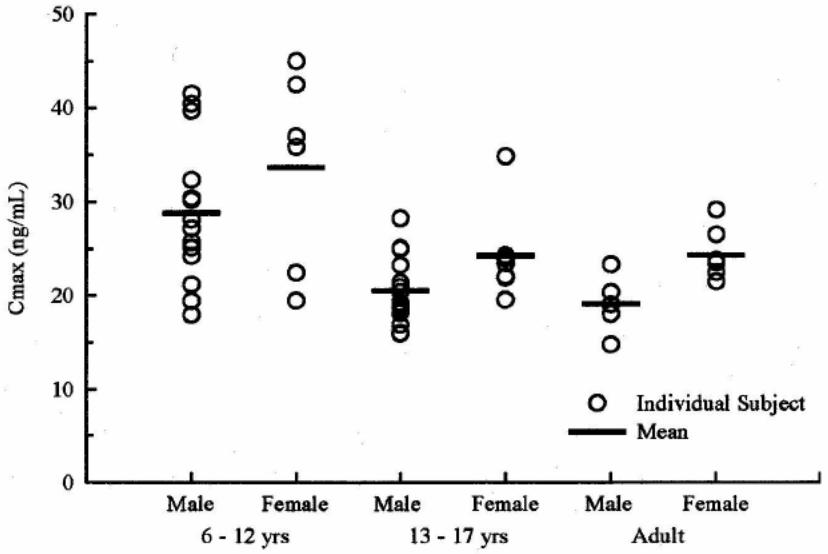


Figure 35: Relationship between Tmax and gender for d-amphetamine after oral administration of ADDERALL XR®.

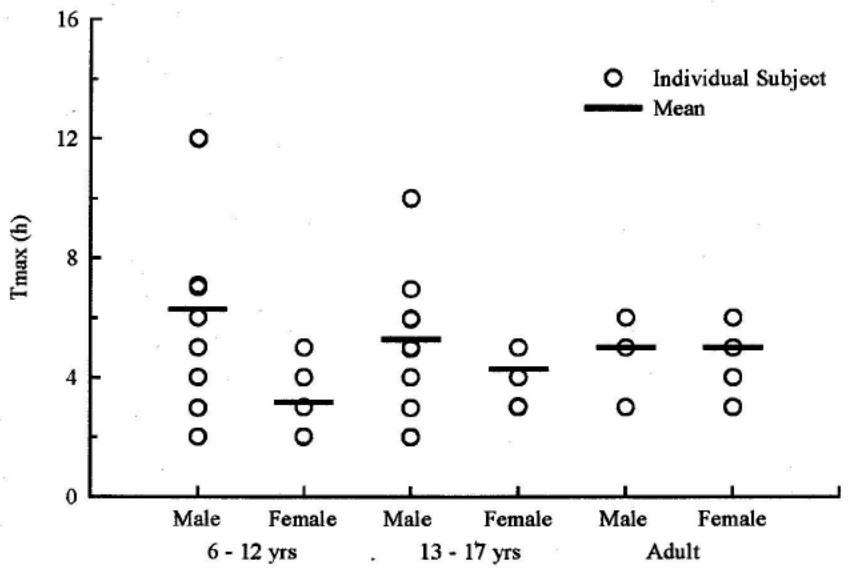


Figure 36: Relationship between Tmax and gender for l-amphetamine after oral administration of ADDERALL XR®.

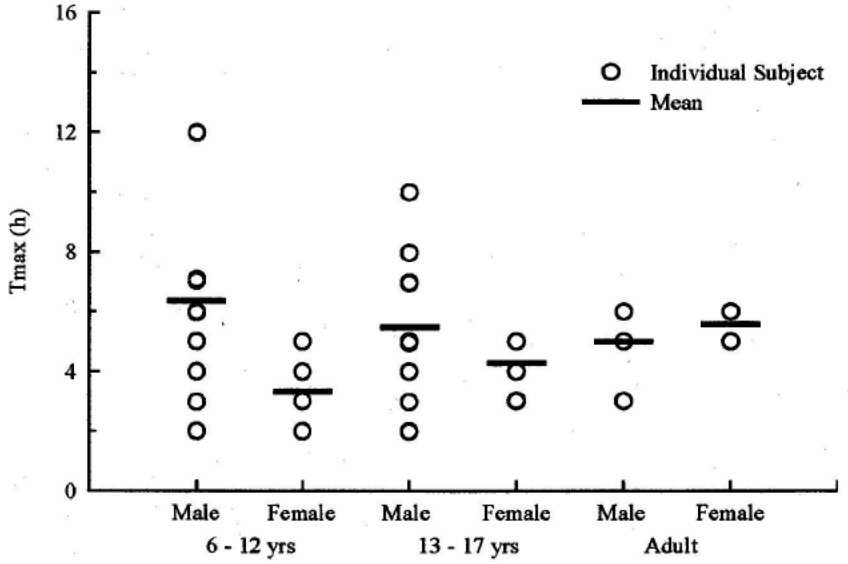


Table 6: Statistical comparison of pharmacokinetic parameters for d- and l-amphetamine by gender after oral administration of ADDERALL XR®.

	p-value[1]	
Parameter	d-amphetamine	l-amphetamine
AUC_∞ (h•ng/mL)	0.5272	0.5332
CL/F (mL/min)	0.5666	0.5275
Vz/F (L)	0.5227	0.5211
t½ (h)	0.1445	0.1805
Cmax (ng/mL)	0.1501	0.1147
Tmax (h)	0.0324	0.0517

[1]p-value for the effect of gender from an analysis of variance.

Source: Appendix V

Appendix I
Pharmacokinetic and Demographic Analysis Data Set

Assay	Age Group	Study	Subject	Cmax (ng/mL)	Tmax (h)	AUC (hxng/mL)	t½ (h)	CL/F (mL/min)	CL/F (mL/min/kg)	Vz/F (L)	Vz/F (L/kg)	Age (yr)	Weight (lb)	Sex
d-amphetamine	6 - 12	381.107	1	91.10	12.0	.	.	.	.	.	.	7	51.0	M
			2	75.11	12.0	.	.	.	.	.	.	8	76.0	M
			3	100.21	4.0	1,756.10	10.40	284.72	7.46	256.35	6.71	9	84.0	M
			4	90.46	5.0	1,612.94	8.13	309.99	8.86	218.26	6.24	10	77.0	M
			5	151.54	4.0	1,948.37	8.78	256.62	7.33	195.04	5.57	11	77.0	F
			6	135.96	7.0	2,180.02	7.97	229.36	6.55	158.27	4.52	11	77.0	M
			7	75.05	3.0	983.99	8.04	508.13	8.22	353.82	5.72	12	136.0	F
			8	80.81	4.0	1,709.93	10.65	292.41	7.66	269.56	7.06	12	84.0	M
			9	121.25	5.0	1,511.05	7.29	330.90	8.93	208.89	5.64	8	81.5	F
			10	54.16	7.1	1,046.11	7.80	477.96	6.01	322.83	4.06	12	175.0	M
			11	120.01	6.0	1,764.61	8.40	283.35	9.74	205.94	7.08	8	64.0	M
			12	133.98	2.0	2,195.94	7.73	227.69	8.21	152.32	5.49	9	61.0	F
			13	109.50	3.0	1,680.38	8.14	297.55	7.44	209.70	5.24	10	88.0	M
			14	87.64	3.0	1,343.40	8.92	372.19	7.80	287.46	6.02	10	105.0	M
			15	135.48	2.0	1,898.11	7.31	263.42	8.78	166.57	5.55	9	66.0	M
			16	66.10	6.0	1,236.27	7.40	404.44	10.00	259.17	6.41	11	89.0	M
			17	67.05	12.0	.	.	.	.	.	.	12	81.0	M
			18	68.18	3.0	1,017.56	8.59	491.37	5.97	365.44	4.44	12	181.0	F
			19	88.08	5.0	1,304.42	8.08	383.31	9.98	268.14	6.98	12	84.5	M
			20	120.61	2.0	1,567.86	6.29	318.91	11.89	173.58	6.47	10	59.0	F

Appendix 1

Pharmacokinetic and Demographic Analysis Data Set

Assay	Age Group	Study	Subject	Cmax (ng/mL)	Tmax (h)	AUC (hxng/mL)	t½ (h)	CL/F (mL/min)	CL/F (mL/min/kg)	Vz/F (L)	Vz/F (L/kg)	Age (yr)	Weight (lb)	Sex
d-amphetamine	Adult	381.108	1	75.51	3.0	1,679.70	13.20	297.67	3.99	340.20	4.56	25	164.0	M
			2	55.70	6.0	1,299.10	13.00	384.88	4.25	431.64	4.77	32	199.0	M
			3	77.30	6.0	1,257.20	10.00	397.71	6.29	342.85	5.43	40	139.0	F
			4	62.57	5.0	1,296.30	11.10	385.71	5.55	372.07	5.35	32	153.0	M
			5	73.33	4.0	1,117.40	9.10	447.47	6.19	350.95	4.86	22	159.0	F
			6	63.35	5.0	982.20	9.80	509.06	5.54	432.02	4.71	27	202.0	F
			7	47.69	5.0	931.60	9.50	536.71	5.49	440.53	4.51	44	215.0	M
			8	68.18	6.0	1,114.70	8.10	448.55	6.21	314.04	4.35	32	159.0	F
			9	75.54	5.0	1,370.40	9.90	364.86	5.95	311.40	5.07	46	135.0	F
			10	85.25	3.0	1,579.90	10.20	316.48	5.20	278.42	4.57	29	134.0	F
			11	63.50	6.0	1,388.40	9.30	360.13	5.28	290.42	4.26	22	150.0	M
			12	67.39	6.0	1,225.50	10.10	408.00	5.98	356.33	5.23	40	150.0	F

Appendix I
Pharmacokinetic and Demographic Analysis Data Set

Assay	Age Group	Study	Subject	Cmax (ng/mL)	Tmax (h)	AUC (hxng/mL)	t½ (h)	CL/F (mL/min)	CL/F (mL/min/kg)	Vz/F (L)	Vz/F (L/kg)	Age (yr)	Weight (lb)	Sex
l-amphetamine	6 - 12	381.107	1	30.16	12.0	.	.	.	.	.	.	7	51.0	M
			2	24.23	12.0	.	.	.	.	.	.	8	76.0	M
			3	30.37	4.0	617.79	12.40	269.78	7.07	289.69	7.59	9	84.0	M
			4	28.05	6.0	536.33	9.42	310.75	8.88	253.31	7.24	10	77.0	M
			5	45.00	4.0	699.08	10.83	238.41	6.81	223.58	6.39	11	77.0	F
			6	40.42	7.0	721.14	9.13	231.11	6.60	182.75	5.22	11	77.0	M
			7	22.42	3.0	299.18	8.12	557.07	9.01	391.33	6.33	12	136.0	F
			8	25.10	4.0	612.97	12.88	271.90	7.12	303.03	7.94	12	84.0	M
			9	36.96	5.0	484.42	7.59	344.05	9.29	225.99	6.10	8	81.5	F
			10	17.93	7.1	359.67	8.11	463.38	5.83	325.47	4.09	12	175.0	M
			11	39.67	6.0	629.73	9.71	264.66	9.10	222.55	7.65	8	64.0	M
			12	42.50	2.0	826.82	8.82	201.58	7.27	153.94	5.55	9	61.0	F
			13	32.32	3.0	592.42	9.72	281.33	7.03	236.76	5.92	10	88.0	M
			14	25.68	3.0	443.91	9.68	375.45	7.87	314.63	6.59	10	105.0	M
			15	41.51	2.0	637.19	8.18	261.57	8.72	185.13	6.17	9	66.0	M
			16	19.41	6.0	393.06	8.01	424.02	10.48	294.11	7.27	11	89.0	M
			17	21.18	12.0	.	.	.	.	.	.	12	81.0	M
			18	19.44	3.0	333.48	10.19	499.78	6.07	440.85	5.36	12	181.0	F
			19	27.14	5.0	426.35	9.00	390.92	10.18	304.45	7.93	12	84.5	M
			20	35.83	3.0	547.99	7.97	304.14	11.34	209.93	7.83	10	59.0	F

Appendix I
Pharmacokinetic and Demographic Analysis Data Set

Assay	Age Group	Study	Subject	Cmax (ng/mL)	Tmax (h)	AUC (hxng/mL)	t½ (h)	CL/F (mL/min)	CL/F (mL/min/kg)	Vz/F (L)	Vz/F (L/kg)	Age (yr)	Weight (lb)	Sex
l-amphetamine	13 - 17	381.110	101	34.84	5.0	603.87	10.98	276.00	5.76	262.26	5.47	14	105.5	F
			102	24.97	5.0	558.53	10.81	298.40	6.31	279.28	5.91	13	104.0	M
			103	16.00	2.0	491.19	15.57	339.31	4.67	457.41	6.29	17	160.0	M
			104	18.12	4.0	356.46	11.31	467.56	7.24	457.87	7.09	14	142.0	M
			106	23.25	2.0	552.56	14.60	301.63	5.35	381.29	6.76	14	124.0	M
			107	18.84	10.0	827.63	19.82	201.38	3.10	345.41	5.31	16	143.0	M
			108	23.44	5.0	379.38	10.55	439.31	6.20	401.21	5.66	15	156.0	F
			109	23.96	5.0	589.57	15.81	282.69	4.68	386.86	6.40	16	133.0	F
			110	15.89	10.0	419.59	12.16	397.21	5.96	417.96	6.28	17	146.5	M
			111	22.03	3.0	428.69	11.55	388.78	6.68	388.56	6.68	15	128.0	F
			112	28.22	7.0	555.95	9.10	299.79	6.80	236.20	5.36	13	97.0	M
			113	25.05	5.0	544.57	14.50	306.05	4.37	384.14	5.49	15	154.0	M
			114	21.42	4.0	882.68	28.42	188.82	2.88	464.43	7.10	15	144.0	M
			116	20.38	8.0	522.49	15.32	318.99	4.81	422.97	6.37	16	146.0	M
			117	24.27	5.0	600.88	11.99	277.37	4.18	287.99	4.34	14	146.0	F
			201	19.19	5.0	348.12	10.54	478.76	5.72	436.66	5.22	15	184.0	M
			202	19.53	3.0	444.77	14.01	374.73	4.66	454.61	5.65	16	177.0	F
			203	18.48	5.0	332.88	12.84	500.68	6.26	556.54	6.96	15	176.0	M
			204	16.86	7.0	452.32	16.28	368.47	4.61	519.22	6.49	15	176.0	M
			205	20.91	3.0	571.10	17.42	291.84	3.94	440.05	5.94	16	163.0	M
			206	21.91	4.0	518.19	17.08	321.63	4.07	475.45	6.01	17	174.0	F

Appendix I
Pharmacokinetic and Demographic Analysis Data Set

Assay	Age Group	Study	Subject	Cmax (ng/mL)	Tmax (h)	AUC (hxng/mL)	t½ (h)	CL/F (mL/min)	CL/F (mL/min/kg)	Vz/F (L)	Vz/F (L/kg)	Age (yr)	Weight (lb)	Sex
l-amphetamine	Adult	381.108	1	23.27	3.0	640.50	16.50	260.21	3.49	370.85	4.97	25	164.0	M
			2	18.01	6.0	518.20	16.70	321.63	3.56	465.00	5.14	32	199.0	M
			3	26.48	6.0	479.30	11.80	347.73	5.50	355.43	5.63	40	139.0	F
			4	20.34	5.0	469.00	13.20	355.37	5.11	406.91	5.85	32	153.0	M
			5	23.52	5.0	412.20	11.30	404.33	5.59	394.47	5.46	22	159.0	F
			6	21.46	6.0	423.20	12.80	393.82	4.29	436.77	4.76	27	202.0	F
			7	14.76	5.0	360.20	12.10	462.71	4.73	485.36	4.97	44	215.0	M
			8	22.45	6.0	394.20	9.20	422.80	5.85	338.24	4.68	32	159.0	F
			9	23.77	5.0	482.00	11.50	345.78	5.63	345.78	5.63	46	135.0	F
			10	29.11	5.0	644.20	12.90	258.72	4.25	290.15	4.76	29	134.0	F
			11	19.03	6.0	485.20	11.40	343.50	5.04	338.98	4.97	22	150.0	M
			12	23.44	6.0	501.50	12.60	332.34	4.87	361.89	5.31	40	150.0	F

4.3. OCPB Filing/Review Form

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

General Information About the Submission

	Information		Information
NDA Number	**21-303/S-009**	**Brand Name**	**Adderall XR**
OCPB Division (I, II, III)	**Division I**	**Generic Name**	**Dextroamphetamine Sulfate Dextroamphetamine Saccharate Amphetamine Aspartate Monohydrate Amphetamine Sulfate**
Medical Division	**Neuropharmacology**	**Drug Class**	**Attention Disorder**
OCPB Reviewer	**Andre Jackson**	**Indication(s)**	**ADHD**
OCPB Team Leader	**Ray Baweja**	**Dosage Form**	**XR Capsules**
		Dosing Regimen	**10 mg/day adjustable in 5 mg increments to 30 mg/day**
Date of Submission	**September 17, 2004**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**2/10/05**	**Sponsor**	**Shire Laboratories**
PDUFA Due Date	**3/11/05**	**Priority Classification**	**6-month priority**
Division Due Date	**2/24/05**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-Pediatrics		[redacted]		
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	[redacted]			
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:	X			
geriatrics:	NA			
renal impairment:	NA			
hepatic impairment:	NA			
PD:	**NA**			
Phase 2:				
Phase 3:				

PK/PD:	**NA**			
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**NA**			
Data rich:				
Data sparse:				
II. Biopharmaceutics	**NA**			
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**NA**			
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**NA**			
Dissolution:	**NA**			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	**NA**			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

Filability and QBR comments		
	"X" if yes	**Comments**
Application fileable ?	**YES**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1.What are the effects of the covariates of age, weight and gender on the pharmacokinetics of Adderall XR in pediatric patients? 2.Are the kinetics of Adderall XR linear in pediatric patients? 3.How do the kinetics of pediatric patients compare to adults?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-303 HFD-850 (Lee), HFD-120 (Taylor), HFD-860 (Mehta, Rahman, Jackson, Baweja,Yasuda), CDR (Biopharm-CDR)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kofi Kumi
2/28/05 10:14:38 PM
BIOPHARMACEUTICS

Sally Yasuda
3/1/05 09:32:37 AM
BIOPHARMACEUTICS