CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021303Orig1s009

Trade Name:	ADDERALL XR
Generic or Proper Name:	Dextroamphetamine Saccharate , Amphetamine Aspartate Monohydrate Dextroamphetamine Sulfate Amphetamine Sulfate
Sponsor:	Shire
Approval Date:	07/21/2005
Indication:	ADDERALL XR™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

CENTER FOR DRUG EVALUATION AND RESEARCH

021303Orig1s009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-303/S-009

Shire Development, Inc.
Attention: Charles LaPree, RAC
Senior Director, Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Mr. LaPree:

Please refer to your supplemental new drug application dated and received September 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall XR (mixed salts of a single-entity amphetamine product) Extended-Release Capsules.

We acknowledge receipt of your additional submissions dated:

October 27, 2004	December 17, 2004	December 22, 2004	January 11, 2005	March 8, 2005
October 29, 2004	December 21, 2004	January 7, 2005	January 13, 2005	May 27, 2005

Your submission of May 27, 2005 constituted a complete response to our March 15, 2005 action letter.

This supplemental new drug application provides for the use of Adderall XR in the treatment of adolescents with attention-deficit hyperactivity disorder.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-303/S-009**." Approval of this submission by FDA is not required before the labeling is used.

Pediatric Research and Equity Act (PREA)
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Psychiatry Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,
{See appended electronic signature page}

Thomas Laughren, M.D.
Acting Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Thomas Laughren
7/21/05 03:17:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-303/S-009

Shire Laboratories, Inc.
Attention: Charles LaPree, RAC
Senior Director, Regulatory Affairs
U.S. Research and Development
1801 Research Blvd., Suite 600
Rockville, MD 20850

Dear Mr. LaPree:

Please refer to your supplemental new drug application dated and received September 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall XR (mixed salts of a single-entity amphetamine product) Extended-Release Capsules.

We acknowledge receipt of your additional submissions dated:

October 27, 2004	December 17, 2004	December 22, 2004	January 11, 2005
October 29, 2004	December 21, 2004	January 7, 2005	January 13, 2004

This supplemental new drug application provides for the use of Adderall XR in the treatment of adolescents with attention-deficit hyperactivity disorder.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

1. We note that you provided several literature references with your submission. Please provide a discussion and summary of the literature references you provided. Please also provide the search terms and methods that you used in the search. In addition, provide a brief statement of your conclusions about the information that you found in your search.

2. We note the serum creatinine was not part of the laboratory analytical profile in the clinical study. Please explain why this was not included in the routine laboratory profile for patients in the large clinical trial.

3. We ask that you perform separate demographic analyses of the drug: placebo odds of each common and drug-related adverse-event within each demographic subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

4. We note that you provided shift tables as an analysis of outliers for clinical laboratory studies. It appears that these are analyses based on patients who fluctuated from normal values to values outside of the normal range. We are more interested in patients whose values reach potentially clinically significant (PCS) ranges. In many cases this may simply be outside of the laboratory specified normal range, but for example, for liver enzymes, we usually consider 3X the upper limit of normal as the PCS range. Would you please provide

a set of criteria for potentially clinically significant laboratory values and provide an analysis of the number of patients who start in the normal range and then have excursions into PCS ranges during treatment.

5. Please present, by dose, the proportion of patients who had a 5, 10, or 15 mm Hg increase in systolic blood pressure, and the proportion of patients, by dose, who had a 2, 4, 6, or 8 mm Hg increase in diastolic blood pressure in the controlled trial.

6. We believe you should document, in a Phase 4 clinical study, the responsiveness of Adderall-induced hypertension to various classes of anti-hypertensive agents. We would be happy to discuss the design of such a study with you.

Clinical Pharmacology & Biopharmaceutics

The metabolic pathways of amphetamine are not described in the labeling of Adderall. Although there appears to be a role for CYP2D6, amphetamine metabolism has not been well characterized in the literature. We recommend that in *vitro* studies be performed to characterize the metabolic pathways and specific enzymes involved in the metabolism of Adderall. This type of information will determine the importance of specific pathways and the potential for drug interactions mediated by these pathways and will help determine the necessity for *in vivo* evaluation. Similarly, it would be useful to characterize the effect of Adderall on drug metabolizing enzymes. For guidance, you can refer to the Draft Preliminary Concept Paper "Drug Interaction Studies – Study design, data Analysis, and Implications for Dosing and Labeling" (http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1_04_Topic2-TabA.pdf).

In addition, before this application may be approved, you must submit draft labeling for this drug. The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Adderall XR upon approval of this supplemental application. The base document used for our draft labeling is your last approved labeling. Although sections of this proposal are taken verbatim from the labeling proposed by you in the sNDA, other sections have been revised. Please also note that we have embedded in brackets throughout the text of the attached draft labeling several comments and further revisions of the labeling. We also ask that when you submit draft labeling for Adderall XR, you include in the labeling all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes and identify which version of labeling was used as the base document. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,
{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

12 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Russell Katz

3/15/05 04:13:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

LABELING

ADDERALL® XR CAPSULES **CII Rx Only**

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

DESCRIPTION

ADDERALL XR® is a once daily extended-release, single-entity amphetamine product. ADDERALL XR® combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate. The ADDERALL XR® capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from ADDERALL XR® compared to the conventional ADDERALL® (immediate-release) tablet formulation.

EACH CAPSULE CONTAINS:	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg

Inactive Ingredients and Colors: The inactive ingredients in ADDERALL XR® capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR® have been conducted in healthy adult and pediatric (6-12 yrs) subjects, and adolescent (13-17 yrs) and pediatric patients with ADHD. Both ADDERALL® (immediate-release) tablets and ADDERALL XR® capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of ADDERALL® (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for ADDERALL XR® is about 7 hours, which is about 4 hours longer compared to ADDERALL® (immediate-release). This is consistent with the extended-release nature of the product.

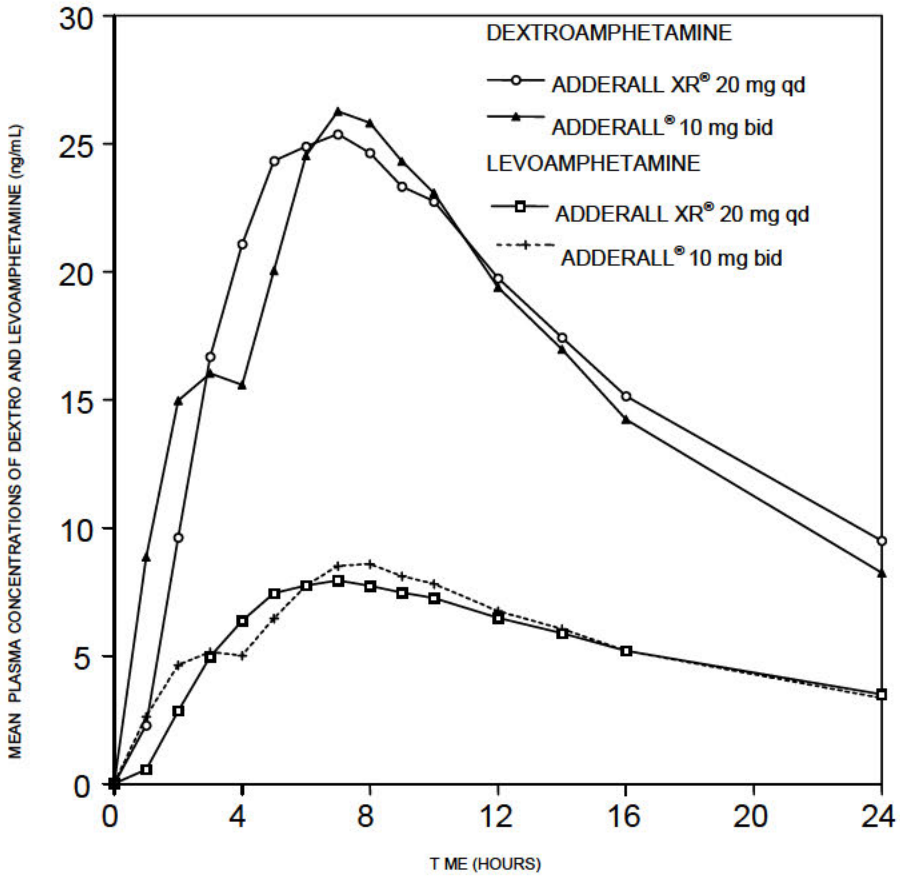

Figure 1 Mean d-amphetamine and l-amphetamine plasma concentrations following administration of ADDERALL XR® 20 mg (8am) and ADDERALL® (immediate-release) 10 mg bid (8am and 12 noon) in the fed state.

A single dose of ADDERALL XR® 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL® (immediate-release) 10 mg bid administered 4 hours apart.

The mean elimination half-live for d-amphetamine is 10 hours in adults; 11 hours in adolescents aged 13-17 years and weighing less than or equal to 75 kg/165 lbs; and 9 hours in children aged 6 to 12 years. For the l-amphetamine, the mean elimination half-life in adults is 13 hours; 13 to 14 hours in adolescents; and 11 hours in children aged 6 to 12 years. On a mg/kg body weight basis children have a higher clearance than adolescents or adults (See Special Populations).

ADDERALL XR® demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and adolescents weighing greater than 75 kg/165lbs, and over the dose range of 10 to 40 mg in adolescents weighing less than or equal to 75 kg/165 lbs, and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal) for d-amphetamine and 2.1 hours (from 5.6 hrs at fasted state to 7.7 hrs after a high fat meal) for l-amphetamine after administration of ADDERALL XR® 30 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of ADDERALL XR® strengths are bioequivalent.

Metabolism and Excretion

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively.

Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30%-40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased, (See PRECAUTIONS).

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.

Pediatric Patients

On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR®, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender

Systemic exposure to amphetamine was 20-30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished. Age and gender had no direct effect on the pharmacokinetics of d- and l-amphetamine.

Race

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

Clinical Trials

Children

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6-12 (N=584) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed dose treatment groups receiving final doses of 10, 20, or 30 mg of ADDERALL XR® or placebo once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all ADDERALL XR® doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all ADDERALL XR® subjects were receiving a dose of 10 mg/day. Patients who received ADDERALL XR® showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg or 30 mg ADDERALL XR® demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

Adolescents

A double-blind, randomized, multi-center, parallel-group, placebo-controlled study was conducted in adolescents aged 13-17 (N=327) who met DSM-IV-TR criteria for ADHD. The primary cohort of patients (n=287, weighing ≤ 75kg/165lbs) was randomized to fixed dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10 mg, 20 mg, 30 mg, and 40 mg ADDERALL XR® or placebo once daily in the morning; patients randomized to doses greater than 10 mg were titrated to their final doses by 10 mg each week.. The secondary cohort consisted of 40 subjects weighing >75kg/165lbs who were randomized to fixed dose treatment groups receiving final doses of 50 mg and 60 mg ADDERALL XR® or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the ADHD-RS-IV total scores for the primary cohort. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (ADDERALL XR® 10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adults

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV-TR criteria for ADHD. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40, or 60 mg of ADDERALL XR® or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18-item scale that measures the core symptoms of ADHD, were observed at endpoint for all ADDERALL XR® doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

INDICATIONS

ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort;

loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations: Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment Program: ADDERALL XR® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of ADDERALL XR® for long-term use, i.e., for more than 3 weeks in children and 4 weeks in adolescents and adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ADDERALL XR® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR® generally should not be used in children, adolescents, or adults with structural cardiac abnormalities.

PRECAUTIONS

General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension.

Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication.

In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving ADDERALL XR® 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥ 8 mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) ADDERALL XR®-treated patients. Similar results were observed at higher doses.

In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg ADDERALL XR®, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.

Tics: Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's Syndrome in children and their families should precede use of stimulant medications.

Effects on Weight: Amphetamines have been associated with decreased appetite. Absolute weight increases in treated children over time, but the increases are smaller than expected based on CDC normative values. These reductions in expected weight attenuate over time and are greatest in the heaviest children. In the controlled trial in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and –2.8 lbs., respectively, for patients receiving 10 mg and 20 mg ADDERALL XR®. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents* -Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines.
Urinary acidifying agents -These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.
Adrenergic blockers -Adrenergic blockers are inhibited by amphetamines.
Alkalinizing agents -Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR® and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.
Antidepressants, tricyclic -Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain;
cardiovascular effects can be potentiated.
MAO inhibitors -MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Antihistamines -Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives -Amphetamines may antagonize the hypotensive effects of antihypertensives.
Chlorpromazine -Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.
Ethosuximide -Amphetamines may delay intestinal absorption of ethosuximide.
Haloperidol -Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.
Lithium carbonate -The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.
Meperidine -Amphetamines potentiate the analgesic effect of meperidine.
Methenamine therapy -Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.
Norepinephrine -Amphetamines enhance the adrenergic effect of norepinephrine.
Phenobarbital -Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.
Phenytoin -Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.
Propoxyphene -In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.
Veratrum alkaloids -Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility: No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m ^{2} body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the E. coli component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis).

Pregnancy: Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Usage in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: ADDERALL XR® is indicated for use in children 6 years of age and older.

Use in Children Under Six Years of Age: Effects of ADDERALL XR® in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: ADDERALL XR® has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for ADDERALL XR® included exposures in a total of 1315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 adult patients, and 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, and one open-label clinical study, and two single-dose clinical pharmacology studies (N= 40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR® in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

Adverse event	% of pediatric patients discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7

In a separate placebo-controlled 4-week study in adolescents with ADHD, eight patients (3.4%) discontinued

treatment due to adverse events among ADDERALL XR®-treated patients (N=233). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headaches, light-headedness, and anxiety.

In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and, 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adolescents and adults, respectively, treated with ADDERALL XR® or placebo are presented in the tables below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR® (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Events Reported by 5% or more of Adolescents Weighing ≤ 75 kg/165 lbs Receiving ADDERALL XR® with Higher Incidence Than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
Digestive System	Loss of Appetite [b]	36%	2%
Nervous System	Insomnia [b]	12%	4%
	Nervousness	6%	6%[a]
Metabolic/Nutritional	Weight Loss [b]	9%	0%

[a] Appears the same due to rounding
[b] Dose-related adverse events

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adolescent patients receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.

*Included doses up to 40 mg

Table 3 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=191)	Placebo (n=64)
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following events did not meet the criterion for inclusion in Table 3 but were reported by 2% to 4% of adult patients receiving ADDERALL XR® with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

*included doses up to 60 mg.

The following adverse reactions have been associated with amphetamine use:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

ADDERALL XR® is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states,
hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of mixed amphetamine salts from ADDERALL XR® should be considered when treating patients with overdose.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the therapeutic needs and response of the patient.
ADDERALL XR® should be administered at the lowest effective dosage.

Children

In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The maximum recommended dose for children is 30 mg/day; doses greater than 30 mg/day of ADDERALL XR® have not been studied in children. Amphetamines are not recommended for children under 3 years of age. ADDERALL XR® has not been studied in children under 6 years of age.

Adolescents

The recommended starting dose for adolescents who are 13-17 years of age with ADHD is 10 mg/day. The dose may be increased to 20 mg/day after one week if ADHD symptoms are not adequately controlled.

Adults

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

Patients Currently Using ADDERALL®- Based on bioequivalence data, patients taking divided doses of immediate-release ADDERALL®, for example twice a day, may be switched to ADDERALL XR® at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

ADDERALL XR® capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

ADDERALL XR® may be taken with or without food.

ADDERALL XR® should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy**.**

HOW SUPPLIED:
ADDERALL XR® 5 mg Capsules: Clear/blue (imprinted ADDERALL XR 5 mg), bottles of 100, NDC 54092-381-01
ADDERALL XR® 10 mg Capsules: Blue/blue (imprinted ADDERALL XR 10 mg), bottles of 100, NDC 54092-383-01
ADDERALL XR® 15 mg Capsules: Blue/white (imprinted ADDERALL XR 15 mg), bottles of 100, NDC 54092-385-01
ADDERALL XR® 20 mg Capsules: Orange/orange (imprinted ADDERALL XR 20 mg), bottles of 100, NDC 54092-387-01
ADDERALL XR® 25 mg Capsules: Orange/white (imprinted ADDERALL XR 25 mg), bottles of 100, NDC 54092-389-01
ADDERALL XR® 30 mg Capsules: Natural/orange (imprinted ADDERALL XR 30 mg), bottles of 100, NDC 54092-391-01

Dispense in a tight, light-resistant container as defined in the USP.
Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

ANIMAL TOXICOLOGY
Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

Manufactured for Shire US Inc., Wayne, PA 19087. Made in USA.

For more information call 1-800-828-2088 or visit www.adderallxr.com

ADDERALL® and ADDERALL XR® are registered in the US Patent and Trademark Office

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

SUMMARY REVIEW

Clinical Psychiatry/Psychopharmacology Review
BPCA Summary Review

PRODUCT (Generic Name):	Mixed Salts of Amphetamine
PRODUCT (Brand Name):	Adderall XR
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	5, 10, 15, 20, 25, 30 (b) (4)
NDA:	21-303 SE5-009
NDA TYPE:	Supplement for ADHD in adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	September 17, 2004
SPONSOR:	Shire Laboratories, Inc.
OND DIVISION:	Division of Neuropharmacological Drug Products

Executive Summary

1.0 BACKGROUND

Adderall XR is an extended-release formulation of Adderall®. Adderall XR is described as mixed salts of amphetamine and includes the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate, and the mixed d- and l-amphetamine aspartate monohydrate.

Adderall XR is approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6-12 years and in adults. This submission provides data to support a claim that Adderall XR is safe and effective in the treatment of ADHD in adolescents aged 13-17 years. This submission also comes to the Division as a response to a Pediatric Written Request (PWR) that was issued May 6, 2003. The review of this submission was therefore required to be performed on a priority basis.

The submission contains clinical results from a pharmacokinetic (PK) study and a placebo controlled fixed-dose study of adolescents with ADHD with doses ranging from 10-60-mg/day.

This memo summarizes primary reviews from the clinical, statistical, biopharmaceutics and chemistry teams.

2.0 CHEMISTRY

The primary Chemistry Team reviewer was Chhagan Tele, PhD. He recommends that the supplement may be approved from a chemistry standpoint. There were no changes in the HOW SUPPLIED or DESCRIPTION sections of labeling.

3.0 PHARMACOLOGY

Adderall XR is an approved product. There were no preclinical pharmacology data reviewed for this submission.

4.0 BIOPHARMACEUTICS

The single PK study in this submission was SLI381-110. The study was reviewed by Kofi Kumi, PhD of OCPB. This study included 23 adolescents aged 13-17 years with ADHD. The study was an open-label single-dose study with 3-treatment periods randomized crossover. There was a 7-day washout period in between these treatments. It included two cohorts of subjects-greater than and less than 75-Kg.

Dr Kumi states in his review:
"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."

Dr Kumi recommends an approval action from an OCPB standpoint.

5.0 CLINICAL DATA

June Cai, MD was the primary clinical reviewer on this supplement. The primary statistical reviewer was Kun He, PhD.

5.1 Efficacy Data

The sponsor presents data from the single study (SLI381-314) as the basis for the claim that Adderall XR is effective in the treatment of ADHD in adolescents. This study had two phases designated A and B. The trial had one 4-week double-blind treatment phase (part A), and followed by a 6-month open-label phase (part B). Part A was the source of efficacy data for the proposed claim and part B provided a source for safety data on growth.

Part A was the randomized, double-blind, parallel group, placebo-controlled trial conducted in 50 centers in the USA, evaluating the use of Adderall XR (fixed dose groups of 10, 20, 30, and 40 mg/day and placebo) in subjects (age 13-17) with Attention Deficit Hyperactivity Disorder (ADHD). The primary cohort (designed for the primary objective) consisted of subjects whose weights were less than or equal to 75 kg/165 lbs, and the secondary cohort (designed for the secondary objective and exploratory analysis) consisted of subjects whose weights were greater than 75 kg/165 lbs. In this latter cohort patients were treated with fixed doses of either Adderall XR 50 or 60-mg/day or placebo. A total of 329 subjects enrolled in the study, and resulted 327 randomized to the double-blind phase. The ITT population included 287 subjects in the primary cohort, and 40 subjects in the secondary cohort. The primary efficacy endpoint was the mean change in ADHD-RSIV total score from baseline at Week 4 (LOCF) in the ITT population. The primary analysis was an ANCOVA model with terms for treatment, site, and the corresponding baseline score as the covariate.

Completion rates in the study were very good with 93% of the placebo and 89% of the drug group completion in the primary cohort. The summary of the results follow in Table 1 (extracted from Dr He's review).

Table 1-Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	**10 mg (N=54)**	**20 mg (N=53)**	**30 mg (N=58)**	**40 mg (N=61)**
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	**-9.4 (10.6)**	**-14.9 (12.1)**	**-20.7 (11.2)**	**-19.0 (11.1)**	**-16.5 (11.6)**
LS mean difference	--	**-5.59**	**-12.23**	**-9.23**	**-8.49**
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

There is a marked dose response between 10 and 20-mg/day, but the best effect of all measured doses (10-40-mg/day) appears to be at the 20-mg dose. The sponsor acknowledges this in their draft labeling.

The 50 and 60-mg/day dose groups for children who weighed greater than 75-Kg did not separate from placebo statistically and the mean change in the 60-mg group was roughly equal to placebo (see Table 2 below). The 50-mg group had roughly the same magnitude of a treatment difference as the 10-mg group in the light weight cohort (<75-Kg). Doses of less than 50-mg/day were not assessed in this cohort.

Table 2 Analyses of ADHD-RS-IV Total Score in the Secondary Cohort (ITT-LOCF)

	Placebo (N=15)	**50 mg (N=15)**	**60 mg (N=10)**
Baseline Mean (SD)	35.7 (8.7)	30.4 (10.2)	32.3 (8.6)
Endpoint Mean (SD) **Mean change (SD)** **LS mean difference (95% CI)** **p-value**	23.1 (13.1) **-12.5 (10.1)**	13.5 (8.9) **-16.9 (12.4)** **-5.63** (-17.08, 5.83) 0.3145	18.3 (11.5) **-14.0 (12.5)** **-1.41** (-13.97, 11.15) 0.8156

These data support the claim that Adderall XR is effective in the treatment of ADHD in adolescents and that there appeared to be no increased benefit at doses of greater than 20-mg/day. 20-mg/day appeared to be superior to 10-mg/day with roughly twice the improvement in efficacy measures.

5.2 Safety

There were no unlabeled or unexpected adverse events that were likely to be drug related that were detected in this submission.

There were no deaths during any part of either study.

Serious Adverse Events

There were three serious adverse events in the adolescent population in which Dr. Cai did not think drug-relatedness could be ruled out. One patient was reported in the initial submission while the other two were reported in the 4-month safety update. All were in open-label treatment so there is no reliable placebo comparison rate.

Patient 34-006, a 14-year-old female, developed depression after 6-months of treatment and was hospitalized for suicidal ideation (COSTART term-thinking abnormally) for a period of 5-days and discharged from the hospital. During her hospitalization, she was treated with sertraline and the Adderall XR 30-mg was discontinued. Dr Cai disagrees with the investigator's opinion that the event is "totally unrelated to the study drug". This case represents a positive de-challenge; however, Adderall XR treatment initiation was not temporally related to the initiation of the depressive episode and no re-challenge with Adderall was performed. I therefore believe that no causal connection can be made in this case.

Subject # 27-002, a 14 year-old female who continued on to Part B from Part A of SLI-381-314, developed major depressive disorder (COSTART term: depression) during the second month of treatment while on 40mg of Adderall XR. The subject discontinued from the study due to this event, but the sponsor reports it was resolved without sequelae. There was no re-challenge with Adderall.

Subject # 56-003, a 13 year-old female who continued on in a new study after Part B of SLI-381-314, developed suicidal ideation (COSTART term: depression) and was hospitalized two months after entering the new study (in addition to the 6-months treatment in part B) while on 30mg of Adderall XR. The patient discontinued from the study due to this event, and the sponsor reports it was resolved without sequelae, but there was no re-challenge with Adderall.

I do not see a suggestion of causality in these cases since two of them lack temporal association with the initiation of treatment. Two of the three cases are 6 to 8 months removed from the initiation of Adderall XR therapy and there was no re-challenge attempt. On the other hand, one can not absolutely prove lack of causality given the data. All things considered, I do not believe that these cases represent an as yet unseen signal for what could reasonably be considered as Adderall XR induced suicide related adverse events.

Vital Signs and ECG

Mean changes and tabulations of outliers for vital signs were compiled for both the PK and efficacy studies. Mean change and outlier analyses in the efficacy study did not produce clinically concerning increases in blood pressure, pulse, or ECG parameters. The PK study however did demonstrate peak increases in pulse and blood pressure at the 2-4 hour post dose measurements. Increases in pulse were approximately 10-bpm across most dose groups without any signal for dose dependence. On the other hand there appeared to be a suggestion of peak effect with dose dependence at the 2-hour post dose recording of systolic and diastolic blood pressure. The effect on systolic blood pressure seems to endure in the secondary cohort at 60-hours post dose. These are included in the table below. I do not believe that these represent new findings.

Subjects & Cohorts		Adderall XR Groups					
		Primary Cohort			Secondary Cohort		
Dose Groups		**10mg**	**20mg**	**40mg**	**20mg**	**40mg**	**60mg**
Total N in Each Group		15	15	15	6	6	6
Systolic Blood Pressure Changes(mmHg)	**Baseline**	107.1	109.6	108.9	111.5	109.3	107.7
	@ 2-hour	4.7	12.4	17.7	8.0	25.7	18.7
	@ 4-hour	6.3	7.7	20.9	12.7	25.0	20.3
	@ 24-hour	3.1	2.3	7.1	6.0	7.8	13.2
	@ 60-hour	7.7	8.5	8.9	8.0	11.8	17.5
Diastolic	**Baseline**	60.6	60.4	63.8	58.7	59.2	60.7
Blood Pressure Changes (mmHg)	**@ 2-hour**	0.1	7.0	8.5	5.7	11.3	10.0
	@ 4-hour	2.6	8.5	7.7	2.8	8.8	9.7
	@ 24-hour	3.1	3.1	2.9	0.3	5.5	4.3
	@ 60-hour	3.5	6.8	3.5	4.7	5.5	8.8

Laboratory Analytes

There were a few statistically significant differences between Adderall XR and placebo with respect to laboratory analytes; however, Dr. Cai felt that none were clinically significant and I concur. Dr Cai noted the lack of serum creatinine data in this submission. Dr Cai states that the sponsor should explore this analyte during future studies but does not suggest that this deficiency would impede approval of this supplement. I agree that the lack of creatinine data in this submission should not impede its approval. In a MEDLINE search using amphetamine or Adderall and creatinine, there were no reports of renal impairment associated with therapeutic amphetamine use. It is, however, reasonable to ask the sponsor why they did not include serum creatinine as part of the clinical laboratory profile for these studies. Dr Cai notes that in another ongoing Adderall study in adult patients serum creatinine values are included.

Growth

Weight loss with the initial use of amphetamine is a common treatment emergent event. There was significant weight loss between all dose groups and placebo in the 4-week controlled trial. These changes were dose related with a maximum mean difference between the 60-mg/day and placebo groups in weight loss of 10.0 pounds over the 4-week period. Characterizing the long-term effects of amphetamine on growth and development is a much more important question. In the 6-month data there was a statistically significant difference in z-score for weight and BMI over the observation period. There was a significant decrease in the z-score for patients in the upper 75th percentile of height, but not for those in the 25-75th or below the 25th percentile group.

The lack of change in height is not particularly reassuring as it was measured over a period as short as 6-months; however, the sponsor is generating much more definitive 2-year data that will better examine the effects of amphetamine treatment on both height and Tanner staging.

6.0 WORLD LITERATURE

Dr Cai found that the sponsor provided a list of references from a world literature search but did not include the dates included for the search or a review and comment on their contents. The sponsor must provide a review and comment on the literature search prior to approval of this submission.

7.0 FOREIGN REGULATORY ACTIONS

On February 9, 2005 Health Canada suspended the marketing of Adderall XR. This action was based on the report of what Health Canada identified as sudden death and stroke in children and adults. The Health Canada alert stated:

> Health Canada's decision comes as a result of a thorough review of safety information provided by the manufacturer, which indicated there were 20 international reports of sudden death in patients taking either ADDERALL® (sold in the United States, not in Canada) or ADDERALL XR® (sold in Canada). These deaths were not associated with overdose, misuse or abuse. Fourteen deaths occurred in children, and six deaths in adults. There were 12 reports of stroke, two of which occurred in children. None of the reported deaths or strokes occurred in Canada.
>
> A preliminary review of safety data for the other related stimulants authorized for use in the treatment of ADHD in Canada has been conducted. In that review, the incidence of serious adverse reactions leading to death was higher in ADDERALL® and ADDERALL XR combined than in the other drugs of this class.

Health Canada contacted the Division prior to taking their action. The Division was able to clarify what cases were reviewed by Health Canada and found that the cases in question were known to the Division, the Office of Drug Safety (ODS), and the Division of Drug Risk and Evaluation (DDRE) at the FDA. The FDA concluded that given the same data, the FDA did not agree with the conclusion reached by Health Canada that the risks associated with the use of Adderall XR outweighed its benefits. The Agency also decided that it would not remove Adderall XR from the market; however, given Health Canada's action, the FDA issued a Public Health Alert. The FDA Public Health Alert stated:

> Health Canada, the Canadian drug regulatory agency, has suspended the sale of Adderall XR in the Canadian market. Adderall XR is a controlled release amphetamine used to treat patients with Attention Deficit Hyperactivity Disorder (ADHD). The Canadian action was based on U.S. post-marketing reports of sudden deaths in pediatric patients.
>
> Adderall XR is approved in the United States for the treatment of adults and pediatric patients 6 years of age and older with ADHD, and Adderall, the immediate-release formulation of the drug, is approved for pediatric patients with ADHD. The Food and Drug Administration (FDA) has been aware of these post-marketing cases, and evaluated the risk of sudden death with Adderall XR prior to approving the drug for treatment of ADHD in adults last year.

> Of 12 total cases, five occurred in patients with underlying structural heart defects (abnormal arteries or valves, abnormally thickened walls, etc.), all conditions that increase the risk for sudden death. Several of the remaining cases presented problems of interpretation, including a family history of ventricular tachycardia, association of death with heat exhaustion, dehydration and near-drowning, very rigorous exercise, fatty liver, heart attack, and type 1 diabetes mellitus. One case was reported three to four years after the event and another had above-toxic blood levels of amphetamine. The duration of treatment varied from one day to 8 years. The number of cases of sudden deaths reported for Adderall is only slightly greater, per million prescriptions, than the number reported for methylphenidate products, which are also commonly used to treat pediatric patients with ADHD.
>
> The FDA is continuing to evaluate these and other post-marketing reports of serious adverse events in children, adolescents, and adults being treated with Adderall and related products. When one considers the rate of sudden death in pediatric patients treated with Adderall products based on the approximately 30 million prescriptions written between 1999 and 2003 (the period of time in which these deaths occurred), it does not appear that the number of deaths reported is greater than the number of sudden deaths that would be expected to occur in this population without treatment. For this reason, the FDA has not decided to take any further regulatory action at this time. However, because it appeared that patients with underlying heart defects might be at increased risk for sudden death, the labeling for Adderall XR was changed in August 2004 to include a warning that these patients might be at particular risk, and that these patients should ordinarily not be treated with Adderall products.

The alerts from Health Canada (HC) and the FDA differ in the reported number of cases of sudden unexplained death (SUD). HC reports 20 cases where the FDA reports 12. The 20 deaths from the HC report include 14 children and 6 adults. The FDA Public Health Advisory focuses on the 12 deaths in children for two primary reasons. First, the FDA had already performed an extensive review of post marketing adverse events in adults prior to the approval of Adderall XR in the adult population with ADHD. The reporting rate for SUD in adults was well below the reported background rate for SUD in the adult population; therefore, the adult deaths were not mentioned in the advisory. Secondly, the background rates for SUD in children were less reliable, so less could be said about the comparative rates of reports of SUD for pediatric patients on drug versus the naturally occurring event without amphetamine treatment.

The FDA case count for SUD in pediatric patients whose demise was uncomplicated by abuse, overdose, or misuse differed by two with HC (HC-n=14, FDA-n=12). By the FDA's accounting one of the 14 Canadian cases was counted twice (STX1-2002-00145 and STX1-2001-00167 appear to be the same patient). The other case counted

by HC but not by FDA was (SUS1-2003-00501). Though HC also excluded cases of overdose misuse or abuse this patient had been abusing cocaine for the two-weeks prior to his death and was therefore not counted by the FDA.

As noted above, a warning statement about the risk of death in patients with underlying structural heart disease was incorporated into the US labeling for Adderall XR with the approval for its use in the adult ADHD population. This FDA action was taken prior to Health Canada's suspension of Adderall XR marketing. Therefore given the Agency's recent in-depth investigation of post-marketing reports of death and serious cardiovascular related adverse events during the review of the adult ADHD application, the extensive discussions with Drs, Katz, Temple, Galson, Jenkins and Office of Drug Safety, the Division of Drug Risk and Evaluation and Health Canada officials, and the recent publication of new labeling, the Public Health Advisory, Patient Information, and Prescriber Information for Adderall XR, I do not recommend any further action at this time.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has presented data that support the claim that Adderall XR is effective in the treatment of ADHD in the adolescent population (aged 13-17 years). This study showed a peak therapeutic effect at a dose of 20-mg/day. Clinical benefit at 20-mg/day as measured by the ADHD-RS was roughly twice as good as at 10-mg; however, doses higher than 20-mg/day showed numerically less symptom relief than 20-mg/day. In order for this supplement to be approved the sponsor must address the following clinical comments and questions that will be provided to them in the action letter:

- We note that you provided several literature references with your submission. Please provide a discussion and summary of the literature references you provided. Please provide the search terms and methods that you used in the search. Please provide a brief statement of your conclusions about the information that you found in your search.
- We note the serum creatinine was not part of the laboratory analytical profile in the clinical study. Would you please explain why this was not included in the routine laboratory profile for patients in the clinical trial?
- Please perform separate demographic analyses of the drug: placebo odds of each common and drug-related adverse-event within each demographic subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.
- We note that you provided shift tables as an analysis of outliers for clinical laboratory studies. It appears that these are analyses based on patients who fluctuated from normal values to values outside of the normal range. We are more interested in patients whose values reach potentially clinically significant (PCS) ranges. In many cases this may simply be outside of the laboratory specified normal range, but for example, for liver enzymes, we usually consider 3X the upper limit of normal as the PCS range. Would you please provide a set of criteria for potentially clinically significant laboratory

values and provide an analysis of the number of patients who start in the normal range and then have excursions into PCS ranges during treatment.

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/s/

Paul Andreason

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Clinical Pharmacology and Biopharmaceutics Review
BPCA Summary Review

Product (Generic Name):	Mixed salts of a single entity amphetamine product
Product (Brand Name):	Adderall XR
Dosage Form:	Extended release capsules
Dosage Strength:	5, 10, 15, 20, 25, 30 mg
NDA:	21-303 (SE5-009)
NDA Type:	Supplement for ADHD in adolescents in response to FDA Pediatric Written Request Letter
Submission Date:	9/17/04
Sponsor:	Shire
OND Division:	HFD-120

Executive Summary

Adderall XR capsules have been approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (6- 12 years) and adults. This sNDA provides support to change the current Adderall XR prescription labeling to include an indication for treatment in adolescents age 13 – 17 years, to include once daily dosage of up to 20 mg/day.

The sNDA included a single dose pharmacokinetic study in adolescents with doses up to 40 mg in adolescents ≤ 75 kg/165 lbs or up to 60 mg in adolescents > 75 kg/165 lbs, one randomized, double blind, placebo controlled study to assess the safety and efficacy in doses up to 60 mg/day for adolescents with ADHD and one long term safety extension study.

The pharmacokinetic study (Study SLI381.110) was an open label, single dose, 3-treatment, 3-period, randomized, crossover, trial. The primary cohort included 17 adolescents (12 males and 5 females) with ADHD, weighing less than or equal to 75 kg/165 lbs. Each of the groups in the cohort received a single oral dose of 10, 20 or 40 mg Adderall XR after an overnight fast in period 1. Then, they were crossed over to the alternate treatment after a 7-day washout period. Six adolescents with ADHD weighing > 75 kg/165 lbs enrolled in a secondary cohort. Each of the groups in the 2nd cohort received single oral dose of 20, 40 or 60 mg Adderall XR after an overnight fast in period 1. Then, they were crossed over to the alternate treatment after 7-day washout period.

The overall conclusions from the pharmacokinetic study in adolescents were:

1) The pharmacokinetics of d- and l-amphetamine after administration of Adderall XR to adolescents (13 – 17 years) weighing ≤ 75 kg/165 lbs were linear between 10 to 40 mg

2) The pharmacokinetics of d- and l-amphetamine after administration of Adderall XR to adolescents (13 – 17 years) weighing > 75 kg/165 lbs were linear between 20 to 60 mg

3) The pharmacokinetics of d- and l- amphetamine after administration of Adderall XR were similar in males and females

4) Differences in pharmacokinetics were observed between pediatric patients (6- 12 years) and adolescents (13 – 17 years), pediatric patients and adults. There were no significant differences in the pharmacokinetics between adolescents and adults.

5) Covariate analysis using data from children, adolescents and adults indicated that body weight primarily accounted for apparent differences in pharmacokinetics. Exposure (AUC and Cmax) decreased with increases in body weight.

Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, this sNDA is acceptable with the labeling recommendations suggested by the reviewer.

The sponsor's proposed dosing recommendations for the adolescent population are acceptable from a pharmacokinetics perspective provided the medical reviewer from a clinical perspective agrees that it is a safe and effective dose.

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/s/

Kofi Kumi
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Sally Yasuda
3/7/05 04:10:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

MEDICAL REVIEW(S)

Clinical Review

NDA 21,303/S-009 Response to Approvable Letter

Sponsor:	Shire
NDA:	21-303/S-009)
Type of Submission	Response to Approvable Letter
Date of Correspondence:	May 27, 2005
Date Received:	May 28, 2005
Drug Name:	ADDERALL XR
Drug Class:	Stimulant
Dosage Strengths:	10 mg and 20 mg
Indication	Attention Deficit Hyperactivity Disorder in Adolescents (ages 13 to 17 years)

I. Background

On September 17, 2004, the sponsor submitted supplemental NDA 21-303/S-009 to support the use of ADDERALL XR in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adolescents (ages 13 to 17 years). On March 15, 2005, the Division issued an Approvable Letter. The sponsor has submitted a response to the Approvable Letter. The Division requested that the sponsor address a number of issues, including a literature review, analysis of adverse events according to demographic variables, renal function tests, clinical laboratory outliers, increases in blood pressure, treatment of Adderall-induced hypertension, amphetamine metabolism, safety updates, and labeling.

II. Literature Summary

The Division requested that the sponsor provide a discussion and summary of the literature references that were originally included in the SNDA submission. The sponsor has provided individual summaries (abstracts) of 33 journal articles pertaining to ADHD and treatment with stimulants. A discussion and general summary of the literature references were not provided. The search was performed using Medline and Embase databases. The search terms included 'Adderall,' 'Adderall XR,' 'mixed amphetamine salts,' 'mixed salts of a single-entity amphetamine,' dextroamphetamine,' 'amphetamine aspartate,' and amphetamine sulphate.' All North American publications related to these terms were included, with the exception of publications regarding the illicit use amphetamines.

In my opinion, the information from the journal abstracts submitted and reviewed would not affect a potential approval decision. The sponsor has responded adequately, and the summaries provide some useful information about the safety, pharmacokinetics, drug interactions, metabolism, and effectiveness of stimulant treatment in children and adolescents. One article included a case report of acute psychosis in a 7-year-old boy receiving treatment with Adderall for ADHD. Another article discussed a case of new onset of seizures in a child treated with Adderall.

III. Lack of Serum Creatinine Testing

The Division requested that the sponsor provide an explanation for not having included monitoring of serum creatinine concentrations as part of the safety analysis. The sponsor states that serum creatinine determinations were inadvertently not requested to be performed for studies SLI381.314 Part A (controlled, double-blind) or SLI381.314 Part B (open-label). The sponsor also states that Blood Urea Nitrogen (BUN) concentrations were measured and the BUN is an appropriate substitute for serum creatinine in the pediatric population studied, as it is sensitive to changes in both renal function and volume status. There were no significant changes in BUN concentration in subjects during treatment with Adderall. The sponsor states that serum creatinine concentration will be monitored in a long-term, open-label safety study (SLI381.315).

In my opinion, the lack of serum creatinine monitoring in the studies is a significant omission.

IV. Analysis of Adverse Events By Demographic Variables

The Division requested that the sponsor perform a demographic analysis of the drug: placebo odds of each common and drug-related adverse event within each demographic subgroup, along with a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups. The subgroups were: male, female, white, other race, 13 to 14-years-old, 15 to 17-years old. The common and drug-related adverse events were abdominal pain, anorexia, anxiety, asthenia, depression, hallucinations, headache, insomnia, nervousness, somnolence, and twitching. There were no statistically significant differences in odds ratios between demographic subgroups for any of these adverse events. The sponsor has responded adequately to this request.

V. Outlier Analysis of Clinical Laboratory Parameters

The Division requested that the sponsor define criteria for clinical laboratory abnormalities that are potentially clinically significant and provide a relevant outlier analysis. The sponsor provided a table entitled "Criteria for Abnormal Laboratory Values: Parameters for Treatment-Emergent Abnormal Values Definition." The sponsor states that these criteria are defined in the FDA DNDP Guidelines. Leber, P., US Food and Drug Administration, CDER, DNDP. Form and Content of NDA Reviews: Strategies for the Efficacy Analysis. The table includes the normal ranges for CBC with Differential, clinical chemistry tests (10), and urinalysis.

Results of the outlier analysis reveal no significant differences in clinical laboratory abnormalities between the placebo and Adderall groups. There are small differences between treatment groups in the proportion of subjects who were outliers. For 5 of the 12 relevant parameters, there was an excess of outliers in the placebo group. There was an excess of outliers in the Adderall group compared to the placebo group for the following 7 parameters: platelet count (0.4% [n=1] vs. 0), eosinophils (0.4% vs. 0), hemoglobin

(0.4% vs. 0), potassium (2.6% vs. 1.5%), AST (0.4% vs. 0), ALT (0.4% vs. 0), and total protein (0.4% vs. 0).

VI. Analysis of Blood Pressure Increases

The Division requested that the sponsor present blood pressure data by Adderall dose, proportion of subjects who had an increase in systolic blood pressure of 5, 10, and 15 mm Hg, and the proportion of subjects who had an increase in diastolic blood pressure of 2, 4, 6, and 8 mm Hg in the placebo-controlled trial. The data are illustrated in the table below. For most of the Adderall dose levels compared to placebo, there does not appear to be a clear relationship between Adderall treatment and the proportion of subjects who had an increase in systolic blood pressure. However, for the 40 mg, 50 mg, and 60 mg groups, there may be an increased proportion of subjects who had an increase in systolic blood pressure compared to placebo. For the changes in diastolic blood pressure, there was no clear difference between treatment groups.

Systolic BP incr. (mmHg)	Visit	Placebo	10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	Total 10-60 mg
	Visit 1	13	15	8					15
$\geq$ 5 & < 10	Visit 2	14	8	14	29	33			14
	Visit 3	8	8	8	9	15	0		9
	Visit 4	14	10	6	4	8	8	0	7
	Visit 1	10	9	4					9
$\geq$ 10 & < 15	Visit 2	8	6	14	0	11			11
	Visit 3	8	12	6	8	23	22		10
	Visit 4	10	2	10	10	9	23	11	10
	Visit 1	7	4	4					5
> 15	Visit 2	11	2	5	14	22			5
	Visit 3	9	2	6	7	8	11		6
	Visit 4	10	4	10	13	6	0	22	8

Diastolic BP incr. (mmHg)	Visit	Placebo	10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	Total 10-60 mg
	Visit 1	7	9	8					9
$\geq$ 2 & < 4	Visit 2	9	11	14	7	11			13
	Visit 3	8	8	6	9	8	0		9
	Visit 4	5	10	6	9	15	8	0	10
	Visit 1	12	3	12					8
$\geq$ 4 & < 6	Visit 2	9	6	4	14	0			9
	Visit 3	9	10	8	8	8	11		9
	Visit 4	2	4	16	15	6	23	11	11
	Visit 1	7	7	8					3
> 6 & < 8	Visit 2	9	6	7	0	0			6
	Visit 3	6	2	4	8	0	0		3
	Visit 4	8	6	4	11	6	0	0	6
	Visit 1	18	21	8					20
> 8	Visit 2	20	21	45	14	22			19
	Visit 3	13	16	28	18	23	11	22	20
	Visit 4	26	18	26	15	18	8		20

VII. Treatment of Adderall-induced Hypertension

During a teleconference on April 22, 2005, the Division and the sponsor agreed that it was not necessary to conduct a Phase 4 study of the treatment of Adderall-induced hypertension.

VIII. Metabolism of Amphetamine

The sponsor has responded adequately to the Division's request for more information pertaining to the metabolism and potential drug interactions with Adderall. The sponsor provided results from a number of in vitro studies as well as a pertinent review by the National Toxicology Panel. There have been no human studies of Adderall metabolism. It appears that isoenzymes CYP2D6 and CYP2C19 could be clinically significant in the metabolism of amphetamine and methamphetamine. In addition, amphetamine may be a competitive inhibitor of CYP2D6.

IX. Safety Updates

A. Investigational Safety Update

There are no new safety data to report. On January 13, 2005, the sponsor submitted a 4-Month Safety Update for NDA 21-303/S-009, which provided a final integrated summary of safety from the studies reviewed (SLI381.110 and SLI314 Part A & Part B) as well as new interim data (as of September 23, 2004) from Study SLI381.315 (a 24-month, open-label study of Adderall XR in the treatment of adolescents with ADHD).

B. Worldwide Safety Update

The sponsor notes that on February 9, 2005, Health Canada suspended the sales of Adderall XR on the basis of safety data reviewed in the process of aligning the Canadian Product Monograph with changes made in U.S. labeling for Adderall XR (during the course of review and approval of NDA 21-303/S-005: Adderall XR for the Treatment of Adults with Attention Deficit Hyperactivity Disorder). Information added to the U.S. Package Insert in the BLACK BOXED WARNING, WARNINGS, and ADVERSE EVENTS section pertains to sudden death in children with underlying structural cardiovascular disease.

X. Labeling

The sponsor's proposed labeling is acceptable. The OCPB reviewers have proposed additional labeling language regarding drug metabolism and drug-drug interactions (please refer to the review by Ronald E. Kavanagh B.S. Pharm).

A. Clinical Trials Section

The sponsor accepted the Division's request to delete specific language regarding results on (b) (4)

The sponsor appropriately included language regarding the lack of evidence (b) (4) (b) (4) when doses of Adderall XR > 20 mg are used.

B. PRECAUTIONS Hypertension

The sponsor has included appropriate, accurate language regarding changes in blood pressure associated with Adderall XR treatment and the need for dose-reduction and/or anti-hypertensive treatment.

C. PRECAUTIONS Weight Loss

The sponsor has included appropriate language pertaining to weight loss and decreased appetite in association with Adderall XR treatment.

D. Adverse Events

The sponsor has responded adequately to the Division's request to include a table listing the adverse events that were dose-related in the adolescent study. In the Common Adverse Events table (> 5%), the sponsor added a footnote to identify AE that were dose-related (loss of appetite, insomnia, and weight loss).

E. Dosage and Administration

The sponsor has proposed acceptable language regarding the Adderall starting dose (10 mg/day) and recommended titration schedule (increasing to 20 mg/day after one week of therapy if needed to control ADHD symptoms) in adolescents.

F. OCPB Proposed Language

Dr. Kavanagh has proposed labeling language for the following section:
Clinical Pharmacology- Pharmacokinetics- Metabolism and Excretion

XI. Summary and Conclusions

In my opinion, the sponsor has responded adequately to the Division's requests specified in the Approvable Letter. I recommend that the Division take an Approval Action.

_____

Robert Levin, M.D., July 12, 2005
Medical Reviewer
FDA CDER ODE1 DNDP HFD 120

cc: NDA
HFD 120
T Laughren
P Andreason
J Cai
R Taylor

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/s/

Robert Levin
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MEDICAL OFFICER

Thomas Laughren
7/12/05 11:03:27 AM
MEDICAL OFFICER
I agree that this supplement can be approved once we reach agreement on final labeling.--TPL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 1, 2005

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Supplement SE5-009- Adderall XR for the Treatment of ADHD in Adolescents (aged 13-17years)

TO: File NDA 21-303
[Note: This memo should be filed with the September 17, 2004 original submission of this NDA.]

1.0 BACKGROUND

Adderall XR is an extended-release formulation of Adderall®. Adderall XR is described as mixed salts of amphetamine and includes the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate, and the mixed d- and l-amphetamine aspartate monohydrate.

Adderall XR is approved for the treatment of Attention Deficit Hyperactive Disorder (ADHD) in children aged 6-12 years and in adults. This submission provides data to support a claim that Adderall XR is safe and effective in the treatment of ADHD in adolescents aged 13-17 years. This submission also comes to the Division as a response to a Pediatric Written Request (PWR) that was issued May 6, 2003. This review was therefore performed on a priority basis.

The submission contains clinical results from a pharmacokinetic (PK) study and a placebo controlled fixed-dose study of adolescents with ADHD for doses ranging from 10-60-mg/day.

This memo summarizes primary reviews from the Clinical, Biometrics, and Chemistry Review Teams, the Division of Scientific Investigation (DSI), and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

2.0 CHEMISTRY

The primary Chemistry Team reviewer was Tele Chhagan, PhD. He recommends that the supplement may be approved from a chemistry standpoint. There are no changes in the HOW SUPPLIED or DESCRIPTION sections of labeling.

3.0 PHARMACOLOGY

Adderall XR is an approved product. There was no preclinical pharmacology data reviewed for this submission.

4.0 BIOPHARMACEUTICS

The single PK study in this submission was SLI381-110. The study was reviewed by Kofi Kumi, PhD of OCPB. This study included 23 adolescents aged 13-17 years with ADHD. The study was an open-label single-dose study with 3-treatment periods randomized crossover. There was a 7-day washout period in between these treatments. It included two cohorts of subjects-greater than and less than 75-Kg.

Dr Kumi states in his review:
"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."

Dr Kumi recommends an approval action from an OCPB standpoint.

5.0 CLINICAL DATA

June Cai, MD was the primary clinical reviewer on this supplement. The primary statistical reviewer was Kun He, PhD.

5.1 Efficacy Data

The sponsor presents data from the single study (SLI381-314) as the basis for the claim that Adderall XR is effective in the treatment of ADHD in adolescents. This study had two phases designated A and B. The trial had one 4-week double-blind treatment phase (part A), and followed by a 6-month open-label phase (part B). Part A was the source of efficacy data for the proposed claim and part B provided a source for safety data on growth.

Part A was a randomized, double-blind, placebo-controlled trial conducted in 50 centers in USA, evaluating the use of Adderall XR (10mg/day to 40 mg/day) in subjects (age 13-17) with Attention Deficit Hyperactivity Disorder (ADHD). The primary cohort (designed for the primary objective) consisted of subjects whose weights were less than or equal to 75 kg/165 lbs, and secondary cohort (designed for secondary objective and exploratory analysis) consisted of subjects whose weights were greater than 75 kg/165 lbs. A total of 329 subjects enrolled in the study, and resulted 327 randomized to the double-blind phase. ITT included 287 subjects in the primary cohort, and 40 subjects in the

secondary cohort. The primary efficacy endpoint was the mean change in ADHD-RSIV total score from baseline at Week 4 LOCF in the ITT population. The primary analysis was ANCOVA model with terms for treatment, site, and the corresponding baseline score as the covariate.

Completion rates in the study were very good with 93% placebo and 89% drug group completion in the primary cohort. The summary of the results follow in Table 1 (extracted from Dr He's review).

Table 1-Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)					
	Placebo (N=52)	**10 mg (N=54)**	**20 mg (N=53)**	**30 mg (N=58)**	**40 mg (N=61)**
Baseline Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	**-9.4 (10.6)**	**-14.9 (12.1)**	**-20.7 (11.2)**	**-19.0 (11.1)**	**-16.5 (11.6)**
LS mean difference	--	**-5.59**	**-12.23**	**-9.23**	**-8.49**
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

There is a marked dose response between 10 and 20-mg/day, but the best effect of all measured doses (10-40-mg/day) appears to be at the 20-mg dose. The sponsor acknowledges this in their draft labeling.

The 50 and 60-mg/day dose groups for children who weighed greater than 75-Kg did not separate from placebo statistically and the mean change in the 60-mg group was roughly equal to placebo (see Table 2 below). The 50-mg group had roughly the same magnitude of a treatment difference as the 10-mg group in the light weight cohort (<75-Kg). Doses of less than 50-mg/day were not measured in the cohort weighing greater than 75-Kg.

Table 2 Analyses of ADHD-RS-IV Total Score in the Secondary Cohort (ITT-LOCF)			
	Placebo (N=15)	**50 mg (N=15)**	**60 mg (N=10)**
Baseline Mean (SD)	35.7 (8.7)	30.4 (10.2)	32.3 (8.6)
Endpoint Mean (SD)	23.1 (13.1)	13.5 (8.9)	18.3 (11.5)
Mean change (SD)	**-12.5 (10.1)**	**-16.9 (12.4)**	**-14.0 (12.5)**
LS mean difference		**-5.63**	**-1.41**
(95% CI)		(-17.08, 5.83)	(-13.97, 11.15)
p-value		0.3145	0.8156

These data support the claim that Adderall XR is effective in the treatment of ADHD in adolescents and that there appeared to be no benefit to doses of greater than 20-mg/day. 20-mg/day appeared to be superior to 10-mg/day with roughly twice the improvement in efficacy measures.

5.2 Safety

There were no unlabeled or unexpected adverse events that were likely to be drug related that were detected in this submission.

There were no deaths during any part of either study.

Serious Adverse Events
There were three serious adverse events in the adolescent population where Dr. Cai did not think drug-relatedness could be ruled out. One patient was reported in the initial submission while the other two were reported in the 4-month safety update. All were in open-label treatment

Patient 34-006, a 14-year-old female, developed depression after 6-months treatment and was hospitalized for suicidal ideation for a period of 5-days and discharged from the hospital. During her hospitalization, she was treated with sertraline and the Adderall XR 30-mg was discontinued. Dr Cai disagrees with the investigator's opinion that the event is "totally unrelated to the study drug". This case represents a positive de-challenge; however, Adderall XR treatment initiation was not temporally related to the initiation of the depressive episode and no re-challenge was performed. . I therefore believe that no causal connection can be made in this case.

Subject # 27-002, a 14 year-old female who rolled over from Part A of SLI-381-314, developed major depressive disorder (COSTART term: depression) during the second month of treatment while on 40mg of Adderall XR. The subject discontinued from the study due to this event, but the sponsor reports it was resolved without sequelae. There was no re-challenge.

Subject # 56-003, a 13 year-old female who rolled over from Part B of SLI-381-314, developed suicidal ideation (COSTART term: depression) and was hospitalized two months after entering the new study (additionally after 7-months treatment in part A and B) while on 30mg of Adderall XR. The patient discontinued from the study due to this event, the sponsor reports it was resolved without sequelae, but there was no re-challenge.

Though one can not prove lack of causality, I do not believe that these cases represent an as yet unseen signal for Adderall XR induced suicide related adverse events. Two of the three cases are 6 to 8 months removed from the initiation of Adderall XR therapy and there was no re-challenge attempt.

Vital Signs and ECG
Mean changes and tabulations of outliers for vital signs were compiled for both the PK and efficacy studies. Mean change and outlier analyses in the efficacy study did not produce clinically concerning increases in blood pressure, pulse, or ECG parameters. The PK study however did demonstrate peak increases in pulse and blood pressure at the 2-hour post dose measurement. Increases in pulse were approximately 10-bpm across most dose groups without any signal for dose dependence. On the other hand there appeared to be a suggestion of peak effect with dose dependence at the 2-hour post dose recording of systolic and diastolic blood pressure. The effect on systolic blood pressure seems to endure in the secondary cohort at 60-hours post dose. These are included in the table below. I do not believe that these represent new findings.

Subjects & Cohorts		Adderall XR Groups					
		Primary Cohort			Secondary Cohort		
Dose Groups		**10mg**	**20mg**	**40mg**	**20mg**	**40mg**	**60mg**
Total N in Each Group		15	15*	15	6	6	6
Systolic Blood Pressure Changes(mmHg)	**Baseline**	107.1	109.6	108.9	111.5	109.3	107.7
	@ 2-hour	4.7	12.4	17.7	8.0	25.7	18.7
	@ 4-hour	6.3	7.7	20.9	12.7	25.0	20.3
	@ 24-hour	3.1	2.3	7.1	6.0	7.8	13.2
	@ 60-hour	7.7	8.5	8.9	8.0	11.8	17.5
Diastolic Blood Pressure Changes (mmHg)	**Baseline**	60.6	60.4	63.8	58.7	59.2	60.7
	@ 2-hour	0.1	7.0	8.5	5.7	11.3	10.0
	@ 4-hour	2.6	8.5	7.7	2.8	8.8	9.7
	@ 24-hour	3.1	3.1	2.9	0.3	5.5	4.3
	@ 60-hour	3.5	6.8	3.5	4.7	5.5	8.8

Laboratory Analytes

There were a few statistically significant differences between Adderall XR and placebo with respect to laboratory analytes; however, Dr. Cai felt that there were no clinically significant differences between placebo and drug treatment groups with respect to laboratory analytes and I concur. Dr Cai states that the lack of serum creatinine is a major deficiency in this submission. Dr Cai states that the sponsor should explore this analyte during future studies but does not suggest that this deficiency would impede approval of this supplement. I agree. In a MEDLINE search using amphetamine or Adderall and creatinine, there were no reports of renal impairment associated with therapeutic amphetamine use. It is, however, reasonable to ask the sponsor why they did not include serum creatinine as part of the clinical laboratory profile for these studies.

Weight and Height

Weight loss with the initial use of amphetamine is a common treatment emergent event. The mean difference between the 60-mg/day and placebo groups in weight change was 10.0 pounds over the 4-week period. Characterizing the long-term effects of amphetamine on growth and development is a much more important question. In the 6-month data there was a statistically significant difference in z-score for weight and BMI over the observation period. There was a significant decrease in the z-score for patient sin the upper 75th percentile of height, but not for those in the 25-75th or below the 25th percentile group. The lack of change in height is not particularly reassuring when it is measured over a period as short as 6-months; however, the sponsor is generating much more definitive 2-year data that will better examine the effects of amphetamine treatment on both height and Tanner staging.

5.3 Clinical Sections of Labeling

Draft labeling is attached to this package. Comments to the sponsor are noted in bracketed sections [ ].

6.0 WORLD LITERATURE

Dr Cai reports that the sponsor provided a list of references from a world literature search but did not include a review and comment on their contents. The sponsor must provide a review and comment on the literature search prior to approval of this submission.

7.0 FOREIGN REGULATORY ACTIONS

On February 9, 2005 Health Canada suspended marketing Adderall XR. This action was based on the report of what Health Canada identified as sudden death and stroke in children and adults. The Health Canada alert stated:

> Health Canada's decision comes as a result of a thorough review of safety information provided by the manufacturer, which indicated there were 20 international reports of sudden death in patients taking either ADDERALL® (sold in the United States, not in Canada) or ADDERALL XR® (sold in Canada). These deaths were not associated with overdose, misuse or abuse. Fourteen deaths occurred in children, and six deaths in adults. There were 12 reports of stroke, two of which occurred in children. None of the reported deaths or strokes occurred in Canada.
>
> A preliminary review of safety data for the other related stimulants authorized for use in the treatment of ADHD in Canada has been conducted. In that review, the incidence of serious adverse reactions leading to death was higher in ADDERALL® and ADDERALL XR combined than in the other drugs of this class.

Health Canada contacted the Division prior to taking their action. The Division was able to clarify the cases that were reviewed by Health Canada and found that the cases in question were known to the Division, the Office of Drug Safety (ODS), and the Division of Drug Risk and Evaluation (DDRE) at the FDA. The FDA concluded that given the same data, the FDA did not agree with the conclusion reached by Health Canada that the risks associated with the use of Adderall XR outweighed its benefits. The Agency also decided that it would not remove Adderall XR from the market. The FDA Public Health Alert stated:

> Health Canada, the Canadian drug regulatory agency, has suspended the sale of Adderall XR in the Canadian market. Adderall XR is a controlled release amphetamine used to treat patients with Attention Deficit Hyperactivity Disorder (ADHD). The Canadian action was based on U.S. post-marketing reports of sudden deaths in pediatric patients.
>
> Adderall XR is approved in the United States for the treatment of adults and pediatric patients 6 years of age and older with ADHD, and Adderall, the immediate-release formulation of the drug, is approved for pediatric patients with ADHD. The Food and Drug Administration (FDA) has been aware of these post-marketing cases, and evaluated the risk of sudden death with Adderall prior to approving the drug for treatment of ADHD in adults last year.
>
> Of 12 total cases, five occurred in patients with underlying structural heart defects (abnormal arteries or valves, abnormally thickened walls, etc.), all conditions that increase the risk for sudden death. Several of the remaining cases presented problems of interpretation, including a family history of ventricular tachycardia, association of death with heat exhaustion, dehydration and near-drowning, very rigorous exercise, fatty liver, heart attack, and type 1 diabetes mellitus. One case was reported three to four years after the event and another had above-toxic blood levels of amphetamine. The duration of treatment varied from one day to 8 years. The number of cases of sudden deaths reported for Adderall is only slightly greater, per million prescriptions, than the number reported for methylphenidate products, which are also commonly used to treat pediatric patients with ADHD.
>
> The FDA is continuing to evaluate these and other post-marketing reports of serious adverse events in children, adolescents, and adults being treated with Adderall and related products.

> When one considers the rate of sudden death in pediatric patients treated with Adderall products based on the approximately 30 million prescriptions written between 1999 and 2003 (the period of time in which these deaths occurred), it does not appear that the number of deaths reported is greater than the number of sudden deaths that would be expected to occur in this population without treatment. For this reason, the FDA has not decided to take any further regulatory action at this time. However, because it appeared that patients with underlying heart defects might be at increased risk for sudden death, the labeling for Adderall XR was changed in August 2004 to include a warning that these patients might be at particular risk, and that these patients should ordinarily not be treated with Adderall products.

The alerts from Health Canada (HC) and the FDA differ in the number of cases of SUD. HC reports 20 cases where the FDA reports 12. The cases from HC report of 20 deaths include 14 children and 6 adults. The FDA Public Health Advisory focuses on 12 children. The focus on the 12 children is because the FDA had already performed an extensive review of post marketing adverse events in adults prior to the approval of Adderall XR for adult ADHD. The reporting rate for SUD in adults was well below the reported background rate in the adult population; therefore, the adult deaths were not mentioned in the advisory. The background rates for SUD in children were less reliable so less could be said about the comparative rates of reports of SUD for patients on drug versus the naturally occurring event without amphetamine treatment.

The FDA case count of SUD in pediatric patients whose demise was uncomplicated by abuse, overdose, or misuse differed by two cases (HC-n=14, FDA-n=12). By the FDA's accounting one of the 14 Canadian cases was counted twice (STX1-2002-00145 and STX1-2001-00167 appear to be the same patient). The other case that HC included that the FDA did not was (SUS1-2003-00501). Though HC also excluded cases of overdose misuse or abuse, this patient had been abusing cocaine for two-weeks prior to his death.

The 12 deaths in children reported in the FDA Advisory were incorporated into the labeling for Adderall XR with the approval for its use in the adult ADHD population. This FDA action was taken prior to Health Canada's suspension of Adderall XR marketing. Therefore given our recent in-depth investigation of post-marketing reports of death and serious cardiovascular related adverse events during the review of the adult ADHD application, the extensive discussions with Drs, Katz, Temple, Galson, Jenkins and offices Drug Safety, the Division of Drug Risk and Evaluation and Health Canada officials, and the recent publication of new labeling, the Public Health Advisory, Patient Information, and Prescriber Information for Adderall XR, I do not recommend any further action at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We did not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

DSI inspections were performed by Robert Stasko, MD who is a child psychiatrist. Dr Stasko found that the data at sites Vince-037 and Arnold-003 were acceptable. There were minor violations noted at site 003. Three subjects did not have CGI data (a secondary variable) transferred to the CRF and one subject had an incomplete diagnostic interview. There were no violations at the Vince-037 site.

Dr. Stasko notes that weight loss was common at site-003 but may not have been reported as a spontaneous adverse event. Dr. Arnold stated that weight loss was reported as an adverse event if it

was considered significant. Weight was systematically measured, so whether or not the weight loss is judged to be an AE and reported as such is not, in my opinion, crucial to this review.

10.0 APPROVABLE ACTION LETTER

Draft labeling is attached to the proposed approvable letter in this action package.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has presented data that support the claim that Adderall XR is effective in the treatment of ADHD in the adolescent population (aged 13-17 years). This study showed a peak therapeutic effect at a dose of 20-mg/day. Clinical benefit at 20-mg/day as measured by the ADHD-RS was roughly twice as good as at 10-mg; however, doses higher than 20-mg/day showed numerically less symptom relief than 20-mg/day. In order for this supplement to be approved the sponsor must address the following clinical issues:

- We note that you provided several literature references with your submission. Please provide a discussion and summary of the literature references you provided. Please provide the search terms and methods that you used in the search. Please provide a brief statement of your conclusions about the information that you found in your search.
- We note the serum creatinine was not part of the laboratory analytical profile in the clinical study. Would you please explain why this was not included in the routine laboratory profile for patients in the large clinical trial?
- Please perform separate demographic analyses of the drug: placebo odds of each common and drug-related adverse-event within each demographic subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.
- We note that you provided shift tables as an analysis of outliers for clinical laboratory studies. It appears that these are analyses based on patients who fluctuated from normal values to values outside of the normal range. We are more interested in patients whose values reach potentially clinically significant (PCS) ranges. In many cases this may simply be outside of the laboratory specified normal range, but for example, for liver enzymes, we usually consider 3X the upper limit of normal as the PCS range. Would you please provide a set of criteria for potentially clinically significant laboratory values and provide an analysis of the number of patients who start in the normal range and then have excursions into PCS ranges during treatment.
- Please review the attached draft labeling. Specific comments are included in brackets [ ] in the body of the labeling text.

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

/s/

Paul Andreason
3/1/05 11:03:58 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-303
Submission Number	009
Submission Code	SE5
Letter Date	Sept. 17, 2004
Stamp Date	Sept. 17, 2004
PDUFA Goal Date	Mar 17, 2004
Reviewer Name	June Cai, M.D.
Review Completion Date	Feb. 8, 2004
Established Name	Mixed Amphetamine Salts
(Proposed) Trade Name	Adderall XR
Therapeutic Class	Sympathomimetic amine
Applicant	Shire Pharmaceutical Inc.
Priority Designation	P
Formulation	Capsules
Dosing Regimen	10-20mg once daily
Indication	Adolescent ADHD
Intended Population	Age 13-17 year-old

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an approvable action. The sponsor needs to submitted required safety information to correct the deficiencies in the submission before final approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

Continue pursuing the long term safety tolerability study, Study SLI381-315, as stated in our pediatric exclusivity approve letter.

1.2.3 Other Phase 4 Requests

I would like to recommend including serum creatinine in the chemistry panel in future studies because this gives a more complete data on routine clinical assessment for renal function, esp. given four subjects had protenuria in Adderall XR group and none in placebo group in the submitted controlled study.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In response to the FDA Written Request for pediatric studies in adolescents with Attention Deficit Hyperactivity Disorder (ADHD), the sponsor submits this supplemental NDA which consists of one pharmacokinetic (PK) study (Study SL1381.110) and one controlled clinical trial in adolescents ages 13-17 year-old with ADHD (SL1381.314). This controlled clinical trial includes two parts: Part A and Part B. Part A is a phase III, randomized, multi-center, double-blind, parallel-group, placebo-controlled safety and efficacy study of ADDERALL XR in adolescents aged 13-17 with (ADHD), whereas Part B is a 6-month open label safety extension study of Part A.

The sponsor included a total of 327 subjects in the two cohorts of the controlled clinical trial: The 287 subjects with body weight of no more than 75kg /165lbs were included in the primary cohort and 40 subjects who weighted more than 75kg/165lbs were included in the secondary

cohort. Active treatment group completion rate for primary cohort was 89% (208/233) and that of secondary cohort was 88% (22/25).

1.3.2 Efficacy

Study SLI381-314 Part A is a four-week, fixed-dose, double-blind, placebo-controlled study. The fixed doses were 10, 20, 30, and 40 mg/day in the primary cohort and 50 and 60 mg/day in the secondary cohort. The primary efficacy variable was the mean change from baseline to endpoint in the ADHD-RS-IV total score. It demonstrates the efficacy of Adderall XR for treatment of adolescents (weighed ≤75kg/165lbs) with ADHD in the primary cohort. The most effective dose from this study is 20mg/day from the primary analysis. Increasing dose from 20 to 40mg/day did not show increased efficacy.

1.3.3 Safety

The primary safety database consisted of a four-week, placebo-controlled study and a six-month open-label safety study as well as a single dose crossover pharmacokinetic study. In addition, Four-Month Safety Update from a just started ongoing open-label safety study (Study SLI381-315) was also examined.

Though no significant previously unrecognized adverse events associated with Adderall XR treatment were discovered, it is noteworthy that major deficiencies in the assessment of safety exist, including lack of serum creatinine in the original safety database and missing narrative descriptions and case report forms of dropout cases in the Safety Update.

1.3.4 Dosing Regimen and Administration

10mg to 20mg daily.

1.3.5 Drug-Drug Interactions

No drug-drug interaction study was conducted for this submission.

1.3.6 Special Populations

No studies of subjects with liver, kidney, or any other organ failure were conducted. However, the subjects' age itself constitutes as a special population (13-17 year-old).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Adderall XR is an extended-release formulation of Adderall®. It combines the following chemical entities: The neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate, and the mixed d- and l- amphetamine aspartate monohydrate.

Adderall XR capsule has a hard gelatin capsule which contains two types of pellets: Immediate release pellets that release the first half of the dose and delayed-release pellets that release the second half of the dose of mixed amphetamine salts 4-6 hours after dosing. Pellet core is a sugar sphere commonly used and the drug layer is a mixture of the above mentioned amphetamine salts in the same ratios as in Adderall® with a (b) (4) hydroxyl-propylmethyl-cellulose (HPMC). Thus, oral administration of Adderall XR delivers a dose of mixed amphetamine salts via a two-pulse release.

Adderall XR has been approved by FDA for treatment of ADHD in adults as well as in children ages 6-12 year-old. In this submission, the sponsor is proposing to use Adderall XR 10 (b) (4) for treatment of ADHD in adolescents aged 13-17.

2.2 Currently Available Treatment for the Indication

Both pharmacologic and non-pharmacologic treatment modalities are available and needed for ADHD in adolescents. Among medication treatments, several antidepressants, such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and bupropion (Wellbutrin) demonstrated some efficacy in children and adults with ADHD. However, psychostimulants remain to be the primary treatment of ADHD even though the non-stimulant atomoxetine (Strattera) is now available. Available psychostimulants for treatment of ADHD include methylphenidate (Ritalin), pemoline (Cylert), dextroamphetamine (Dexedrine), Adderall, and Adderall XR.

Psychosocial treatment (family and educational interventions that involve both parents and teacher) and behavioral therapies (biofeedback, meditation, perceptual stimulation and training) can provide effective and useful management and are adjunctive to medication treatment. Dietary management and herbal and homeopathic treatments have been proposed but with limited effect.

2.3 Availability of Proposed Active Ingredient in the United States

Active ingredients of Adderall XR include amphetamine, the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate, and the mixed d- and l- amphetamine aspartate monohydrate. Adderall XR has been widely available for both adults and children in the US for several years. Sudden death has been reported in

association with amphetamine treatment at usual doses in children with structural cardiac abnormalities, according to recent labeling. Thus, Adderall XR is generally not recommended to be used in anyone with structural cardiac abnormalities.

2.4 Important Issues With Pharmacologically Related Products

Amphetamine is racemic β-phenylisopropranolamine; Dextroamphetamine is the d-isomer of amphetamine that is three to four times more potent than its l-isomer as a central nervous stimulant. Amphetamine drug products are controlled substances (Schedule II). It is known that tolerance to the amphetamine-induced euphoria and its sympathomimetic effect develops rapidly but is rare to therapeutic effects in ADHD. Amphetamine can be abused orally and intravenously. Chronic abusers often take doses that would be otherwise very toxic or lethal for non-tolerant individuals. Chronic use of high dose amphetamine may also cause psychotic syndromes with prominent paranoid ideation, formication, emotional lability, irritability, and stereotype movements. Movement disorders, such as dyskinesia, tics, Gilles de la Tourette syndrome can be worsened or precipitated. When overdosed, toxic psychosis or delirium, marked sympathetic hyperactivity, and even grand mal seizures can occur. Death may result from uncontrolled seizures, hypertension, hyperthermia, and arrhythmias. With prolonged use of high doses, patients can develop hypersomnia, hyperphasia, severe depression and also experience anhedonia, dysphoria, and drug craving in the long-term. Currently, there is no proven pharmacologic treatment for its dependence or withdrawal. Patients should be observed for emergence of depressive syndrome and suicidality.

Data are insufficient to determine if chronic use of amphetamine in children is causally associated with suppression of growth. Thus, treatment should be only continued with continuing growth and weight gain in children.

2.5 Presubmission Regulatory Activity

The original FDA Written Request (WR) for this submission was issued on May 6, 2003. In the WR, Agency required the sponsor to conduct and submit a PK study, a pediatric efficacy and safety study, and a pediatric safety study in adolescents aged 13-17 year-old with DSM-IV diagnosis of ADHD.

According to the original WR, a minimum of 12 patients was required for a traditional PK study; or, population PK of safety trials or controlled efficacy trial, which should be effective, must be provided. PK parameters must be assessed on both dextro- and levo-amphetamine with full treatment dose range and compared with values from adults and children of 6-12 year-old.

For the pediatric efficacy and safety study, the WR specifies that it must be fixed dose study with sufficient number of subjects to provide a power of 85%. A detailed statistic plan to show this power at conventional levels of statistic significance (with α=0.05 and two-tailed analysis) was required. In addition, the sponsor was asked to justify an instrument being used as sensitive and specific and add CGI. Finally, the WR defined the primary outcome as changes from baseline to endpoint on ADHD scales.

To evaluate safety, the WR specifies that the trial can be controlled or open-label trial with a minimum of 100 patients for at least 6 months. Dosage must be at or above the dose or doses identified as effective. If lack of efficacy, long term safety data still must be collected at the doses at least as high as the typical treatment doses. Essential items to be monitored include: Vitals with weight and height, chemistry, hematology, urinalysis, ECG, and AEs. Tanner Stage on growth and development should also be monitored.

In addition, the WR requires the sponsor to commit to obtain follow-up data on a cohort of patients who have been treated chronically for at least two years. The data can be from both controlled trial and long term follow-up trial: The primary outcomes of interest are height and weight and they must be obtained at roughly 4-month intervals. Growth-curve data on height and weight may be used to assess open-label trials by using z-scores. Each subject's z-score should be determined at the beginning and at the end of observation. Detailed plan for this follow-up study with descriptive analysis of the safety data is required.

Afterwards, this original WR was amended three times:

1) Sept 17, 2003 –Though it indicated full text revision of the WR, this amendment focused on the following changes: i) Lowering the percentage of requirement for female subjects (20% instead of 25%) for the efficacy and safety study. ii) The requirement of total number of patients for the efficacy and safety study was also lowered (75 instead of 100). iii) Z-score for each subject's height and weight was required. The rest content remained the same as the original WR.

2) May 7, 2004 –The second amendment focused on demographic categorization of patients according to §18 of Best Pharmaceutical Children Act (BPCA). It was required to categorize subjects to five race groups and ethnicities.

3) Sept 16, 2004 –The third amendment mainly changed "must" to "should" in using the above criteria for categorization of patients.

2.6 Other Relevant Background Information

"Pediatric Exclusivity" has been granted for Adderall XR at the Pediatric Exclusivity Board meeting on October 20, 2004 after this application was discussed. Based on the safety data in the current submission and the proposed 18-month trial, the board required the sponsor to commit a study lasting at least 24 months consecutively instead. The sponsor submitted changed protocol (SLI381-315) to comply with this issue on November 8, 2004.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Acceptable.--Please refer to CMC review by FDA Chemist, Chhagan G. Tele, PhD.

3.2 Animal Pharmacology/Toxicology

No new preclinical data were provided in this submission.

3.3 Biopharmaceutics

Please see review by FDA Biopharmaceutics Reviewer, Kofi Kumi, PhD.

3.4 Statistics

Please see review by FDA Statistician, Kun He, PhD.

3.5 Division of Scientific Investigations

Please see review by FDA Inspector, Robert Statsko, M.D.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The PK study (SLI381-110) was done at one site—the Clinical Study Centers of LLC. Samuel W. Boellner, MD recruited 23 subjects for this study.

The efficacy and safety study (SLI381-314) was done in 50 centers for Part A and 32 centers for Part B. Please see Table 1 in the Appendix for the centers and Principal Investigators involved in these two parts of the efficacy and safety study.

4.2 Tables of Clinical Studies

The following table shows the clinical studies in the overall clinical development program in this submission:

Table 1. Description of Overall Clinical Studies in This Submission

Study No.		Title of Studies	Dose Groups	Subjects		
SLI381.110		A Phase I Randomized, *Crossover* Study to Assess the Pharmacokinetics of *Single Doses* of ADDERALL XR in Adolescents Aged 13-17 with ADHD	-Adderall XR 10, 20, & 40mg	Primary Cohort 17		23
			-Adderall XR 20, 40 & 60mg	Second Cohort 6		
SLI381.314	Part A	A Phase III, Randomized, Multi-Center, *Double-Blind*, Parallel-Group, *Placebo-Controlled* Safety and Efficacy Study of ADDERALL XR in Adolescents Aged 13-17 with ADHD (*Fixed Doses*)	-Placebo	54	Primary Cohort 287	327
			-Adderall XR 10, 20, 30, & 40 mg/day	233		
			-Placebo	15	Second Cohort 40	
			-Adderall XR 50 & 60mg/day	25		
	Part B	A Phase III, Multi-Center, *Open-Label*, *Uncontrolled* Multi-dose Safety Study of ADDERALL XR in Adolescents Aged 13-17 with ADHD (*Flexible Doses)*	-Adderall XR 10 – 60mg /day	31* +107**		138[1]

[1]From the placebo* and Adderall XR** groups of Part A study, respectively.

4.3 Review Strategy

The above listed studies are reviewed separately as they have different designs. PK study is mostly reviewed by FDA biopharmaceutical science reviewer, Kofi Kumi, Ph.D. Nonetheless, its safety issues will be included in the Section of "Integrated Review of Safety" below.

4.4 Data Quality and Integrity

The study sites were audited and inspected by Robert Stasko, MD, Inspector of FDA Division of Scientific Investigations (DSI). Please see Dr. Stasko's review for details.

I have audited 5% of the Case Report Forms (CRF) and checked the appropriateness of the coding of verbatim terms to preferred terms (see below). Deficiencies of data are detailed in the Section 7.2.8 "Assessment of Completeness and Quality of Data."

4.5 Compliance with Good Clinical Practices

The sponsor declares that the studies were done under Good Clinical Practice standards. Please refer to the review by Dr. Robert Stasko of DSI for details.

Major protocol violations include being noncompliant with treatment (6, 1.8%), using incorrect study drug (2. 0.6%), using excluded medications (27, 8.3%), violations of inclusion/exclusion criteria (10, 3.1%), unblended to study drug (9, 2.8%), and others (5, 1.5%). Up to 54 subjects (16.5%) had at least one major protocol violation which excluded them. Using excluded medications was the most common protocol violation in all treatment groups.

4.6 Financial Disclosures

For Part A of Study SLI381-314, all (100%) investigators submitted certificates for financial disclosure; For Part B of the study, up to 93.8% (30/32) of the investigators submitted the certificate. (Exceptions are Mark Wolraich, MD and Lawrence Ginsberg, MD.) No investigator disclosed any financial interests as defined as 21 CFR 54.2.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Previously submitted PK studies of Adderall XR were conducted in healthy adults and in children of 6-12 years-old with or without ADHD. Mean $T_{1/2}$ is slightly shorter in children (9-11 hours) than that in adults (10-13 hours). However, children have higher systemic exposure to amphetamine (Cmax and AUC) than adults for a given dose unless it was a dose based on mg/kg. A previous study also showed linear pharmacokinetics over 20-60mg in adults and 5-30mg in children aged 6-12 years. Tmax is about 7 hours, which is 4 hours longer than Adderall. Food doesn't affect absorption of Adderall XR but prolongs its Tmax.

In this submission, Study SLI381-110 involves 23 adolescents aged 13-17 years with ADHD. The study is an open-label single-dose study with 3-treatment periods randomized crossover. There is a 7-day washout period in between these treatments. It included two cohorts of subjects:

Table 2. Subject Groups in Study SLI381-110

Cohorts			**Primary**	**Secondary**
Weight			≤75kg/165lbs	>75kg/165lbs
Dose Groups (mg)			10, 20, 40	20, 40, 60
Subject	**Age (year)**	**Mean**	14.8	15.7
		Range	13-17	15-17
	Numbers		17	6
	Gender (F:M)		29%:71%	33%:67%
	Ethnicity	**Black (%)**	5 (29%)	3 (50%)
		Caucasian (%)	12 (71%)	3 (50%)

Study design fulfills the requirements of FDA WR. The pharmacokinetics of d- and l-amphetamine are linear over doses ranging from 10-40mg in pediatric patients with ADHD weighing ≤ 75kg/165lbs as well as over doses ranging from 20-60mg in the same population weighing ≥ 75kg/165lbs. Log-log plots of C_{max} and AUC∞ vs. dose were linear with slopes ≈ 1 in both groups. (See Dr. Kofi Kumi's review for detail.) According to FDA biopharmaceutics reviewer, Kofi Kumi, Ph.D., this PK study concludes that clearance and AUC of d- and l-amphetamine are related to weight across all age groups: Lower body weight is associated with lower clearance and thus, higher AUC∞ and Cmax. Age and gender have no effect on

pharmacokinetics of d- and l-amphetamine. Tmax is at about 6 hours. (For details, please see Dr. Kumi's review.)

5.2 Pharmacodynamics

Like Adderall and other psychostimulants, Adderall XR increases presynaptic norepinephrine, dopamine, and serotonin. At the same time, it inhibits reuptake of norepinephrine and dopamine and mild MAOI effects. Together, these two effects make it a potent stimulant for sympathetic nervous system and can increase blood pressure, both systolic and diastolic, as well as heart rate if dose is high enough. By stimulating monoamine release by the reticular activating system, it increases alertness. Its effect on hypothalamus probably is related to appetite suppression. Euphoria and locomotor stimulation are probably resulted from facilitating dopaminergic neurotransmitter in the striatum and limbic system. However, its exact mechanism for treatment of ADHD is still unclear. No psychodynamic studies performed for this submission.

5.3 Exposure-Response Relationships:

There is no PK data for the efficacy study SLI381-314 Part A. Efficacy increases with dose increase from 10mg to 20mg daily. However, beyond 20mg, there was no increased response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

ADHD is among one of the most commonly diagnosed psychiatric disorders in school-age children with a prevalence of 3-7%. It is found more often among first degree relatives of the patients and those families with mood and anxiety disorders, learning disorders, substance-related disorders, and antisocial personality disorders. Differential diagnosis include age appropriate behaviors in active children, under-stimulated academic environment, oppositional behavioral disorder, stereotyped movement disorder, pervasive developmental disorder, mental retardation, and other common psychiatric disorders.

As stated above, the sponsor performed one efficacy study in response to FDA WR for treatment of ADHD in adolescents aged 13-17.

6.1.1 Methods

This efficacy review is based on the one efficacy study that the sponsor conducted and submitted in response to FDA WR (see Presubmission Regulatory Activity section): Study SLI381-314 Part A--"A Phase III, Randomized, Multi-Center, Double-Blind, Parallel-Group, Placebo-Controlled, Safety and Efficacy Study of ADDERALL XR in Adolescents Aged 13-17 with Attention Deficit Hyperactivity Disorder (ADHD)." Thus, the following general sections include specific study information from this individual study review.

6.1.2 General Discussion of Endpoints

The sponsor's primary study objective was to assess the safety and efficacy of Adderall XR (10–40 mg/day) compared to placebo in the treatment of adolescents, aged 13–17 year-old and weighed less than 75kg/165lbs, with ADHD using clinician administered ADHD-Rating Scale (ADHD-RS-IV).

Hence, the sponsor used the following efficacy measures:

1) Primary Variable: Change of ADHD-Rating Scale total score in Primary Cohort from baseline to endpoint of the study.

ADHD-RS-IV is a semi-structured interview with the subjects' parents or primary caregiver and the subject. It consists 18 items that reflect current symptomatology of ADHD based on DSM-IV criteria with a total possible score of 54. Each item is scored from a range of 0 (no symptoms) to 3 (severe symptoms). These items can be grouped into two subscales: Even numbered items contribute to hyperactivity/impulsivity subscale; Odd numbered items contribute to inattentiveness (inattentive subscale). It has been commonly used in the trials for ADHD. This scale was rated at baseline, and at every visit. (See Appendix Table 2)

2) Secondary Variables:

- CGI-I change of Primary Cohort.
- Change from baseline of ADHD-RS-IV total score in Secondary Cohort.

CGI-I is Clinical Global Impressions Rating Scale-Improvement which is rated by the clinician investigators on a 7-point scale, ranging from 0 (not assessed) to 7 (most extremely ill) with 4 indicating no change.

There were no key secondary efficacy variables.

Subjects were assessed for six visits. CGI-Severity was performed at screening (Visit A-1) and baseline (Visit A0); ADHD-RS-IV and CGI-I were performed at baseline (Visit A0) and then on weekly basis (Visits A1, A2, A3, and A4).

6.1.3 Study Design

The sponsor randomized 327 subjects into two cohorts based on their weight in this study (randomization stratified by subject cohort) and each cohort received different dosages (see Table 3). Subjects were then randomly assigned into each dose groups within each cohort roughly at 1:1:1:1 or 1:1:1 ratio. The main part of the trial with primary cohort was 4 weeks long. A total of 233 subjects in primary cohort received the active drug treatment, Adderall XR and almost 90% of subjects completed the trial. Thus, it fulfills the requirement set by the FDA WR. The completion rate for the secondary cohort is comparable, up to 88%.

Table 3. Study Design and Dose Schedule of SLI381-314 Part A

	Primary Cohort	**Secondary Cohort**
Sample/Subjects	Weighed ≤75kg/165lbs	Weighed >75kg/165lbs
Length of Study	4 weeks*	4weeks**
Dose Range	10-40mg/day	50-60mg/day
Dose Groups (*forced dose titration*)	Placebo Adderall XR 10mg 20mg 30mg 40mg	Placebo Adderall XR 50mg Adderall XR 60mg
Numbers of Subjects Randomized	287	40
Radomization Ratio	1:1:1:1:1	1:1:1
Completers in Active Treatment Group	89% (208/233)	88% (22/25)

*Not all dose groups were on a specific dose for 4 weeks. –See next paragraph.
**Starting doses were 20mg/day. Doses were increased gradually and reached the maximum target by Week 4.

Dose Schedule:
All Adderall XR treatment groups were started at 10mg/d for Primary Cohort. Dose was then increased to 20mg/d on Week 2 for groups 20mg, 30mg, and 40mg; Dose was further increased to 30mg/d on Week 3 for groups 30mg and 40mg, and eventually increased to 40mg/d on Week 4 for group 40mg. Thus, the placebo group and 10mg-group received their target dose for four weeks, while 20mg-group was on that dose for three weeks, 30mg-group was for two weeks, and 40mg-group was for one week only.

For Secondary Cohort, doses in the two Adderall XR dose groups were increased gradually as follows:

1) From 20mg/day (Week 1)→30mg/day (Week 2)→ 40mg/day (Week 3)→50mg/day (Week 4);
2) From 20mg/day (Week 1)→40mg/day (Week 2)→ 50mg/day (Week 3)→60mg/day (Week 4).

Protocol Amendments:
The protocol of SLI381-314 was amended several times. However, important amendments have been incorporated into the overview and description of the study in this review.

Criteria for Subjects Selection:
In addition to subjects' legal representatives' willingness and ability to comply with the requirements and signing the consents, the subjects must meet the following criteria:

1) Age between 13–17 year-old (inclusive) with a minimum 80 IQ;
2) Meeting diagnostic criteria of ADHD, either hyperactive or predominantly inattentive subtype, or combined;
3) BP (blood pressure) must be within 95 percentile for age, gender, and height;
4) No clinically significant ECG or other comorbid illness (including, other psychiatric disorders such as conduct disorder, substance abuse at the screening or within 6 months of screening, seizure during the last 2 years, hypertension, uncontrolled thyroid

abnormality, or allergic to Adderall XR, etc) that would affect efficacy, safety, or tolerability, or in any way interfere with the subject's participation in the study.

Moreover, subjects must not:

1) Be known non-responder to stimulants;
2) Be underweight (BMI-for-age<5th percentile) or overweight (BMI-for-age≥95th percentile)
3) Have a history of tic disorder and/or current diagnosis or a family history of Tourette's disorder.
4) Take a medication that would affect HR or BP;
5) Take an investigational drug within 28 days prior to baseline.
6) Be pregnant or lactating as female subjects.
7) Take any drugs that would affect CNS performance, such as antihistamines, decongestants, etc.

Subjects were screened for a period of 1-7 days. Eligible ones then enter "baseline" period which was also up to 7 days. Previous treatments were washed out if necessary during this period.

Demographics: The following tables illustrate subject demographic distribution of each study group in ITT population of primary cohort. "Other" denotes biracial. No subject was considered Asian or Pacific Islander. There were 34.5% female subjects, which meets the requirement of FDA WR. The treatment groups were reasonably balanced in terms of demography.

Table 4. Subject Demographics of Primary Cohort in Part A of Study SLI381-314 (ITT)

Treatment Groups of Primary Cohort		Placebo Group	Adderall XR				
			10mg	20mg	30mg	40mg	Total
Subjects in ITT		**N=52**	**N=54**	**N=53**	**N=58**	**N=61**	**N=278**
AGE (Years)	**Mean**	14.5	14.4	14.2	14.2	14.0	14.2
	SD	1.3	1.2	1.2	1.2	1.2	1.2
	Range	13-17	13-17	13-17	13-17	13-17	13-17
Sex	**F (%)**	17(32.7)	21(38.9)	16 (30.2)	20 (34.5)	22 (36.1)	96 (34.5)
	M (%)	35(67.3)	33 (61.1)	37 (69.8)	38 (13.2)	39 (63.9)	182 (65.5)
RACE (%)	**White**	38(73.1)	38 (70.4)	39 (73.6)	43 (74.1)	47 (77.0)	205 (73.7)
	Black	11(20.4)	10 (17.9)	9 (16.1)	8 (13.8)	6 (9.5)	44 (15.3)
	Hispanic	3 (5.8)	2 (3.7)	3 (5.7)	5 (8.6)	6 (9.8)	19 (6.8)
	Native American	0	2 (3.7)	0	0	2 (3.3)	4 (1.4)
	Other	0	2 (3.7)	2 (3.8)	2 (3.4)	0	6 (2.2)

Analysis:

The efficacy review will be drawn from the Part A of Study SLI381-314, which is double-blind, placebo controlled, fixed dose study. The primary outcome is the change of total score of ADHD-RS-IV from baseline to endpoint in the Primary Cohort. The ITT population is defined

as all subjects who were randomized to a treatment and had one baseline and at least one post baseline ADHD-RS-IV measurement recorded in the Case Report Forms (CRF), regardless of protocol compliance or study completion. The primary efficacy endpoint score was the last valid score (LOCF). The primary analysis, a two-way analysis of covariance, ANCOVA, was used to analyze the data from the ITT population. The sponsor used this analysis for active treatment (all doses combined) vs. placebo with site as a main effect and the corresponding baseline score as covariate. For the ANCOVA, the type one error rate for rejecting a null hypothesis was set at an alpha level of 0.05. Each active dose was then further compared with placebo using the same ANCOVA model and alpha level (pairwise comparisons). The significant treatment effect of each active dose vs. placebo was based on a closed-testing procedure starting from the highest dose (i.e. the 40mg/day) to control the type one error rate at 0.05. If the assumptions for ANCOVA model didn't meet, non-parametric methods would be used where appropriate.

One of the secondary efficacy variables, CGI-I, was suggested in FDA WR. The result of CGI-I was summarized and analyzed through dichotomized method: Improvement verses no improvement. The "improvement" category includes those very much improved and much improved while "no improvement" category includes the rest of the changes.

6.1.4 Efficacy Findings

Baseline Characteristics:

Most subjects were diagnosed with ADHD, inattentive type or with both inattentive and hyperactive features (combined type). Very few were hyperactive type only. (When analyzing the efficacy on subtypes of ADHD, the sponsor pooled the hyperactive type with the combined type together to compare with the inattentive type.) CGI-S at baseline showed that up to 48% subjects in placebo group were markedly ill and 44% were moderately ill. The rest were distributed equally among the mildly and severely ill. In Adderall XR treatment groups, average over 50% (50-62%) were moderately ill and 31-43% were markedly ill; the higher dosage groups (30-40mg/day) included some more severely ill subjects (4.9-8.6%).

The table below (Table 5) exhibits baseline characteristics of the subjects' mental and physical condition. Note that height was only measured at screening (A-1 visit), which could be up to 7 days for the procedures, per protocol. Following this, another period of up to 7 days for wash-out of prior treatment may be needed before a subject entering baseline (Visit 0). Thus, the period between screening and baseline could be up to 14 days. The baseline BMI listed was apparently calculated from weight at baseline and height at screening. There were no large imbalances among the treatment groups in terms of these factors.

Table 5. Baseline Characteristics of Primary Cohort of Part A of Study SLI381-314

Treatment Groups of Primary Cohort		Placebo Group	Adderall XR			
			10mg	20mg	30mg	40mg
ITT Population		**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Type of ADHD	**Inattentive (%)**	23 (44.2)	20 (37.0)	25 (47.2)	20 (34.5)	26 (42.6)
	Hyperactive* (%)	0	3 (5.6)	1 (1.9)	1 (1.7)	2 (3.3)
	Combined (%)	29 (55.8)	31 (57.4)	27 (50.9)	37 (63.8)	33 (54.1)
ADHD-RS-IV Total Score	**Mean**	35.1	34.9	33.9	35.1	32.6
	-(SD)	(9.7)	(10.4)	(9.1)	(10.8)	(10.8)
ADHD-RS-IV Subscale Mean Scores	**Inattentiveness**	21.4	19.9	21.0	20.0	19.6
	-(SD)	(4.6)	(4.8)	(4.9)	(5.2)	(5.0)
	Hyperactivity	13.8	15.0	13.0	15.1	13.0
	-(SD)	(7.2)	(7.0)	(6.8)	(6.9)	(7.5)
Weight (lbs) at Baseline	**Mean**	131.6	125.7	124.6	128.6	125.3
	-SD	18.2	22.7	20.7	18.9	22.9
	Range	78-165	83-162	83-161	80-164	70-165
Height (Inches) at *Screening*	**Mean**	65.4	64.1	64.4	64.1	64.3
	-SD	3.6	3.6	3.6	3.1	3.6
	Range	58-72	57-71	57-73	56-72	55-72
BMI at Baseline	**Mean**	21.7	21.4	21.1	22.0	21.2
	-SD	2.8	2.6	2.9	2.9	2.6
	Range	16-29	16-27	15-27	16-28	15-26

*Hyperactive type is also referred as hyperactive/impulsive type. Hyperactivity subscale is also referred as hyperactivity/impulsivity subscale.

Disposition:

The disposition of the 287 primary cohort patients who were randomized is summarized in Table 6 below. Nearly 97% of the Primary Cohort subjects (278/287) turned into the Intent-To-Treat (ITT) population and almost 90% completed the trial (see table below). Overall, the most common reason for drop-out was withdrawal of consent (10/287=3.5%, 5 of them from 40mg group), followed by lost to follow-up (2.1%, 6/287), adverse events, and protocol violation, each of which was 1.7% (5/287). Three subjects dropped out for "other" reasons, one from placebo group and two from Adderall XR groups.

Table 6. Primary Cohort Subject Disposition in Part A of Study SLI381-314

Treatment Groups & Disposition	Placebo Group	Adderall XR				Total
		10mg	20mg	30mg	40mg	
Subjects Randomized	54	56	56	58	63	287
Subjects in ITT (Baseline) (%)	52 (96.3)	54 (96.4)	53 (94.6)	58 (100.0)	61 (96.8)	278 (96.9)
Subjects Completed (%)	50 (92.6)	49 (87.5)	51 (91.1)	55 (94.8)	53 (84.1)	258 (89.9)

The next table shows enumeration of ITT patients in-study over time:

Table 7. Part A: Enumeration of Patients In-Study over Time

Time Interval & Disposition	Total Subjects	Placebo Group	Adderall XR			
			10mg	20mg	30mg	40mg
	N	N	N	N	N	N
Baseline	278	52	54	53	58	61
Week 1	277	52	54	53	58	60
Week 2	269	51	52	53	55	58
Week 3	259	50	49	50	55	55
Week 4	257	50	49	50	55	53

Dose information:

As stated above in the Study Design Section, this study is fixed dose study with forced-dose titration design. However, not all subjects reached the targeted dose for the same length of the time. Since doses needed to be titrated up on a weekly basis, the higher dose groups were only exposed to the higher doses for shorter period of time. (Please see Table 7 above.)

Prior and Concomitant Medications:
Overall, up to 20% (66/327) of all the subjects (both primary cohort and secondary cohort) had previous treatment for ADHD. Most common treatments received were methylphenidate hydrochloride (27/66, 40.9%) and Obetrol (26/66, 39.4%).

A total of 56% (183/327) of all the subjects (both primary and secondary cohorts) used a concomitant medication during the study. The most common ones are ibuprofen (66/183, 36.1%), paracetamol (39/183, 21.3%), and salbutamol (17/183, 9.3). Among medications that might affect CNS, one subject in secondary cohort received Trazodone and another received methylphenidate. Two subjects received pseudoephedrine (one in placebo, one in secondary cohort)

6.1.5 Efficacy Results and Conclusions:

Results of the primary efficacy analysis in Primary Cohort showed statistically significant difference among all the treatment groups ($p<0.0001$) . Pairwise comparisons were examined next: The table displayed below illustrates these differences in ITT population (LOCF). The results are similar in observed cases. The mean change was smallest largest at a dose of 10mg; the largest mean change was observed at 20mg. As dose increased from 20 to 40mg, the magnitude of mean change was actually lessened. The difference was also increased as weeks passed by during the study with the final week being most significant across all dose groups. Similar trends are also seen in the analysis of the two subscales of ADHD-RS-IV, inattentiveness and hyperactivity/impulsivity subscales.

Table. 8 Change of ADHD-RS-IV Total Score from Baseline to Endpoint in Primary Cohort (ITT Population) (LOCF)

Treatment Groups of Primary Cohort		Placebo Group	Adderall XR				*P**-value
			10mg	20mg	30mg	40mg	
ITT Population		N=52	N=54	N=53	N=58	N=61	
Endpoint ADHD-RS-IV Total Score	Mean Score	25.7	20.0	13.3	16.1	16.0	< 0.0001
	(SD)	(13.4)	(11.8)	(10.3)	(11.0)	(11.2)	
	Mean Change	-9.4	-14.9	-20.7	-19.0	-16.5	
	(SD)	(10.6)	(12.1)	(11.2)	(11.1)	(11.6)	
	p-value**	--	0.043	<0.0001	<0.0001	<0.0001	

*P-value here is based on type III sum of squares from an ANCOVA model for the change from baseline in ADHD score, including treatment and pooled center as fixed effects, and baseline balue as a covariate.
**A closed testing procedure is used to test for a difference between each active treatment group and the placebo beginning with 40mg vs. placebo and stopping when significance (p-value<0.05) is not reached.

Dichotomized analysis of CGI-I shows that the differences in percentage with improvement in Adderall XR group versus placebo increase with the length of treatment. Pairwise comparison shows such difference is statistically most significant in the 30mg Adderall XR group (44.9%, p<0.0001, versus 44.0%, 41.9% and p=0.0001 in both 20mg and 40mg groups). (See Vol. 4-13 Page 8A-1449—Table 2.4.3.)

Demographic Factors on Efficacy:

Gender: Table 9 shows the sponsor's analysis of change of ADHD-RS-IV total score from baseline to endpoint by gender. Statistical significance seems to favor Adderall XR is apparent in male subjects, with 20mg group being most significant. However, according to our FDA statistician, Kun He, PhD, the study is not powered for subgroup analysis. (Please see Dr. He's review.)

Table 9. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Gender

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR				*p*-Value
		10mg	20mg	30mg	40mg	
ITT Population	N=52	N=54	N=53	N=58	N=61	
Female	17	21	16	20	22	
Mean Change (SD)	-12.4 (10.6)	-10.4(8.8)	-21.4(10.5)	-17.5(10.7)	-15.1(13.1)	0.0692
***p*-value**		--	--	--	0.1738	
Male	35	33	37	38	39	
Mean Change (SD)	-7.9 (10.4)	-17.8(13.1)	-20.4(11.6)	-19.8(11.4)	-17.3(10.7)	<0.0001
***p*-value**		0.0002	<0.0001	<0.0001	<0.0001	

Race: Race effect on efficacy was analyzed by grouping subjects into Caucasian group and non-Caucasian group. The two groups are not balanced. Thus, no conclusion can be drawn here.

Age: Though the sponsor provides the analysis of the age effect, the two age groups are not balanced and not powered enough. (See Dr. Kun He's statistic review.)

Table 10 and Table 11 show the magnitude of changes of ADHD-RS-IV total score from baseline to endpoint by race and age, respectively.

Table 10. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Race

Treatment Groups Of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Caucasian	38	38	39	43	47
Mean Change (SD)	-11.3 (9.5)	-16.1(13.3)	-20.6(11.3)	-19.0 (10.2)	-16.2 (11.5)
Non-Caucasian	14	16	14	15	14
Mean Change (SD)	-4.0 (11.8)	-12.8(8.1)	-20.9(11.3)	-19.2(13.9)	-17.6(12.2)

Table 11. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Age

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
13-14 year-old	31	30	37	37	44
Mean Change (SD)	-8.0(10.9)	-17.2(13.3)	-21.4(11.7)	-20.1 (11.2)	-16.0 (11.1)
15-17 year-old	21	24	16	21	17
Mean Change (SD)	-11.3(10.0)	-12.1(9.9)	-19.1(10.1)	-17.2(11.1)	-17.9(12.8)

Subtypes of ADHD: The following table shows mean changes of ADHD-RS-IV total score by analysis of subtype of ADHD in this population. (Also see Table 2.1.10 on page 8A-1380 of Vol. 4.13.) Again, Dr. Kun He, the Statistician of FDA, considers the groups are not powered enough to calculate p-Values here.

Table 12. Analysis of Change of ADHD-RS-IV Total Score from Baseline to Endpoint by Subtypes of ADHD

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Inattentive Subtype	23	20	25	20	26
Mean Change (SD)	-11.3 (9.3)	-14.4 (12.9)	-18.4(8.3)	-15.3 (10.7)	-13.7 (8.8)
Combined Subtype*	29	34	28	38	35
Mean Change (SD)	-7.8 (11.4)	-15.2 (11.7)	-22.7 (13.0)	-21.0 (11.0)	-18.6 (13.0)

*It includes subjects of hyperactive/impulsive subtype as well

CGI-I: CGI-I was requested in FDA WR. The following table shows the percentage of CGI-I improvement at the endpoint. Dichotomized analysis of CGI-I over time also shows the efficacy increases with duration of treatment (see page 8A-1449-50 of Vol 4.13).

Table 13. Summary and Analysis of Dichotomized CGI-I in Primary Cohort

Treatment Groups of Primary Cohort	Placebo Group	Adderall XR			
		10mg	20mg	30mg	40mg
ITT Population	**N=52**	**N=54**	**N=53**	**N=58**	**N=61**
Dichotomized CGI-I Improvement	26.9%	51.9%	66.0%	70.7%	63.9%
Difference in % with Improvement in Active Group vs Placebo		24.9%	39.1%	43.8%	37.0%
***P*-Value**		0.0098	0.0002	<0.0001	0.0001

Conclusion:
The results of this short term, fixed dose, double-blind, placebo-controlled study, Study SLI381-314 Part A, demonstrate the efficacy of Adderall XR for treatment of adolescents (weighed ≤75kg/165lbs) with ADHD. The most effective dose from this study is 20mg/day from the primary analysis. Increasing dose from 20 to 40mg/day doesn't show increased efficacy. Along with the ADHD-RS-IV total scores, there are improvements in both subscales.

Similar efficacy trend can be seen in the secondary cohort, however, due to limited subjects, secondary cohort is statistically not powered enough.

The demographic analysis of gender, race, and age effect on efficacy are inconclusive, so is the subtype analysis.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Since both the PK study (Study SLI138-110) and Part B of Study SLI381-314 are open-label studies, only deaths, serious adverse events, and drop-outs are reviewed from those datasets. For the efficacy and safety study part, Part A, which is double-blind and placebo-controlled, detailed safety review, including common adverse events and special searches, are reviewed.

7.1.1 Deaths

No death occurred in these studies.

7.1.2 Other Serious Adverse Events

No serious adverse event (SAE) was reported in the PK study (Study SLI381-110). A total of

three subjects in Study SLI381-114 (one in Part A, two in Part B of the study) reported three serious adverse events. The table below describes these three events.

Table 14. Descriptive Summary of Subjects with Serious Adverse Events in SLI381-314 (Part A & Part B)

Subject Number	Study Group	Dosage Given	Treatment Duration	Serious Adverse Events
49-008	Part A: Second Cohort (50mg group)	40mg/day	15 days	17 year-old Native American male received Adderall XR on Sept 4, 2003. He developed chest pain with spontaneous pneumothorax (COSTAR term: lung disorder) on Sept 18, 2003. Adderall XR was continued. The subject recovered in 6 days and completed the study. He also experienced severe mid-clavicle chest pain secondary to incision. I agree that this incidence is probably not drug-related.
34-006	Part B	30mg/day	At least 27 weeks	14 year-old female of "other" ethnicity received her first dose of Adderall XR in Part B on Sept 2, 2003. She developed symptoms of depression in Feb. 2004 and on (b) (6), she was hospitalized for suicidal ideation (COSTAR term: thinking abnormal). (b) (6) later, the subject was prescribed with sertraline hydrochloride and was discharged from the hospital. Due to her concomitant use of sertraline, she was determined becoming ineligible for the study and Adderall XR was discontinued on Mar 7, 2004. "Depression" has been one of the AEs that caused dropouts in pediatric patients in current Adderall XR labeling. I disagree that this event is totally unrelated to the study drug.
37-004	Part B	30mg/day	At least 9 weeks	14 year-old white male was prescribed first dose of study drug on July 2, 2003. (b) (6) later, he had a right ankle fracture (COSTAR term: accidental injury). On (b) (6), he went through surgical repair of the fracture. He recovered shortly afterwards. Adderall XR was withheld on the same day of his surgery till Oct. 8, 2003. In the meantime, he was given oxycodone and acetaminophen for treatment. Though it is unclear how the accident happened, I agree that this is probably unrelated.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Three subjects (13%, 3/23) dropped out from the PK study prematurely, one of them was due to adverse event (see next section 7.1.3.2). A total of 20.2% (66/327) subjects dropped out from Study SLI381-314: Among them, 33 (11.5%, 33/287) from Part A and 33 (23.9%, 33/138) from Part B. In Part A, 28 (10.9%, 28/258) subjects were from those who received Adderall XR and 5 (7.2%, 5/69) from the placebo group. In both Part A of the study (10/258, 3.9%) and overall (18/289, 6.2%), withdrawal of consent was the most common reason for dropout among those who received Adderall XR.

7.1.3.2 Adverse events associated with dropouts

During the PK study (Study SLI381-110), a 13 year-old boy (weighed 84lbs and height 60" tall) in primary cohort dropped out two days after receiving Adderall XR 20mg due to "emotional distress". It was determined as a "drug-unrelated event". (This subject also had a BP changed from 106/64mmHg to 138/70mmHg at 2 hours after dosing, accompanied by anxiety, nausea, and syncope).

Although the sponsor states that in Study SLI381-314 a total of 14 subjects discontinued the study due to adverse events (8 in Part A and 6 in Part B), these numbers didn't include the one subject (#34-006) who had SAE and dropped out (see above section). Thus, the total number for dropouts is 15 (8 in Part A and 7 in Part B).

Among those dropped from Part A study, five of them were from the Primary Cohort (5/287 =1.7%) and three from the Secondary Cohort (3/40 = 7.5%). No subject dropped from the placebo group. (In the 40mg, and 50mg dose groups of Part A study, there were two dropouts; in each of the other dose groups, there was one dropout.) Reasons lead to drop-out include: Insomnia (3), depression (1), anxiety (1), dizziness (1), headache (1), and twitching/motor tics (1).

Among the seven subjects dropped from Part B of the study, four (57.1%) were in the 30mg dose group, including subject #34-006 (see above section). In the open-label, Part B of the study, the most common reason for discontinuation was anorexia, weight loss, abdominal pain, nervousness/anxiety, and depression (2 for each of these symptoms). One of these depressed patients also had suicidal ideation.

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

No other search strategies conducted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In addition to review of system and laboratory tests at certain study points, the subjects were asked a non-leading question, such as "how are you feeling," or questions regarding any changes in their health or concomitant medication usage since their last visit in the PK study; For both the short term placebo-controlled study and the long term safety study, AEs were elicited through spontaneous reports during each visit. The principal investigator reviewed each AE and made the determination of relationship to study drug, such as unrelated, possibly related, and probably related. If SAE occurs, it was reported to the (b) (4), by phone or fax, within 24 hours. The investigators followed SAEs until resolution (either the subject's health returned to his/her baseline status or all parameters returned to normal), the event stabilized, an outcome is reached, or the event could be explained otherwise.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Verbatim coding was mostly appropriate based on my audit of the coding for all verbatim (or investigator) terms. Some of them include broad information, such as "accidental injury" that varies from abrasions, laceration, to burns; from tooth cap break to injuries in legs and wrists. Still, "ecchymosis" includes "bruises" and "contusion" which may be part of injury as well. Any appetite decreases, from "mild appetite loss" to "no appetite" were coded under "anorexia". Both "depression" and "dysphoric" were coded as "depression." yet, "increased moodiness, crying, moody, labile mood, mood swings" were all coded as "emotional lability," and "irritability, jitteriness, increased irritability, and restlessness" were all included in "nervousness." Though not common, it is noted that "feeling hyper" was coded as "hyperkinesia."

7.1.5.3 Incidence of common adverse events

Only Part A of Study SLI381.314 is fixed dose, placebo-controlled study. It includes two cohorts: Primary cohort (weighted less than 75kg/165lbs and on one of four fixed Adderall XR doses: 10, 20, 30, or 40mg/day) and secondary cohort (those weighted at least 75kg/165lbs and were given Adderall XR up to 50-60mg/day.) The sponsor states that 71.3% of subjects (233/278) in this part of the study reported 624 treatment-emergent events. Overall, compared to the placebo group, the subjects taking Adderall XR have a higher incidence of adverse events (74.0% vs 60.9%), particularly anorexia, insomnia, abdominal pain, and weight loss.

7.1.5.4 Common adverse event tables

Common adverse events that are ≥ 2% in any Adderall XR dose groups in primary and secondary cohorts of Study SLI381.314 Part A are listed separately in the Appendix (see Appendix Tables 2 and 3.)

7.1.5.5 Identifying common and drug-related adverse events

In primary cohort, Adderall XR 40mg group had the highest incidences of insomnia, abdominal pain, and also somnolence; Adderall XR 30mg group had the highest incidences of anorexia, diarrhea, weight loss, and emotional lability. Nausea and Vomiting happened even at 10-20mg doses. Incidences of nervousness and dizziness among subjects taking Adderall XR were not significantly more than those taking placebo in primary cohort; however, they were more common in secondary cohort. Note, since only 40 subjects were in secondary cohort (25 taking Adderall XR, 15 taking placebo), even 1 subject can change the percentage of the listing significantly (6.7%). Tables 5 and 6 in the appendix list the drug-related adverse events in the short-term placebo-controlled fixed dose study.

7.1.5.6 Additional analyses and explorations

The sponsor provides the tables for demographic effects on adverse event reporting rates for those AEs that were reported at >5% and with greater incidence than placebo in both Part A and Part B of Study SLI381-314. The sponsor essentially compares the placebo group with all subjects taking Adderall XR. The sponsor neither separates the dose groups for these demographic analyses nor provides analysis for drug:placebo odds ratios of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds ratios between the subgroups. Thus, effects of age, gender, and ethnicity/race can't be readily determined. Of note, emotional lability is not in the table presented for ethnicity analysis.

7.1.6 Less Common Adverse Events

Less common adverse events are listed in the table provided by the sponsor. Please see Tables 6 and 7 in the Appendix.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests include clinical chemistry (including thyroid function), hematology, and urinalysis. They were drawn at screening and at the end of PK study as well as in the controlled trial where the endpoint was the fourth week or when the subject discontinued from the study. Mean changes from baseline to endpoint are compared across treatment groups using ANCOVA.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Since PK study is a single dose study, the analysis below will focus on the data from the controlled pivotal study.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Mean changes of clinical chemistry:
Analyses of clinical chemistry of primary cohort in each dose group (Vol.14, page 8A-1754–1768) show no significant changes from baseline to endpoint in regard to sodium, potassium, chloride, bicarbonate, BUN, glucose, bicarbonate calcium and total calcium, AST, ALT, GGT, total protein, and TSH; there were significant changes in total bilirubin (p=0.0381), albumin (p=0.0049), and free T4 (p=0.0002).—Further analyses comparing with the placebo group show significant changes of albumin in the Adderall XR 10mg group (p=0.0135) as well as free T4 in the Adderall XR 30mg (mean change of +0.15 with p<0.0001) and 40mg groups (mean change of +0.15 with p=0.0004). However, these changes don't seem to be clinically significant.

In the secondary cohort (Vol.14, page 8A-1769–1783), there was significant change in total calcium (p=0.0345), albumin (p=0.0020), and free T4 (p=0.0299). As in the primary cohort, there was significant change of albumin and free T4 in the Adderall XR 50mg (p=0.0459 and mean change of free T4 +0.17 with p=0.0275, respectively) and 60mg (p=0.0005 and mean change of free T4 +0.21 with p=0.0129, respectively) dose groups comparing with the placebo group; Only Adderall XR 60mg group has significant change of total calcium (p=0.0105).

There was no mention of serum creatinine as part of clinical chemistry in the protocol or study report.

Mean changes of hematological tests:
Analyses of hematological tests of primary cohort in each dose group (Vol.14, page 8A-1713–1725) show no significant changes from baseline to endpoint in platelet count or white blood cell count and its differentials. There was statistically significant change of red blood cell count (p=0.0185), hematocrit (p=0.0137), and hemoglobin (p=0.0165). Further analysis show statistically significant changes of red blood cell in dose groups 20mg (p=0.0426), 30mg (p=0.0070), and 40mg (0.0042); Similarly, statistically significant change in both hematocrit and hemoglobin in dose groups 30mg (mean change of -0.20 with p=0.0029, -0.07 with p= 0.0082, respectively) and 40mg (mean change of -0.16 with p0.0070, +0.04 with p=0.0020, respectively). Again, these changes don't seem to be clinically significant.

In secondary cohort, none of the hematological tests show statistical significant difference from baseline to endpoint in each dose group (Vol.14, page 8A-1726–1738)

7.1.7.3.2 Analyses focused on outliers:

In the response to our filing letter, the sponsor provides subject listing for outliers without enumeration table for outliers.

Review of Urinalysis:

The sponsor reports that four subjects in Part A of Study SLI381-314 had proteinuria, three of them in Adderall XR 40mg group and one in Adderall XR 60mg group at endpoint of the study (see page 8A-1873 of Vol 4.14, Table 3.6.8), and none in placebo group. In addition, only a shift table for PH changes in urinalysis of those taking Adderall XR 10-40mg group and 50-60mg group comparing with placebo is provided. No more detailed information on parameters of urinalysis is provided.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

See above section. The sponsor needs to provide the table for enumeration of outliers. No dropout was reported due to laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

No additional analyses conducted.

7.1.7.5 Special assessments

No special assessments conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs in both protocols of PK study and efficacy-safety study (SLI381-314) included blood pressure, respiratory rate, pulse, and temperature. (However, no data on temperature assessment presented from either of the above.) During PK study, they were obtained at screening, check-in (Day-1), and at 0, 2, 4, 24, and 60 hours of treatment periods 1-3 (Day 1-3). For study SLI381-314, vital sign changes from baseline at endpoint will be reviewed.

The sponsor provides the following items for vital sign assessments: Pulse, respiratory rate, systolic and diastolic blood pressure. All measurements were obtained at sitting position. Weight is also included as part of the vital signs. (See Section "Effect on Weight" below.)

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Since the design of PK study, Part A and Part B of Study SLI381-314 are all different, all data from these studies will be analyzed separately. As Part B is an open label, flexible dose study that inherits patients from both placebo group and Adderall XR group of Part A, its data on vital signs will not be included here. Thus, the following review includes data on vital signs from PK study and the double-blind, placebo-controlled, Part A study.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The sponsor defines "hypertension" ("increased blood pressure") as the blood pressure measured ≥95th percentile for age and gender.

The following tables list the changes of blood pressure (Table 15), pulse (Table 16), and respiratory rate (Table 16) seen in PK study. P-values reflect the difference form baseline, with significant p-values in bold type. Measures at 4-hour is the closest to Tmax which is about 6-hour.

Table 15. Mean Changes of Blood Pressure from Baseline during PK Study

Subjects & Cohorts		**Adderall XR Groups**					
		Primary Cohort			**Secondary Cohort**		
Dose Groups		**10mg**	**20mg**	**40mg**	**20mg**	**40mg**	**60mg**
Total N in Each Group		15	15*	15	6	6	6
Systolic Blood Pressure Changes (mmHg)	**Baseline**	107.1	109.6	108.9	111.5	109.3	107.7
	@ 2-hour (p-Value)	4.7 (0.0557)	12.4 (**0.0031**)	17.7 (**0.0004**)	8.0 (0.0574)	25.7 (**0.0006**)	18.7 (**0.0227**)
	@ 4-hour (p-Value)	6.3 (**0.0415**)	7.7 (**0.0407**)	20.9 (**0.0002**)	12.7 (0.0522)	25.0 (**0.0084**)	20.3 (**0.0327**)
	@ 24-hour (p-Value)	3.1 (0.2522)	2.3 (0.4406)	7.1 (**0.0315**)	6.0 (0.1970)	7.8 (0.2367)	13.2 (**0.0353**)
	@ 60-hour (p-Value)	7.7 (**0.0011**)	8.5 (**0.0040**)	8.9 (**0.0008**)	8.0 (**0.0192**)	11.8 (**0.0133**)	17.5 (**0.0162**)
Diastolic Blood Pressure Changes (mmHg)	**Baseline**	60.6	60.4	63.8	58.7	59.2	60.7
	@ 2-hour (p-Value)	0.1 (0.9543)	7.0 (**0.0121**)	8.5 (**0.0011**)	5.7 (0.0671)	11.3 (**0.0170**)	10.0 (0.0774)
	@ 4-hour (p-Value)	2.6 (0.3743)	8.5 (**0.0035**)	7.7 (**0.0061**)	2.8 (0.2329)	8.8 (0.0907)	9.7 (0.1491)
	@ 24-hour (p-Value)	3.1 (0.3091)	3.1 (0.1978)	2.9 (0.2202)	0.3 (0.8840)	5.5 (0.1369)	4.3 (0.3241)
	@ 60-hour (p-Value)	3.5 (0.2155)	6.8 (**0.0142**)	3.5 (0.0697)	4.7 (0.3782)	5.5 (0.1454)	8.8 (0.0554)

*Though initially there was 16 subjects, from second hour and on, subject number became 15 in this dose group as well. –This is the same in the next table on changes of pulse and respiratory rate. (This may explain the case of "early termination" mentioned earlier. However, no explanation is found in the submission.)

In primary cohort, there were significant changes of systolic BP at 4-hour in all dose groups (10, 20, and 40mg), but changes of diastolic BP at 4-hour only in 20mg and 40mg groups. These changes can appear as early as at 2-hour. In secondary cohort, significant changes of systolic BP at 4-hour in both 40mg and 60mg groups, but such change of diastolic BP is only seen in 40mg group.

Table 16. Mean Changes of Pulse and Respiratory Rate from Baseline during PK Study

Subjects & Cohorts		Adderall XR Groups					
		Primary Cohort			Secondary Cohort		
Dose Groups		**10mg**	**20mg**	**40mg**	**20mg**	**40mg**	**60mg**
Total N in Each Group		15	16*	15	6	6	6
Pulse Change (bpm)	**Baseline**	68.5	68.3	73.3	72.3	63.7	64.0
	@ 2-hour (p-Value)	10.2 (**0.0016**)	9.8 (**0.0050**)	1.5 (0.6537)	-0.8 (0.8358)	13.0 (**0.0042**)	11.8 (0.1052)
	@ 4-hour (p-Value)	8.2 (**0.0248**)	8.2 (**0.0238**)	4.1 (0.2828)	0.2 (0.9646)	16.0 (**0.0112**)	21.3 (**0.0026**)
	@ 24-hour (p-Value)	6.1 (**0.0106**)	4.7 (0.1405)	8.7 (0.0577)	-1.0 (0.8785)	17.7 (**0.0048**)	21.8 (**0.0009**)
	@ 60-hour (p-Value)	4.1 (0.2140)	8.9 (**0.0310**)	8.3 (0.0605)	3.8 (0.3277)	9.8 (0.1143)	9.3 (**0.0113**)
Respiratory Rate Change (bpm)	**Baseline**	17.7	17.8	17.1	15.3	16.0	16.3
	@ 2-hour (p-Value)	-0.1 (0.6702)	-0.3 (0.4320)	0.8 (0.0824)	-0.8 (0.8358)	1.3 (0.1019)	0.0 (1.0000)
	@ 4-hour (p-Value)	-0.3 (0.4985)	-0.1 (0.7744)	1.1 (**0.0406**)	0.2 (0.9646)	1.0 (0.2031)	-0.3 (**0.0026**)
	@ 24-hour (p-Value)	0.3 (0.4985)	-0.1 (0.7513)	1.3 (**0.0031**)	-1.0 (0.8785)	1.3 (0.1019)	0.7 (0.3632)
	@ 60-hour (p-Value)	0.8 (0.1109)	0.0 (1.0000)	1.7 (**0.0005**)	3.8 (0.3277)	2.3 (**0.0127**)	2.3 (0.1099)

In primary cohort, pulse seems to be more affected in the lower dose groups (10 and 20mg), while respiratory rate is more affected in the higher dose group (40mg). In secondary cohort, change of pulse are more affected in the higher dose groups (40 and 60mg)

Tables 17 and 18 on the next two pages list changes of blood pressure, pulse, and respiratory rate during Part A of Study SLI381-314. Again, p-values reflect the difference form baseline, with significant p-values in bold type.

It is noted that the p-value (ANCOVA) for change from baseline is based one ANCOVA model including treatment as a fixed effect and baseline value as covariate. The sponsor indicates that p-value is < 0.05, T-test of the LS means from the ANCOVA model are used to test for a difference between treatment groups and the placebo group. Otherwise, no further statistic analysis performed. This applies to the p-values in the next table as well.

Table 17. Endpoint Mean Changes of Vital Signs from Baseline among Primary Cohort in Part A of Study SLI381-314 (LOCF)

Vital Signs	Time Points	Analysis	Adderall XR				Placebo
			10mg	20mg	30mg	40mg	
			N=52	N=54	N=58	N=61	N=54
Systolic Blood Pressure	Baseline	Mean (SD)	106.3 (7.6)	109.3 (9.4)	107.9 (9.8)	107.8 (9.3)	108.1 (9.2)
	Endpoint	Mean (SD)	104.4 (8.8)	108.6 (9.9)	109.6 (9.5)	107.0 (8.8)	108.4 (8.2)
		Change (SD)	-1.9 (8.0)	-0.6 (10.4)	1.7 (9.8)	-1.1 (9.3)	0.3 (10.3)
		p-Value	0.0513				
Diastolic Blood Pressure	Baseline	Mean (SD)	67.1 (7.6)	67.4 (8.2)	67.1 (7.0)	66.2 (6.6)	67.0 (8.2)
	Endpoint	Mean (SD)	67.4 (7.8)	69.0 (7.8)	68.5 (6.1)	68.5 (7.4)	66.8 (7.0)
		Change (SD)	0.4 (7.8)	1.7 (9.0)	1.4 (6.6)	2.3 (7.5)	-0.2 (8.8)
		p-Value	0.3635				
Pulse	Baseline	Mean (SD)	75.6 (8.2)	73.9 (8.1)	74.1 (9.8)	75.8 (9.2)	73.7 (8.9)
	Endpoint	Mean (SD)	76.0 (9.3)	78.6 (11.0)	73.1 (9.8)	78.5 (13.3)	74.5 (9.4)
		Change (SD)	0.2 (7.8)	4.9 (11.5)	-1.0 (11.1)	2.8 (10.7)	0.5 (9.5)
		p-Value	**0.0111**				
			0.7889	**0.0226**	0.4297	0.0940	
Respiratory Rate	Baseline	Mean (SD)	16.6 (3.0)	17.0 (2.6)	17.2 (3.4)	17.6 (2.9)	17.0 (3.0)
	Endpoint	Mean (SD)	16.9 (3.0)	17.4 (3.0)	17.1 (2.9)	17.5 (3.0)	17.0 (2.6)
		Change (SD)	0.2 (2.0)	0.4 (2.8)	-0.1 (2.9)	-0.1 (3.1)	-0.1 (2.8)
		p-Value	0.8023				

In primary cohort, the only statistically significant change is pulse, which is especially noteworthy in Adderall XR 20mg group. However, from this data the magnitude of change doesn't seem to have clinical significance.

In secondary cohort, the only statistically significant change is also pulse, and it is more noteworthy in Adderall XR 50mg group. Again, its magnitude doesn't seem to be clinically significant.

Table 18. Endpoint Mean Changes of Vital Signs from Baseline among Secondary Cohort in Part A of Study SLI381-314

Vital Signs	Time Points	Analysis	Adderall XR		Placebo
			50mg	60mg	
			15	10	15
Systolic Blood Pressure	Baseline	Mean (SD)	115.9 (9.7)	115.3 (8.1)	115.5 (11.8)
	Endpoint	Mean (SD)	115.7 (9.5)	117.5 (11.4)	116.0 (9.0)
		Change (SD)	-0.2 (9.1)	2.2 (11.3)	0.5 (8.3)
		p-Value	0.8132		
Diastolic Blood Pressure	Baseline	Mean (SD)	71.1 (8.2)	72.3 (7.0)	69.7 (8.8)
	Endpoint	Mean (SD)	70.2 (5.8)	73.9 (8.2)	71.5 (7.4)
		Change (SD)	-0.9 (6.1)	1.6 (11.9)	1.8 (9.8)
		p-Value	0.4825		
Pulse	Baseline	Mean (SD)	76.5 (9.1)	77.3 (14.8)	78.7 (13.4)
	Endpoint	Mean (SD)	85.0 (9.5)	81.4 (13.6)	74.3 (11.7)
		Change (SD)	8.5 (12.1)	4.1 (17.3)	-4.5 (9.0)
		p-Value	**0.0145**		
			0.0043	0.0782	
Respiratory Rate	Baseline	Mean (SD)	17.4 (4.1)	15.5 (2.9)	16.9 (3.4)
	Endpoint	Mean (SD)	18.3 (3.5)	18.3 (2.7)	16.9 (2.4)
		Change (SD)	0.9 (3.6)	2.8 (4.3)	0.0 (3.0)
		p-Value	0.2302		

7.1.8.3.2 Analyses focused on outliers of vital sign measures:

In the PK study, the sponsor reports that in the primary cohort (dosing 10, 20, and 40mg) up to 76% (13/17) subjects had clinically significant elevation in blood pressure. Overall, the sponsor reports that most frequent AE was hypertension, which seems to have increased occurrence with at 20 and 40mg. In the secondary cohort (dosing 20, 40, and 60mg), again, hypertension is the most commonly reported AE (83%).

Table 19. Occurrence of Hypertension with Different Dosage in Pharmacokinetic Study (SLI381-110)

Cohorts	Dosing	Subjects who had Hypertension[1]
Primary	10mg	3/15 = 20%
	20mg	7/16 = 43.7%
	40mg	7/15 = 46.6%
Secondary	20mg	2/6 = 33.3%
	40mg	5/6 = 83.3%
	60mg	4/6 = 66.7%

[1] The Sponsor defines "Hypertension" as measures that are above 95th percentile. In ISS, the sponsor only reported the number of subjects who reported hypertension which was 1 in 10mg group and 3 in 60mg group.

The following tables show number of outliers from blood pressure and pulse analyses among primary cohort (Table 20) and secondary cohort (Table 21) of Part A of Study SLI381-314. Criteria of change are also listed in the tables below.

Table 20. Outliers from Blood Pressure and Pulse Analysis among Primary Cohort of Part A of Study SLI381-314

Vital Signs	Indicators Of Change	Adderall XR				Placebo
		10mg	20mg	30mg	40mg	
		N=54	N=54	N=58	N=61	N=52
Systolic BP	<20mmHg	54 (100%)	50 (92.6%)	56 (96.6%)	61 (100%)	51 (98.1%)
	≥20mmHg	0 (0%)	4 (7.4%)	2 (3.4%)	0 (0%)	1 (1.9%)
Diastolic BP	<10mmHg	48 (88.9%)	42 (77.8%)	51 (87.9%)	50 (82.0%)	43 (82.7%)
	≥10mmHg	6 (11.1%)	12 (22.2%)	7 (12.1%)	11 (18.0%)	9 (17.3)
Pulse	<25bpm	54 (100%)	51 (94.4%)	58 (100%)	59 (96.7%)	51 (98.1%)
	≥25bpm	0 (0%)	3 (5.6%)	0 (0%)	2 (3.3%)	1 (1.9%)

Table 21. Outliers from Blood Pressure and Pulse Analysis among Secondary Cohort of Part A of Study SLI381-314

Vital Signs	Indicators Of Change	Adderall XR		Placebo
		50mg	60mg	
		N=15	N=10	N=15
Systolic BP	<20mmHg	15 (100%)	10 (100%)	15 (100%)
	≥20mmHg	0 (0%)	0 (0%)	0 (0%)
Diastolic BP	<10mmHg	14 (93.3%)	8 (80.0%)	12 (80.0%)
	≥10mmHg	1 (6.7%)	2 (20.0%)	3 (20.0%)
Pulse	<25bpm	13 (86.7%)	9 (90%)	15 (100%)
	≥25bpm	2 (13.3%)	1 (10%)	0 (0%)

In primary cohort, compared with other dose groups, Adderall XR 20mg group had the highest rate of increase of systolic and diastolic BP as well as pulse. There doesn't seem to have significant increase of BP in secondary cohort, while pulse increase is obvious in the both Adderall XR groups.

The sponsor's also presents tables to show that in all dose groups of Adderall XR, whether among primary cohort or secondary cohort, all subjects had pulse less than 110bpm and blood pressure less than 150/100mmHg.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Among primary cohort, Adderall XR 20mg group had the most outliers in terms of blood pressure (systolic and diastolic) and pulse change. In Adderall XR treated groups, maximum change of pulse was 44bpm, of systolic blood pressure, 26mmHg, and of diastolic blood pressure 30mmHg; In placebo group the maximum changes were 32 bpm, 20mmHg, and 24, respectively.

Nonetheless, the analysis in this study is confounded by duration of treatment with the target dose. For example, 40mg patients received 40mg for only one week, which may not be long enough to fully assess effects of higher dose on blood pressure or pulse.

7.1.8.4 Additional analyses and explorations

Statistics on weekly changes of above vital signs from baseline are mostly insignificant, except pulse changes during week 3 and 4 among both primary (p=0.0079 and 0.0209) and secondary cohorts (p=0.0137 and 0.0088).

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No preclinical ECG study for this submission. ECG was only obtained at screening and at the end (Day 3) of PK study.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

As mentioned above, only Part A of Study SLI381-314 is a placebo-controlled study. Thus, the ECG analysis is focused on this part. It includes two cohorts with different weight and given different dosages. Therefore, the analysis presented in two separate tables.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

ECG was obtained at Visit -1 (Screening) and Visit 4 (or early termination).

Tables 22 and 23 on the next two pages show changes of ECG parameters from screening to the endpoint in the two cohorts of Part A of Study SLI381-314.

No change was statistically significant except for heart rate (HR) among the secondary cohort (those who weighed at least 165lbs/75kg and received 50 and 60mg of Adderall XR). (Please see Table 23.)

Table 22. Change of ECG Parameters from Screening of Primary Cohort in Part A of Study SLI381-314

ECG Parameters	Time Points	Analysis	Adderall XR				Placebo
			10mg	20mg	30mg	40mg	
			N=53	N=53	N=56	N=59*	N=51
PR (msec)	Screening	Mean (SD)	148.0 (20.5)	142.1 (17.2)	147.3 (18.7)	144.3 (18.1)	144.6 (17.7)
	Endpoint	Mean (SD)	149.0 (21.6)	137.0 (14.9)	145.6 (17.5)	142.5 (19.3)	144.2 (18.3)
		Change (SD)	-0.1 (14.8)	-4.9 (16.3)	-2.2 (12.3)	-1.7 (14.3)	-0.1 (11.8)
		p-Value	0.0942				
QRS (msec)	Screening	Mean (SD)	83.2 (8.3)	82.2 (9.3)	81.8 (7.6)	84.2 (9.2)	84.1 (9.3)
	Endpoint	Mean (SD)	84.3 (9.4)	83.4 (10.1)	84.3 (9.4)	85.7 (8.8)	84.1 (10.3)
		Change (SD)	1.2 (8.5)	1.4 (7.8)	2.5 (10.3)	1.6 (8.4)	0.1 (8.2)
		p-Value	0.8333				
QTcF (msec)	Screening	Mean (SD)	392.3 (19.8)	393.0 (17.3)	389.0 (18.8)	393.3 (15.3)	393.0 (20.1)
	Endpoint	Mean (SD)	391.5 (17.6)	390.2 (18.2)	387.7 (16.1)	393.1 (17.9)	395.2 (22.1)
		Change (SD)	0.1 (16.9)	-2.2 (15.2)	-0.8 (15.9)	-0.3 (16.7)	2.5 (19.3)
		p-Value	0.4154				
HR (bpm)	Screening	Mean (SD)	67.1 (10.1)	71.0 (10.7)	69.0 (9.7)	70.0 (11.8)	67.1 (8.9)
	Endpoint	Mean (SD)	70.2 (9.2)	75.9 (13.3)	72.2 (10.0)	75.3 (14.5)	71.4 (10.2)
		Change (SD)	3.5 (10.9)	4.7 (12.0)	3.6 (10.7)	5.1 (10.2)	4.5 (9.8)
		p-Value	0.4032				

*For PR interval the subject number was 58.

Table 23. Change of ECG Parameters from Screening of Secondary Cohort in Part A of Study SLI381-314

ECG Parameters	Time Points	Analysis	Adderall XR		Placebo
			50mg	60mg	
			N=15	N=10	N=14
PR (msec)	Screening	Mean (SD)	157.0 (17.4)	152.4 (15.8)	151.6 (19.1)
	Endpoint	Mean (SD)	147.9 (15.6)	143.5 (17.4)	153.4 (18.6)
		Change (SD)	-9.1 (11.2)	-8.9 (20.6)	1.3 (14.5)
		p-Value	0.1445		
QRS (msec)	Screening	Mean (SD)	87.7 (9.9)	84.3 (9.6)	87.6 (9.3)
	Endpoint	Mean (SD)	90.0 (10.0)	86.0 (10.0)	84.2 (8.9)
		Change (SD)	2.3 (9.2)	1.7 (7.8)	-2.0 (5.9)
		p-Value	0.2326		
QTcF (msec)	Screening	Mean (SD)	390.3 (14.2)	391.6 (19.7)	390.1 (13.6)
	Endpoint	Mean (SD)	387.5 (21.5)	385.7 (18.1)	387.0 (15.7)
		Change (SD)	-2.9 (20.3)	-5.9 (16.0)	-2.9 (13.1)
		p-Value	0.9162		
HR (bpm)	Screening	Mean (SD)	71.4 (9.8)	68.5 (13.4)	67.9 (14.7)
	Endpoint	Mean (SD)	77.3 (10.5)	81.0 (7.8)	66.9 (13.5)
		Change (SD)	5.9 (14.9)	12.5 (15.3)	0.4 (8.1)
		p-Value	**0.0103**		
			0.0327	**0.0036**	

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The sponsor analyzed the QTc, QTcB, and QTcF. The following tables show number of subjects who had significant changes of Q-T intervals in primary and secondary cohorts of SLI381-314 Part A. Though 12 subjects of those who received Adderall XR and 4 of those who received placebo didn't have follow up ECG, the sponsor reports no subject had QT ≥500msec in either groups.

Table 24. Subjects with Change of QTcF from Screening to Endpoint among Primary Cohort of Part A of Study SLI381-314

ECG Parameters	Indicators of Change at Endpoint	Adderall XR				Placebo
		10mg	20mg	30mg	40mg	
		N=53	N=53	N=56	N=59	N=51
QTcF (msec)	<30 msec	51 (96.2%)	52(98.1%)	53(94.6%)	58 (98.3%)	48(94.1%)
	30-59 msec	2 (3.8%)	1 (1.9%)	3 (5.4%)	1 (1.7%)	3 (5.9%)
	≥60 msec	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
QT (msec)	<30 msec	51 (96.2%)	51(96.2%)	53(94.6%)	53 (89.8%)	49(96.1%)
	30-59 msec	2 (3.8%)	2 (3.8%)	3 (5.4%)	6 (10.2%)	1 (2.0%)
	≥60 msec	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 25. Subjects with Change of QTcF from Screening to Endpoint among Secondary Cohort of Part A of Study SLI381-314

ECG Parameters	Indicators of Change at Endpoint	Adderall XR		Placebo
		50mg	60mg	
		N=15	N=10	N=14
QTcF (msec)	<30 msec	14 (93.3%)	10 (100%)	13 (92.9%)
	30-59 msec	1 (6.7%)	0 (0.0%)	1 (7.1%)
	≥60 msec	0 (0.0%)	0 (0.0%)	0 (0.0%)
QT (msec)	<30 msec	13 (93.3%)	9 (90%)	12 (92.9%)
	30-59 msec	1 (6.7%)	1(10%)	1 (7.1%)
	≥60 msec	0 (0%)	0 (0%)	0 (0%)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

In Adderall XR 20mg group, one subject whose overall ECG was normal at screening turned to abnormal (clinically significant atrial bigeminy) at the end of Part A study. However, a repeat ECG was normal and his cardiologist didn't restrict him from his previous stimulant-based medication after completion of the study. Otherwise, the sponsor reports there is no marked outliers in Adderall XR groups from ECG analysis.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were conducted. Tanner staging was not performed for the studies in this submission.

7.1.10 Immunogenicity

Not available.

7.1.11 Human Carcinogenicity

No human carcinogenicity data was provided in this application .

7.1.12 Special Safety Studies

No special safety studies were done for this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The sponsor reports that no adverse drug withdrawal effect observed in any subject who discontinued treatment in the studies included in this submission.

Amphetamine is know to have abuse potential. However, no updated information on this or relevant issues is available in this submission.

7.1.14 Human Reproduction and Pregnancy Data

Human reproduction and pregnancy data are not available in this submission.

7.1.15 Assessment of Effect on Growth

Like other psychostimulants, Adderall XR has effects on reducing weight and suppresses growth. The sponsor analyzed mean changes of weight from baseline to endpoint and utilized z-score according to the CDC Growth Chart of weight, height, and BMI for age. Based on the z-score the sponsor created the following three subgroups: Subgroup 1 is defined as at greater than 75 percentile, Subgroup 2 is defined as at 25-75 percentiles, and Subgroup 3 is defined as at less than 25 percentile.

The following table provides the mean changes of weight from baseline to endpoint in Part A of Study SLI381-314. No change in height or BMI reported by the sponsor for this part of the study.

Table 24. Mean Changes of Weight from Baseline to Endpoint in Primary Cohort of Part A of Study SLI381-314 (LOCF)

Weight (lbs)	Adderall XR				Placebo	p-Value
	10mg	20mg	30mg	40mg		
	N=54	N=54	N=58	N=61	N=52	
Baseline (SD)	125.9(22.2)	125.3(20.4)	128.6(18.8)	125.3(22.3)	131.5(18.1)	
Endpoint (SD)	124.6(23.3)	121.6(20.4)	124.5(17.5)	121.3(22.8)	133.1(18.9)	
Mean Change	-1.1	-2.8	-4.0	-4.1	1.5	
p-Value	0.0001	<0.0001	<0.0001	<0.0001		<0.0001

Table 25. Mean Changes of Weight from Baseline to Endpoint in Secondary Cohort of Part A of Study SLI381-314 (LOCF)

Weight (lbs)	Adderall XR		Placebo	p-Value
	50mg	60mg		
	N=15	N=10	N=15	
Baseline (SD)	189.6 (35.2)	191.1 (15.0)	190.5 (35.2)	<0.0001
Endpoint (SD)	182.5 (21.2)	181.6 (14.5)	191.0 (34.5)	
Mean Change	-7.1	-9.5	0.5	
p-Value	0.0001	<0.0001		

Z-scores of weight, height, and body mass index (BMI) from the six-month open-label study, Part B of Study SLI381-314 show significant decrease of weight and BMI in all three subgroups as defined above. Significant change in BMI is probably secondary to the change of weight because z-score of height was not significantly changed among subgroups 2 and 3. There was some significant decrease of z-score of height in subgroup 1. Thus, those whose height at 75

percentile or greater are more affected by the drug than those whose height was even smaller. The following table presents mean changes of weight, height, and BMI in z-scores from baseline to endpoint of Part B of Study SLI381-314.

Table 26. Mean Changes of Z-scores of Weight, Height, and BMI from Baseline to Endpoint of Part B of Study SLI381-314

	Subgroup 1	Subgroup 2	Subgroup 3	Total
Weight z-score				
N	59	62	17	138
Baseline mean (SD)	1.3 (0.5)	0.1 (0.4)	-1.1 (0.5)	0.5 (0.9)
Endpoint mean (SD)	0.8 (0.6)	-0.2 (0.4)	-1.3 (0.5)	0.1 (0.9)
Change mean (SD)	-0.4 (0.3)	-0.3 (0.3)	-0.2 (0.3)	-0.4 (0.3)
p-value[a]	<0.0001	<0.0001	0.0099	<0.0001
Height z-score				
N	26	71	41	138
Baseline mean (SD)	1.3 (0.4)	-0.1 (0.4)	-1.3 (0.6)	-0.2 (1.0)
Endpoint mean (SD)	1.2 (0.5)	-0.1 (0.5)	-1.1 (0.6)	-0.2 (0.9)
Change mean (SD)	-0.1 (0.3)	0.0 (0.2)	0.1 (0.8)	0.0 (0.5)
p-value[a]	0.0268	0.2840	0.2404	0.8801
BMI z-score				
N	70	53	15	138
Baseline mean (SD)	1.3 (0.4)	0.0 (0.4)	-1.1 (0.3)	0.6 (0.9)
Endpoint mean (SD)	0.7 (0.6)	-0.2 (0.4)	-1.4 (0.6)	0.1 (0.9)
Change mean (SD)	-0.6 (0.4)	-0.3 (0.4)	-0.3 (0.4)	-0.4 (0.4)
p-value[a]	<0.0001	<0.0001	0.0081	<0.0001

[a] P-value is based on a one-sample t-test of change from baseline=0.

Though Tanner Staging was mentioned in the FDA WR, it was not required for this submission and the sponsor plans to measure it in the 24-month open-label trial (SLI381-315).

7.1.16 Overdose Experience

The sponsor reports no non-clinical studies relevant to overdose have been performed and no overdose in any of the clinical studies in this submission. As of July 26, 2004, there were seven spontaneous case reports of overdose (see Table 9 in Appendix). Symptoms of acute overdose include various gastrointestinal symptoms such as nausea, vomiting, abdominal cramps, and diarrhea, arrhythmia, dysregulation of blood pressure, circulation collapse, restlessness, tremor, hyperreflexia, hyperpyrexia, rapid respiration, panic states, confusion, hallucinations, agitation, assultiveness, convulsion, and rhabdomyolysis. If severe enough, coma and death can occur.

There is no specific antidote for amphetamine. Treatment for overdose is symptomatic and supportive, including gastric lavage, charcoal and cathartic administration, and sedation. Acidification of urine increases amphetamine excretion but is believed to increase risk of acute renal failure if myoglobinuria is present. Caution should be given to a gradual drop in blood pressure when sufficient sedation is achieved.

7.1.17 Postmarketing Experience

The sponsor reports that Canada (for children 6-12 year-old) is the only country marketed with Adderall XR outside the U.S. (which is for both adults and children 6-12 year-old). since January 21, 2004. The surveillance report extends to September 17 , 2004. From the list of foreign postmarketing experience reports provided, no death is seen. The sponsor didn't provide dosages of these cases or any more detailed information other than patients' age, reported events, and the preferred terms of these events. The consequences of these cases are unknown, including if anyone was hospitalized.

The sponsor didn't present domestic postmarketing experience in this submission. Last review of domestic postmarketing experience was conducted by both FDA ODS and our division safety team in August 2004 for questionable signal for drug related sudden death, stroke, or serious cardiovascular adverse events. The conclusion for that review was no evidence for such signal for these events that is above the background rates for these events. This review was in response to Dr. Glenn Mannheim's concern in his review dated September, 2003.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The pivotal study design and patient enumeration are adequate per FDA WR.

7.2.1.2 Demographics

Demographic distribution of the pivotal study is also adequate according to FDA WR.

Extent of exposure (dose/duration)

Per our request, the sponsor provided the following table illustrating the extent of exposure (maximum dose taken for the longest period that was not interrupted for more than two days) to Adderall XR in both Part A and Part B of Study SLI381-314:

Table 27. Enumeration of Subjects by Maximum Dose of Adderall XR and Duration of Exposure to that Dose in Study SLI381-314 (Parts A & B combined)

Number of Subjects / Days of Exposure	Placebo	Maximum Adderall XR Daily Dose					
		10 mg	20 mg	30 mg	40 mg	50 mg	60 mg
0	1	2	0	0	0	0	0
1 - 7	2	7	9	5	35	8	4
8 - 14	2	5	3	25	14	5	4
15 - 21	1	1	16	15	1	0	1
22 - 28	16	15	12	1	0	1	0
29 - 35	14	10	1	7	2	1	0
36 - 65	2	0	1	3	2	0	2
66 - 95	0	0	1	5	7	1	0
96 - 125	0	0	3	3	5	2	2
126 - 155	0	0	1	5	5	2	2
156 - 185	0	0	11	9	4	2	1
Total	38	40	58	78	75	22	16

In my opinion, the range of dosage studied is sufficient. However, only a small number of adolescent patients have received Adderall XR for an extended duration in these studies. No patients received their maximum dose for longer than 185 days. Only 40 patients received a maximum dose of 40mg or greater for at least 29 days. For the recommended dose of 20 mg/day, 90 patients received a maximum dose of 20 mg/day or higher for at least 29 days. For the purpose of safety evaluation, the sponsor still needs to complete the long term study for safety which requires study treatment of 24 consecutive months.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The only study currently ongoing to evaluate safety at this point is SLI381-315 that will be done for 24 consecutive months. The sponsor provides 4-month Safety Update which is reviewed in Section 7.2.9.

7.2.2.2 Postmarketing experience

As mentioned about in Section 7.1.17, the sponsor provides cases for foreign postmarketing experience from Canada with the cut-off date of Sept. 2004 but didn't present domestic postmarketing experience in this submission. The cases reviewed by Dr. Mannheim were submitted by the sponsor in July, 2003, and those submitted to our division safety team for review had the cut-off date of December 31, 2003.

Thus, foreign postmarketing surveillance needs to be more detailed with case narratives.

7.2.2.3 Literature

The sponsor provided the listing of literature search, but only submitted the following information in the response to our filing letter. In this subsequent submission, the sponsor reports that a member of the US Shire Medical Information Team conducted literature review. The search used Medline and Embase databases and only queried literature of North America. The sponsor explains this is because Adderall XR is only marketed in the U.S. and Canada. The search terms include "Adderall, Adderall XR, mixed amphetamine salts, mixed salts of a single-entity amphetamine sulphate, amphetamine aspartate, dextroamphetamine, amphetamine aspartate." The sponsor states that publications regarding the illicit use of amphetamines were excluded. However, the sponsor still hasn't provided the warrant conclusion from literature search. (See Vol. 8, Page 96-101.)

7.2.3 Adequacy of Overall Clinical Experience

The sponsor fulfilled the requested studies in this population as per FDA WR with the exception of the requirement for 24 month safety data, which will be generated by their ongoing study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This section is not applicable for this NDA supplement.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor has conducted appropriate clinical laboratory testing except for no serum Creatinine and analysis of urinalysis data is incomplete. Thus, we can't know the function of the kidneys from the trial data. Though up to date, renal function has not been a major concern with the use of Adderall XR in other population, and the metabolism of Adderall XR mostly goes through liver, I'd recommend that serum creatinine be added in the future trials (esp. long term ones) for thorough assessment of renal function.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See above Section regarding renal function and serum creatinine. The sponsor needs to submit tables for outliers of laboratory tests and more detailed analysis of urinalysis data if collected.

For detailed information on metabolism and clearance workup, please refer to the review by FDA biopharmaceuticals reviewer, Kofi Kumi, PhD.

According to FDA WR, drug-drug interaction study result was not requested for this submission.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable as this is not a new drug.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the study design meets the requirement of the FDA WR except for the pending 24-month safety information. However, the following items in the submission are still not properly completed or analyzed:

1) In the literature search, the sponsor doesn't have conclusion and warrant for their literature review nor the timeframe for the literature search. The searched literature is just listed.

2) Demographic analysis of common adverse events is not properly conducted (See Section 7.1.5.6).

3) The sponsor doesn't provide explanation on why serum creatinine was not done and only very limited analysis of the urinalysis data is submitted (see Review of Urinalysis).

4) The sponsor only provides the subject listing of outliers of laboratory tests but not summarized table providing the proportion of patients with outlying values by treatment group.

5) The sponsor didn't mention domestic postmarketing exposure in this submission though I was able to find out from our previous analysis with data cut-off date of December 31, 2003.

6) The sponsor submitted a total of 19 Case Report Forms. One of them is very hard to read the copies of laboratory test results clearly.

7) The sponsor has not submitted case report forms and narratives for subjects who dropped out of the ongoing study in the Safety Update (see next section).

7.2.9 Additional Submissions, Including Safety Update

The Four-Month Safety Update includes the same safety date that were submitted for this sNDA and the interim safety data from an ongoing study, Study SLI-381-315, "a phase III, multi-center, 24-month, safety, tolerability, and efficacy study of Adderall XR in adolescents with ADHD." The following review is focused on death, SAEs, and AEs lead to dropout.

The sponsor reports that no death in this new study up to the cut-off date, September 23, 2004. There have been two subjects in the ongoing study reported nonfatal serious adverse events.

1) Subject # 27-002, a 14 year-old female who rolled over from Part A of SLI-381-314, developed major depressive disorder (COSTART term: depression) during the second month of treatment while on 40mg of Adderall XR. The subject discontinued from the study due to this event, but the sponsor reports it was resolved without sequelae and considers this as unrelated to the drug. I don't think the drug-relatedness can be ruled out here.

2) Subject # 56-003, a 13 year-old female who rolled over from Part B of SLI-381-314, developed suicidal ideation (COSTART term: depression) and was hospitalized two months after

entering the new study while on 30mg of Adderall XR. As the above subject, despite this discontinued from the study due to this event, the sponsor reports it was resolved without sequelae and considers this as unrelated to the drug. Again, I don't think the drug-relatedness can be ruled out here.

Up to 11 subjects have dropped out from Study SLI381-315 by the time of Safety Update submission. Together with Part A and Part B of Study SLI381-314, it totals 25 subjects and all of them were from Adderall XR group (only Part A is placebo-controlled double-blind study). In SLI381-315, the most common reason for discontinuation are depression (3, one of them with suicidal ideation and hospitalized—see above narratives) and weight loss (3). (Patients with depression were on 30-40mg and those with weight loss were on 20-30mg.) Somnolence, twitching, irritability, fever with nausea, and abnormal ECG each happened in one subject.

The sponsor provides narratives for SAEs in the Safety Update but hasn't provided narratives or case report forms for dropout cases.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As mentioned above, the demographic analysis of common adverse events is not properly done; Neither serum creatinine nor full urinalysis is provided making it difficult to assess renal function from the trial data; even among those who had proteinuria (all of them were in Adderall XR group), no more detailed related information provided; Finally, only subject listing of outliers of laboratory tests is submitted, instead of summarized table of enumeration of outliers by treatment group. In the Safety Update, the sponsor provides narratives for SAEs but hasn't provided narratives or case report forms for dropout cases.

In my opinion, the sponsor must correct these deficiencies before this NDA can be approved.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Most of the review data for safety is from the pivotal study conducted according to FDA WR. However, serious adverse events and deaths as well as drop-outs during adverse events were reviewed from the PK study, pivotal study (Part A of SLI381-314), as well as the six-month open-label part of the study (Part B) and the 4-Month Safety Update.

7.4.1.2 Combining data

See above Section 7.4.1.1. Data for safety review were not combined for common adverse events and labs, vital signs, and ECG data analysis.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Changes of vital signs, laboratory findings, and ECG as well as adverse events in different dose groups are summarized in Section 7.1.

7.4.2.2 Explorations for time dependency for adverse findings

The sponsor provides information on changes of vital signs, laboratory findings, and ECG. Summaries of these changes from baseline to endpoint are in Section 7.1.7.

7.4.2.3 Explorations for drug-demographic interactions

The sponsor provides information on drug-demographic interaction for those AEs that were reported at >5% and with greater incidence than placebo in both Part A and Part B of Study SLI381-314. Essentially comparison is made based on percentages between the placebo group and the whole Adderall XR group regardless doses. The sponsor didn't separate the dose groups for these demographic analyses and didn't analyze the drug:placebo odds of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.

7.4.2.4 Explorations for drug-disease interactions

There is no explorations for drug-disease interactions. ADHD is the only indicated disease for treatment studied. No study regarding subjects with any organ disease or failure is presented.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interaction studies were done for this submission. The sponsor has no additional new information for drug-drug interaction in the proposed labeling.

7.4.3 Causality Determination

In this review, adverse events of 5% or more and twice of the incidence of placebo group are considered drug-related.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

It can be concluded that dosing regimen for adolescents can be started from 10mg/day, then increase to 20mg/day as needed. From the trial data, dosing beyond 20mg does not show additional clinical benefit but increased risks of adverse events.

8.2 Drug-Drug Interactions

See Section 7.4.2.5.

8.3 Special Populations

The sponsor didn't have study report on patients with renal or liver or other organ system disease or failure.

8.4 Pediatrics

This submission is specifically for adolescents with ADHD.

8.5 Advisory Committee Meeting

No advisory committee meeting was planned or conducted regarding this submission.

8.6 Literature Review

The sponsor provides the list of references but no warrant or conclusions.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan has been submitted.

8.8 Other Relevant Materials

See review of the Four-Month Safety Update in Section 7.2.9.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor conducted the PK and pivotal study according to FDA WR and the studies fulfilled the WR.

9.2 Recommendation on Regulatory Action

I recommend the agency to take approvable action on the use of 20mg of Adderall XR for treatment of ADHD in adolescents age 13-17 years old. The sponsor needs to submit the information which satisfactorily address the above deficiencies for review before the approval action can be granted. These include the items mentioned in Section 7.2.8: Assessment of Quality and Completeness of Data.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activity is recommended at this point.

9.3.2 Required Phase 4 Commitments

Continue the ongoing study to demonstrate long term study for safety and tolerability: Study SLI381-315.

9.3.3 Other Phase 4 Requests

As mentioned in previous sections, I would like to recommend monitoring serum creatinine in the future studies because this gives the thorough assessment for renal function.

9.4 Labeling Review

The labeling review here is focused on clinical issues (see Appendix for details). The sponsor needs to do the following:

1) The sponsor must revise the sentences (b) (4) (b) (4) bottom of the page 2-6 in Vol 4.2

2) The sponsor must remove the sentence on the next page, from lines 3-4, that states, (b) (4) (b) (4)

3) The sponsor should revise Table 2 on page 2-12 (Vol 4.2) to separate the dose groups for adverse events reported by adolescent subjects and compare them with the placebo group, so that the adverse events can be shown more clearly in each dose groups and will not be missed.

9.5 Comments to Applicant

Thanks for your submission. For future references, I recommend including thorough analysis of outlier data, instead of just listings of data for submissions.

10 APPENDICES

10.1 Tables referenced in the review text.

Table 1. Principal Investigators and the Numbers of Subjects Recruited for SLI381-314

Principal Investigators	Location	N in Part A	N in Part B
Scott T. Aaronson, MD	Baltimore, MD 20214	-	-
Howard Abikoff, PhD	New York, NY 10016	2	-
Valerie Arnold, MD	Memphis, TN 38119	15	9
Louise M. Beckett, MD	Oklahoma City, OK 73103	15	10
John C. Burnside, MD	San Antonio, TX 78247	9	1
Regina Bussing, MD	Gainesville, FL 32610	5	-
John Cecil, MD	Paducah, KY 42001	9	4
Mark Chandler, MD	Chapel Hill, NC 27514	11	6
Edward Cherlin, MD	El Centro, CA 92243	10	5
Daniel Coury, MD	Columbus, OH 43205	7	4
Jeanette Cueva, MD	New York, NY 10011	-	-
Andrew J. Cutler, MD	Winter Park, FL 32789	5	-
Robert Dahmes, MD	New Orleans, LA 70114	10	4
Anthony P. Dietrich, MD	Woodstock, VT 05091	6	1
Bradley Diner, MD	Little Rock, AR 72223	5	2
Catherine Ducommun-Nagy, MD	Jenkintown, PA 19046	2	-
David Duesenberg, MD	Chesterfield, MO 63017	11	6
John Gilliam, MD	Richmond, VA 23294	6	1
Lawrence Ginsberg, MD	Houston, TX 77090	4	3
Michael Greenbaum, MD	Libertyville, IL 60048	8	-
James T. Grimm, MD	Eugene, OR 97401	9	-
Howard Hassman, MD	Clementon, NJ 08021	9	5
James Hedrick, MD	Bardstown, KY 40004	12	7
Alexander Horwitz, MD	Salem, OR 97301	6	1
Rakesh Jain, MD	Lake Jackson, TX 77566	2	2
James Knutson, MD	Kirkland, WA 98033	8	1
Elly Lee, MD	Irvine, CA 92618	4	1
James E. Lee, MD	Charlotte, NC 28226	3	2
Robert Lehman, MD	Baltimore, MD 21208	-	-
Alan Levine, MD	Boulder, CO 80304	5	1
David E. Linden, MD	Oklahoma City, OK 733118	6	5
Robert S. Lipetz, DO	Spring Valley, CA 91978	1	-
Frank Lopez, MD	Maitland, FL 32751	16	12
Veena Luthra, MD	Bala Cynwyd, PA 19004	3	-

Table 1. Principal Investigators and the Numbers of Subjects Recruited for SLI381-314 (Continued)

Jeffrey Mattes, MD	Princeton, NJ 08540	3	-
Craig M. McCarthy, MD	Mesa, AZ 85210	4	-
Janice L. Miller, MD	West Palm Beach, FL 33407	10	6
Mario Molina, MD	Hialeah, FL 33016	7	3
Eliot Moon, MD	Temecula, CA 92591	7	-
Kamalesh Pai, MD	Jacksonville, FL 32216	6	3
Anil S. Patel, MD	San Marcos, CA 92078	-	-
Robert A. Riesenberg, MD	Atlanta, GA 30308	4	-
Leon I. Rosenberg, MD	Moorestown, NJ 08057	4	-
Keith E. Saylor, PhD	Bethesda, MD 20814	8	6
Ward T. Smith, MD	Portland, OR 97201	4	-
Craig A. Spiegel, MD	Bridgeton, MO 63044	3	-
William Terry, MD	Boise, ID 83704	8	-
Kathleen Toups, MD	Lafayette, CA 94549	5	3
Bradley Vince, DO	Overland Park, KS 66211	18	13
Richard H. Weisler, MD	Raleigh, NC 27609	2	-
Scott West, MD	Orlando, FL 32806	6	6
Mark Wolraich, MD	Oklahoma City, OK 73117	1	2
Daniel Wynn, MD	Northbrook, IL 60062	1	-
Kashinath G. Yadalam, MD	Lake Charles, LA 70601	4	2

Table 2. Clinician Version of ADHD-Rating Scale-IV (ADHD-RS-IV) Used in the Trials.

Check the box that **BEST DESCRIBES** this subject's behavior in the last week.

	Never or rarely	Sometimes	Often	Very Often
1. Fails to give close attention to details or makes careless mistakes in work	0❑	1❑	2❑	3❑
2. Fidgets with hands or feet or squirms in seat	0❑	1❑	2❑	3❑
3. Has difficulty sustaining attention in tasks or play activities	0❑	1❑	2❑	3❑
4. Leaves seat in classroom or in other situations in which seating is expected	0❑	1❑	2❑	3❑
5. Does not seem to listen when spoken to directly	0❑	1❑	2❑	3❑
6. Runs about or climbs excessively in situations in which it is inappropriate	0❑	1❑	2❑	3❑
7. Does not follow through on instructions and fails to finish work	0❑	1❑	2❑	3❑
8. Has difficulty playing or engaging in leisure activities quietly	0❑	1❑	2❑	3❑
9. Has difficulty organizing tasks and activities	0❑	1❑	2❑	3❑
10. Is "on the go" or acts as if "driven by a motor"	0❑	1❑	2❑	3❑
11. Avoids tasks (e.g., schoolwork, homework) that require sustained mental effort	0❑	1❑	2❑	3❑
12. Talks excessively	0❑	1❑	2❑	3❑
13. Loses things necessary for tasks or activities	0❑	1❑	2❑	3❑
14. Blurts out answers before questions have been completed	0❑	1❑	2❑	3❑
15. Is easily distracted	0❑	1❑	2❑	3❑
16. Has difficulty awaiting turn	0❑	1❑	2❑	3❑
17. Is forgetful in daily activities	0❑	1❑	2❑	3❑
18. Interrupts or intrudes on others	0❑	1❑	2❑	3❑

Table 3. Common Adverse Events Reported by ≥ 2% in Any Adderall XR Dose Groups in Primary Cohort of Part A of Study SLI381.314

Adverse Events (Preferred Terms)	Adderall XR				Placebo
	10mg N=56	**20mg** N=56	**30mg** N=58	**40mg** N=63	N=54
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Total AEs	35 (62.5)	43 (76.8)	45 (77.6)	49 (77.8)	32 (59.3)
Body as a whole					
Abdominal Pain	5 (8.9)	3 (5.4)	6 (10.3)	11 (17.5)	1 (1.9)
Accidental Injury	1 (1.8)	4 (7.1)	1 (1.7)	5 (7.9)	3 (5.6)
Asthenia	2 (3.6)	1 (1.8)	2 (3.4)	1 (1.6)	0
Flu Syndrome[2]	2 (3.6)	0	1 (1.7)	1 (1.6)	1 (1.9)
Headache[4]	8 (14.3)	7 (12.5)	14 (24.1)	9 (14.3)	12 (22.2)
Infection (unspecified)[4]	0	0	2 (3.4)	1 (1.6)	1 (1.9)
Infection (Viral)[1]	0	4 (7.1)	1 (1.7)	2 (3.2)	6 (11.1)
Pain[3]	0	4 (7.1)	0	0	2 (3.7)
Cardiovascular System					
Tachycardia	0	2 (3.6)	0	1 (1.6)	0
Gastroenterology System					
Anorexia	13 (23.2)	19 (33.9)	26 (44.8)	25 (39.7)	1 (1.9)
Diarrhea	0	1 (1.8)	3 (5.2)	0	0
Dry Mouth	1 (1.8)	3 (5.4)	3 (5.2)	3 (4.8)	0
Dyspepesia	2 (3.6)	2 (3.6)	1 (1.7)	2 (3.2)	0
Nausea	3 (5.4)	1 (1.8)	2 (3.4)	1 (1.6)	0
Vomiting	1 (1.8)	3 (5.4)	3 (5.2)	1 (1.6)	0
Metabolic & Nutritious Status					
Weight Loss	1 (1.8)	5 (8.9)	8 (13.8)	8 (12.7)	0
Central Nervous System					
Depression	0	2 (3.6)	1 (1.7)	0	0
Dizziness[1]	3 (5.4)	2 (3.6)	4 (6.9)	4 (6.3)	4 (7.4)
Emotional Lability	2 (3.6)	1 (1.8)	4 (6.9)	0	0
Insomnia	5 (8.9)	8 (14.3)	4 (6.9)	11 (17.5)	2 (3.7)
Nervousness[3]	3 (5.4)	6 (10.7)	2 (3.4)	3 (4.8)	3 (5.6)
Somnolence	2 (3.6)	1 (1.8)	2 (3.4)	6 (9.5)	2 (3.7)
Respiratory System					
Cough Increased	0	2 (3.6)	0	2 (3.2)	1 (1.9)
Pharyngitis[3]	4 (7.1)	9 (16.1)	4 (6.9)	3 (4.8)	5 (9.3)
Rhinitis[3]	2 (3.6)	4 (7.1)	1 (1.7)	2 (3.2)	3 (5.6)
Skin Diseases					
Acne[4]	0	0	2 (3.4)	0	0
Herpes Simplex	2 (3.6)	0	0	1 (1.6)	0
Urogenital					
Albuminuria	0	1 (1.8)	0	3 (4.8)	0

[1]These adverse events are higher in the placebo group: Dizziness, viral infection.
[2]These adverse events are higher than placebo group only in the 10mg group: Flu syndrome,
[3]These adverse events are higher than placebo group only in the 20mg group: Rhinitis, Pharyngitis, nervousness.
[4] These adverse events are higher than placebo group only in the 30mg group: Headache, unspecified infection, acne.

Table 4. Common Adverse Events that ≥ 2% in Any Adderall XR Dose Groups in Primary Cohort of Part B of Study SLI381.314

Adverse Events (Preferred Terms)	Adderall XR		Placebo
	50mg N=15	**60mg** N=10	N=15
	N (%)	**N (%)**	**N (%)**
Total AEs	12 (80.0)	7 (70.0)	10 (66.7)
Body as a whole			
Abdominal Pain	2 (13.3)	2 (20.0)	1 (6.7)
Accidental Injury	1 (6.7)	0	0
Asthenia	1 (6.7)	0	1 (6.7)
Headache	5 (33.3)	3 (30.0)	3 (20.0)
Pain	1 (6.7)	0	0
Infection (Viral)	1 (6.7)	2 (20.0)	0
Cardiovascular System			
Syncope	1 (6.7)	0	0
Tachycardia	1 (6.7)	0	0
Gasterenterology System			
Anorexia	6 (40.0)	5 (50.0)	2 (13.3)
Dry Mouth	2 (13.3)	0	0
Dyspepsia	1 (6.7)	0	0
Gastroenteritis	1 (6.7)	0	0
Increased Appetite	1 (6.7)	0	1 (6.7)
Nausea	0	1 (10.0)	0
Stomach Ulcer	0	1 (10.0)	0
Tooth Disorder	1 (6.7)	0	0
Metabolic & Nutritious Disease			
Weight Loss	3 (20.0)	1 (10.0)	0
Muscularskeletal System			
Tendon Disorder	1 (6.7)	0	0
Central Nervous System			
Anxiety	0	2 (20.0)	0
Dizziness	4 (26.7)	2 (20.0)	0
Insomnia	4 (26.7)	4 (40.0)	0
Nervousness	3 (20.0)	3 (30.0)	0
Paresthesia	1 (6.7)	0	0
Somnolence	1 (6.7)	1 (10.0)	1 (6.7)
Tremor	1 (6.7)	0	0
Vertigo	0	1 (10.0)	0
Respiratory System			
Cough Increased	0	1 (10.0)	0
Lung Disorder	1 (6.7)	0	0
Pharyngitis	0	1 (10.0)	1 (6.7)

Rhinitis	1 (6.7)	1 (10.0)	3 (20.0)
Skin Disease			
Rash	0	1 (10.0)	1 (6.7)
Urogenital			
Albuminuria	0	1 (10.0)	0
Dysmenorrhea	0	1 (10.0)	0

Table 5. Common Drug-Related Adverse Events in Primary Cohort of Part A of Study SLI381.314

Adverse Events (Preferred Terms)	**Adderall XR**				**Placebo**
	10mg	**20mg**	**30mg**	**40mg**	
	N=56	N=56	N=58	N=63	N=54
Gasterenterology System					
Abdominal Pain	5 (8.9%)	3 (5.4%)	6 (10.3%)	11 (17.5%)	1 (1.9%)
Anorexia	13 (23.2%)	19 (33.9%)	26 (44.8%)	25 (39.7%)	1 (1.9%)
Diarrhea	0	1 (1.8%)	3 (5.2%)	0	0
Dry Mouth	1 (1.8%)	3 (5.4%)	3 (5.2%)	3 (4.8%)	0
Nausea	3 (5.4%)	1 (1.8%)	2 (3.4%)	1 (1.6%)	0
Vomiting	1 (1.8%)	3 (5.4%)	3 (5.2%)	1 (1.6%)	0
Central Nervous System					
Emotional Lability	2 (3.6%)	1 (1.8%)	4 (6.9%)	0	0
Insomnia	5 (8.9%)	8 (14.3%)	4 (6.9%)	11 (17.5%)	2 (3.7%)
Somnolence	2 (3.6%)	1 (1.8%)	2 (3.4%)	6 (9.5%)	2 (3.7%)
Metabolic and Nutritious Disease					
Weight Loss	1 (1.8%)	5 (8.9%)	8 (13.8%)	8 (12.7%)	0 (0%)

Table 6. Common Drug-Related Adverse Events in Secondary Cohort of Part A of Study SLI381.314

Adverse Events (Preferred Terms)	**Adderall XR**		**Placebo**
	50mg	**60mg**	
	N=15	N=10	N=15
Body as a whole			
Accidental Injury	1 (6.7%)	0	0
Pain	1 (6.7%)	0	0
Infection (Viral)	1 (6.7%)	2 (20.0%)	0
Cardiovascular System			
Syncope	1 (6.7%)	0	0
Tachycardia	1 (6.7%)	0	0
Gasteroenterology System			
Abdominal Pain	2 (13.3%)	2 (20.0%)	1 (6.7%)
Dry Mouth	2 (13.3%)	0	0
Dyspepsia	1 (6.7%)	0	0
Gastroenteritis	1 (6.7%)	0	0
Nausea	0	1 (10.0%)	0
Stomach Ulcer	0	1 (10.0%)	0
Tooth Disorder	1 (6.7%)	0	0
Muscularskeleton System			
Tendon Disorder	1 (6.7%)	0	0
Central Nervous System			
Anxiety	0	2 (20.0%)	0
Dizziness	4 (26.7%)	2 (20.0%)	0
Insomnia	4 (26.7%)	4 (40.0%)	0
Nervousness	3 (20.0%)	3 (30.0%)	0
Paresthesia	1 (6.7%)	0	0
Tremor	1 (6.7%)	0	0
Vertigo	0	1 (10.0%)	0
Respiratory System			
Cough Increased	0	1 (10.0%)	0
Lung Disorder	1 (6.7%)	0	0
Urogenital			
Albuminuria	0	1 (10.0%)	0
Dysmenorrhea	0	1 (10.0%)	0

Table 7. Summary of Treatment-Emergent Adverse Events by Body System and Preferred Term in Primary Cohort (All Randomized Subjects) of Study SLI381-314 are in the next 4 pages:

Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
Total	32 (59.3%)	63	35 (62.5%)	77	43 (76.8%)	124	45 (77.6%)	128	49 (77.8%)	130	204 (71.1%)	522
BODY AS A WHOLE	20 (37.0%)	30	18 (32.1%)	25	22 (39.3%)	37	21 (36.2%)	32	25 (39.7%)	37	106 (36.9%)	161
ABDOMINAL PAIN	1 (1.9%)	1	5 (8.9%)	5	3 (5.4%)	7	6 (10.3%)	6	11 (17.5%)	13	26 (9.1%)	32
ACCIDENTAL INJURY	3 (5.6%)	3	1 (1.8%)	1	4 (7.1%)	6	1 (1.7%)	1	5 (7.9%)	5	14 (4.9%)	16
ALLERGIC REACTION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
ASTHENIA	0 (0.0%)	0	2 (3.6%)	2	1 (1.8%)	1	2 (3.4%)	2	1 (1.6%)	1	6 (2.1%)	6
BACK PAIN	0 (0.0%)	0	1 (1.8%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2
CHEST PAIN	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
CHILLS	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
FEVER	1 (1.9%)	1	1 (1.8%)	1	2 (3.6%)	2	0 (0.0%)	0	0 (0.0%)	0	4 (1.4%)	4
FLU SYNDROME	1 (1.9%)	1	2 (3.6%)	2	0 (0.0%)	0	1 (1.7%)	1	1 (1.6%)	1	5 (1.7%)	5
HEADACHE	12 (22.2%)	15	8 (14.3%)	11	7 (12.5%)	9	14 (24.1%)	19	9 (14.3%)	12	50 (17.4%)	66
INFECTION	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (3.4%)	2	1 (1.6%)	1	4 (1.4%)	4
INFECTION FUNGAL	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
NECK RIGIDITY	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
PAIN	2 (3.7%)	2	0 (0.0%)	0	4 (7.1%)	4	0 (0.0%)	0	1 (1.6%)	1	7 (2.4%)	7
PHOTOSENSITIVITY REACTION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
VIRAL INFECTION	6 (11.1%)	6	0 (0.0%)	0	4 (7.1%)	4	1 (1.7%)	1	2 (3.2%)	2	13 (4.5%)	13
CARDIOVASCULAR SYSTEM	2 (3.7%)	2	0 (0.0%)	0	4 (7.1%)	4	3 (5.2%)	4	1 (1.6%)	1	10 (3.5%)	11
ELECTROCARDIOGRAM ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
MIGRAINE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	2	0 (0.0%)	0	1 (0.3%)	2
PALPITATION	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	2 (0.7%)	2
POSTURAL HYPOTENSION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
TACHYCARDIA	0 (0.0%)	0	0 (0.0%)	0	2 (3.6%)	2	0 (0.0%)	0	1 (1.6%)	1	3 (1.0%)	3
VASODILATATION	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	2 (0.7%)	2
DIGESTIVE SYSTEM	2 (3.7%)	2	18 (32.1%)	22	25 (44.6%)	30	32 (55.2%)	39	32 (50.8%)	38	109 (38.0%)	131
ANOREXIA	1 (1.9%)	1	13 (23.2%)	13	19 (33.9%)	19	26 (44.8%)	26	25 (39.7%)	28	84 (29.3%)	87
APHTHOUS STOMATITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
DIARRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	3 (5.2%)	3	0 (0.0%)	0	4 (1.4%)	4
DRY MOUTH	0 (0.0%)	0	1 (1.8%)	1	3 (5.4%)	3	3 (5.2%)	3	3 (4.8%)	3	10 (3.5%)	10

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b) (4) (US) 16-MAR-2004 09:47

Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
DYSPEPSIA	0 (0.0%)	0	2 (3.6%)	2	2 (3.6%)	3	1 (1.7%)	1	2 (3.2%)	2	7 (2.4%)	8
GASTRITIS	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
INCREASED APPETITE	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
MELENA	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
NAUSEA	0 (0.0%)	0	3 (5.4%)	3	1 (1.8%)	1	2 (3.4%)	2	1 (1.6%)	1	7 (2.4%)	7
STOMATITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
VOMITING	0 (0.0%)	0	1 (1.8%)	1	3 (5.4%)	3	3 (5.2%)	3	1 (1.6%)	1	8 (2.8%)	8
ENDOCRINE SYSTEM	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPOTHYROIDISM	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HEMIC AND LYMPHATIC SYSTEM	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	3 (5.2%)	3	1 (1.6%)	1	5 (1.7%)	5
ANEMIA	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
ECCHYMOSIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
ERYTHROCYTES ABNORMAL	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
LYMPHADENOPATHY	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	1 (1.6%)	1	2 (0.7%)	2
METABOLIC AND NUTRITIONAL DISORDERS	1 (1.9%)	1	2 (3.6%)	2	5 (8.9%)	5	9 (15.5%)	11	8 (12.7%)	8	25 (8.7%)	27
DEHYDRATION	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	2 (0.7%)	2
SGOT INCREASED	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
SGPT INCREASED	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
WEIGHT GAIN	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
WEIGHT LOSS	0 (0.0%)	0	1 (1.8%)	1	5 (8.9%)	5	8 (13.8%)	8	8 (12.7%)	8	22 (7.7%)	22
MUSCULOSKELETAL SYSTEM	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
MYALGIA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
NERVOUS SYSTEM	9 (16.7%)	12	11 (19.6%)	17	16 (28.6%)	25	15 (25.9%)	26	21 (33.3%)	28	72 (25.1%)	108
AGITATION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
ANXIETY	0 (0.0%)	0	1 (1.8%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2
DEPRESSION	0 (0.0%)	0	0 (0.0%)	0	2 (3.6%)	2	1 (1.7%)	1	0 (0.0%)	0	3 (1.0%)	3
DIZZINESS	4 (7.4%)	5	3 (5.4%)	3	2 (3.6%)	2	4 (6.9%)	6	4 (6.3%)	5	17 (5.9%)	21

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b)(4) US) 16-MAR-2004 09:47

Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
EMOTIONAL LABILITY	0 (0.0%)	0	2 (3.6%)	2	1 (1.8%)	1	4 (6.9%)	4	0 (0.0%)	0	7 (2.4%)	7
HALLUCINATIONS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPERKINESIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HYPERTONIA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
INSOMNIA	2 (3.7%)	2	5 (8.9%)	5	8 (14.3%)	8	4 (6.9%)	5	11 (17.5%)	12	30 (10.5%)	32
NERVOUSNESS	3 (5.6%)	3	3 (5.4%)	3	6 (10.7%)	7	2 (3.4%)	2	3 (4.8%)	4	17 (5.9%)	19
PARESTHESIA	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
SOMNOLENCE	2 (3.7%)	2	2 (3.6%)	2	1 (1.8%)	1	2 (3.4%)	3	6 (9.5%)	6	13 (4.5%)	14
TREMOR	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	1 (1.6%)	1	2 (0.7%)	2
TWITCHING	0 (0.0%)	0	0 (0.0%)	0	2 (3.6%)	2	1 (1.7%)	1	0 (0.0%)	0	3 (1.0%)	3
RESPIRATORY SYSTEM	9 (16.7%)	11	7 (12.5%)	7	14 (25.0%)	17	6 (10.3%)	6	7 (11.1%)	9	43 (15.0%)	50
COUGH INCREASED	1 (1.9%)	1	0 (0.0%)	0	2 (3.6%)	2	0 (0.0%)	0	2 (3.2%)	2	5 (1.7%)	5
DYSPNEA	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
EPISTAXIS	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	2 (0.7%)	2
HYPOVENTILATION	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
PHARYNGITIS	5 (9.3%)	5	4 (7.1%)	4	9 (16.1%)	9	4 (6.9%)	4	3 (4.8%)	3	25 (8.7%)	25
RHINITIS	3 (5.6%)	3	2 (3.6%)	2	4 (7.1%)	5	1 (1.7%)	1	2 (3.2%)	2	12 (4.2%)	13
SINUSITIS	0 (0.0%)	0	1 (1.8%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2
SKIN AND APPENDAGES	2 (3.7%)	2	3 (5.4%)	3	1 (1.8%)	1	4 (6.9%)	5	3 (4.8%)	3	13 (4.5%)	14
ACNE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (3.4%)	3	0 (0.0%)	0	2 (0.7%)	3
CONTACT DERMATITIS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.7%)	1	0 (0.0%)	0	1 (0.3%)	1
HERPES SIMPLEX	0 (0.0%)	0	2 (3.6%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	3 (1.0%)	3
HERPES ZOSTER	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
PRURITUS	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
RASH	1 (1.9%)	1	0 (0.0%)	0	1 (1.8%)	1	1 (1.7%)	1	0 (0.0%)	0	3 (1.0%)	3
SKIN BENIGN NEOPLASM	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
SWEATING	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
SPECIAL SENSES	1 (1.9%)	1	1 (1.8%)	1	2 (3.6%)	2	0 (0.0%)	0	1 (1.6%)	1	5 (1.7%)	5
ABNORMAL VISION	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
EAR PAIN	1 (1.9%)	1	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (0.7%)	2

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

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Body System Preferred Term (Costart)	Placebo (N=54) #(%) Subj	# AEs	Adderall XR 10 mg (N=56) #(%) Subj	# AEs	Adderall XR 20 mg (N=56) #(%) Subj	# AEs	Adderall XR 30 mg (N=58) #(%) Subj	# AEs	Adderall XR 40 mg (N=63) #(%) Subj	# AEs	Total (N=287) #(%) Subj	# AEs
OTITIS EXTERNA	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.6%)	1	1 (0.3%)	1
TINNITUS	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1
UROGENITAL	1 (1.9%)	1	0 (0.0%)	0	2 (3.6%)	2	1 (1.7%)	1	4 (6.3%)	4	8 (2.8%)	8
ALBUMINURIA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	0 (0.0%)	0	3 (4.8%)	3	4 (1.4%)	4
DYSMENORRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (1.8%)	1	1 (1.7%)	1	1 (1.6%)	1	3 (1.0%)	3
METRORRHAGIA	1 (1.9%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (0.3%)	1

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b) (4) US) 16-MAR-2004 09:47

Table 8. Summary of Treatment-Emergent Adverse Events by Body System and Preferred Term in Secondary Cohort (All Randomized Subjects) of Study SLI381-314

Body System Preferred Term (Costart)	Placebo (N=15) #(%) Subj	Placebo (N=15) # AEs	Adderall XR 50 mg (N=15) #(%) Subj	Adderall XR 50 mg (N=15) # AEs	Adderall XR 60 mg (N=10) #(%) Subj	Adderall XR 60 mg (N=10) # AEs	Total (N=40) #(%) Subj	Total (N=40) # AEs
Total	10 (66.7%)	20	12 (80.0%)	45	7 (70.0%)	37	29 (72.5%)	102
BODY AS A WHOLE	5 (33.3%)	6	9 (60.0%)	11	5 (50.0%)	9	19 (47.5%)	26
ABDOMINAL PAIN	1 (6.7%)	1	2 (13.3%)	2	2 (20.0%)	3	5 (12.5%)	6
ACCIDENTAL INJURY	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
ASTHENIA	1 (6.7%)	1	1 (6.7%)	1	0 (0.0%)	0	2 (5.0%)	2
FLU SYNDROME	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
HEADACHE	3 (20.0%)	3	5 (33.3%)	5	3 (30.0%)	4	11 (27.5%)	12
PAIN	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
VIRAL INFECTION	0 (0.0%)	0	1 (6.7%)	1	2 (20.0%)	2	3 (7.5%)	3
CARDIOVASCULAR SYSTEM	0 (0.0%)	0	2 (13.3%)	2	0 (0.0%)	0	2 (5.0%)	2
SYNCOPE	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
TACHYCARDIA	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
DIGESTIVE SYSTEM	5 (33.3%)	5	8 (53.3%)	12	5 (50.0%)	7	18 (45.0%)	24
ANOREXIA	2 (13.3%)	2	6 (40.0%)	6	5 (50.0%)	5	13 (32.5%)	13
DIARRHEA	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
DRY MOUTH	0 (0.0%)	0	2 (13.3%)	2	0 (0.0%)	0	2 (5.0%)	2
DYSPEPSIA	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
GASTROENTERITIS	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
GASTROINTESTINAL DISORDER	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
INCREASED APPETITE	1 (6.7%)	1	1 (6.7%)	1	0 (0.0%)	0	2 (5.0%)	2
NAUSEA	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
STOMACH ULCER	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
TOOTH DISORDER	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
HEMIC AND LYMPHATIC SYSTEM	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
ECCHYMOSIS	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0%)	0	3 (20.0%)	3	1 (10.0%)	1	4 (10.0%)	4
WEIGHT LOSS	0 (0.0%)	0	3 (20.0%)	3	1 (10.0%)	1	4 (10.0%)	4

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b) (4) (US) 16-MAR-2004 09:47

Body System Preferred Term (Costart)	Placebo (N=15) #(%) Subj	# AEs	Adderall XR 50 mg (N=15) #(%) Subj	# AEs	Adderall XR 60 mg (N=10) #(%) Subj	# AEs	Total (N=40) #(%) Subj	# AEs
MUSCULOSKELETAL SYSTEM	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
TENDON DISORDER	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
NERVOUS SYSTEM	2 (13.3%)	2	7 (46.7%)	14	5 (50.0%)	14	14 (35.0%)	30
ANXIETY	0 (0.0%)	0	0 (0.0%)	0	2 (20.0%)	2	2 (5.0%)	2
DIZZINESS	0 (0.0%)	0	4 (26.7%)	4	2 (20.0%)	2	6 (15.0%)	6
EMOTIONAL LABILITY	1 (6.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.5%)	1
INSOMNIA	0 (0.0%)	0	4 (26.7%)	4	4 (40.0%)	4	8 (20.0%)	8
NERVOUSNESS	0 (0.0%)	0	3 (20.0%)	3	3 (30.0%)	4	6 (15.0%)	7
PARESTHESIA	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
SOMNOLENCE	1 (6.7%)	1	1 (6.7%)	1	1 (10.0%)	1	3 (7.5%)	3
TREMOR	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
VERTIGO	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
RESPIRATORY SYSTEM	3 (20.0%)	5	2 (13.3%)	2	1 (10.0%)	3	6 (15.0%)	10
COUGH INCREASED	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
LUNG DISORDER	0 (0.0%)	0	1 (6.7%)	1	0 (0.0%)	0	1 (2.5%)	1
PHARYNGITIS	1 (6.7%)	1	0 (0.0%)	0	1 (10.0%)	1	2 (5.0%)	2
RHINITIS	3 (20.0%)	4	1 (6.7%)	1	1 (10.0%)	1	5 (12.5%)	6
SKIN AND APPENDAGES	1 (6.7%)	1	0 (0.0%)	0	1 (10.0%)	1	2 (5.0%)	2
RASH	1 (6.7%)	1	0 (0.0%)	0	1 (10.0%)	1	2 (5.0%)	2
UROGENITAL	0 (0.0%)	0	0 (0.0%)	0	2 (20.0%)	2	2 (5.0%)	2
ALBUMINURIA	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1
DYSMENORRHEA	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1	1 (2.5%)	1

Note: An AE is considered Treatment-Emergent if the start date occurs on or after the first dispensing day, otherwise it is considered Prior to Treatment. AEs with missing start dates are assumed to be Treatment-Emergent.

Source: \\QRTPNTFS3\SASDATA\SAS\SHIRE\DXA00072100\ANALYSIS\DOUBLE_BLIND\TABLELIB\T_AE_RAND.SAS, (b)(4) (US) 16-MAR-2004 09:47

Table 9. Spontaneously Reported Cases of Overdose on Adderall XR as of July, 2004

Subjects	Demographics and Doses	Symptoms & Signs	Outcome
US-02-044-00	A 10 year-old boy with diagnosis of ADHD, bipolar disorder NOS on Remeron 30mg/day, Wellbutrin SR 200mg/day and *Adderall XR 40mg/day*.	Tremor and hallucinations, angry	Continued on Adderall XR 40mg/day according to the report.
US-02-123-00	A 16 year-old male overdosed *a half bottle of 20mg of Adderall XR*. He was also on creatine and other unspecified over-the-counter products.	Psychosis (hallucinations)	Hospitalized for couple of days
US-02-296-00	A 16 year-old female patient was despondent and impulsively overdosed on *28 tablets of 20mg Adderall XR*. She was also on unspecified antidepressant.	Subsequent increased fidgeting, impulsivity, and clenching of the jaw.	Hospitalized in psychiatric hospital for a week after gastric lavage and treatment. Antidepressant was increased in the hospital.
US-02-323-00	A 12 year-old female took an overdose of 4 capsules of Adderall XR 20mg.	The sponsor reports this patient had "no symptoms".	Multiple follow-ups failed.
SUS1-2003-00072	A 19 year-old male with ADHD and a history of alcohol and substance abuse. He was on venlafaxine together with Adderall immediate release 10mg Bid. Possibly, he overdosed on Adderall 10mg tablets(of unspecified numbers) and other medications.	Amphetamine in the urine. Otherwise, no detailed description.	Admitted to the hospital.
SUS1-2003-00346	A 5 year-old boy had an overdose from a medication error by a pharmacy that filed the 5mg Adderall XR prescription with 30mg capsules. Thus, he took *30mg Adderall XR.*	Non-stop talking, stuttering, not eating stomach ache, rash on face, nervous, mood swings, and headache	Treated with valium in the hospital.
SUS1-2003-	A 17 year-old male overdosed on multiple drugs including	Pulmonary congestion, terminal aspiration of	Completed suicide

00510	Adderall XR, Seroquel, Lamotrigine, Effexor, carbamazepine, and sertraline in foster home. Some were prescribed but Adderall XR was given by a friend.	gastric contents, cerebral edema. Blood level of amephetamine at 2.2mcg/ml which is the only medication reached and was higher than its lethal level (1.0mcg/ml).	

10.2 Review of Individual Study Reports

Since there is only one efficacy study, it is integrated in the Section of Integrated Review of Efficacy.

10.3 Line-by-Line Labeling Review

The sponsor submits the annotated labeling in Vol. 4.2. The review of labeling here is focused on clinical aspect. Please see other disciplinary reviews for their comments.

1) In Vol 4.2, page 2-6, the sponsor inserts a section for adolescents, at the bottom of the page, in which it states, (b) (4) Next, a similar statement applied to the secondary cohort in the trial for receiving final doses of 50mg and 60mg Adderal XR for 4 weeks. (b) (4) .

2) Continuing on the next page, from lines 3-4, the sponsor states (b) (4) the sponsor must remove this sentence.

3) On page 2-12, the sponsor lists common adverse events in adolescents from this trial in Table 2. Even though it is a fixed dose study, the sponsor groups all Adderall XR dose groups together and compared with placebo group. In my opinion, the sponsor should separate the dose groups for these adverse events and compare them with the placebo group (b) (4) , as oppose to what the sponsor claimed that these are not meeting the criteria of being reported by 5% or more of adolescents weighing ≤ 75kg/165lbs in the trial.

All other clinically related changes are appropriate.

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

/s/

June Cai
2/24/05 04:58:00 PM
MEDICAL OFFICER

Paul Andreason
3/1/05 10:37:31 AM
MEDICAL OFFICER
I agree that this supplement is approvable. Please see my memo to the file dated March 1, 2005.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

CHEMISTRY REVIEW(S)

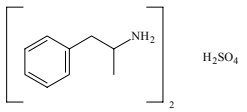
CHEMIST'S REVIEW OF SUPPLEMENT

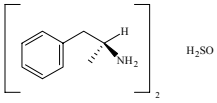
1. ORGANIZATION:	**HFD-120**
2. NDA NUMBER:	**21-303**
3. SUPPLEMENT NUMBER:	**SE5-009**
LETTER DATE	17-SEP-04
STAMP DATE	21-SEP-04
4. AMENDMENTS/REPORTS:	
LETTER DATE	N/A
STAMP DATE	N/A
5. RECEIVED BY CHEMIST:	05-OCT-04

6. APPLICANT NAME AND ADDRESS: Shire Laboratories Inc.
1801 Research Blvd, Suite 600
Rockville, MD 20850

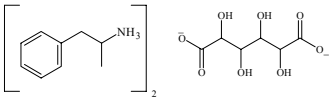
7. NAME OF DRUG: **ADDERALL XR®**

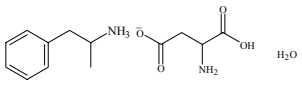
9. NONPROPRIETARY NAME: Amphetamine sulfate (USP) Dextroamphetamine sulfate (USP)





Dextroamphetamine saccharate Amphetamine aspartate monohydrate





10. CHEMICAL NAME / STRUCTURE: Amphetamine sulfate (USP) [(±)-α-methylphenethylamine sulfate (2:1)]; dextroamphetamine sulfate (USP) [(+)-α-methylphenethylamine sulfate (2:1)]

11. DOSAGE FORM(S): Capsules

12. POTENCIES: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, (b) (4)

13. PHARMACOLOGICAL CATEGORY: ADHD/Narcolepsy

14. HOW DISPENSED: **XX (Rx) (OTC)**

15. RECORDS / REPORTS CURRENT: **XX (YES) (NO)**

16. RELATED IND / NDA / DMF(S): N/A

17. CONSULT: None

SUPPLEMENT PROVIDES FOR: the treatment of adolescents with ADHD.

COMMENTS: Through this supplement, Shire is seeking approval for marketing ADDERALL XR® capsule for the treatment of adolescents (ages 13-17) with ADHD. The original submission of NDA 21-303, submitted 03-OCT-00 and approved 11-OCT-01, described three finished drug product strengths, ADDERALL XR® capsules, 10 mg, 20 mg, and 30 mg. NDA 21-303 Supplement 001, dated 26-OCT-01 and approved 22-MAY-02, described three additional finished product strengths, ADDERALL XR® capsules, 5 mg, 15 mg, and 25 mg. NDA 21-303 Supplement 005 submitted on18-DEC-02 and approved on 11-AUG-04 for the treatment of ADHD in adults (b) (4) (b) (4) The applicant provided information on chemistry, manufacturing, and controls to support the ADDERALL XR® Capsules used in clinical studies in adolescents. These trials were conducted with three of the approved strengths – 10 mg, 20 mg, and 30 mg capsules. All the CMC information regarding the drug substance and drug product sections remains unchanged from the approved NDA 21-303 for this efficacy supplement.

CONCLUSIONS AND RECOMMENDATIONS: Based on the information provided, this supplement is recommended for **APPROVAL** from a CMC perspective.

REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
Chhagan G. Tele, Ph.D.		December 23, 2004

cc: Orig.; NDA 21-303
HFD-120/Div. File
HFD-120/PM/RTaylor
HFD-120/CTele
INIT: TOliver

Filename: s21-303.009

REVIEW NOTES:

1/ 2. DRUG SUBSTANCE and DRUG PRODUCT

Shire states that the drug substance (active pharmaceutical ingredients: Amphetamine sulfate, Amphetamine aspartate monohydrate, Dextroamphetamine saccharate (b) (4), and Dextroamphetamine sulfate USP), and drug product used in adolescent patients with ADHD were identical to the marketed formulations of ADDERALL XR® Capsules.

Evaluation: Acceptable, since the ADHD clinical studies used marketed formulations of ADDERALL XR® Capsules, which are approved in NDA 21-303 and its supplements.

3. PACKAGE INSERT AND LABELING

No changes are reported for the **DESCRIPTION** and **HOW SUPPLIED** sections of the label.

Evaluation: Acceptable, since no changes in indication (ADHD) was reported.

4. ENVIRONMENTAL ASSESSMENT

Shire requested for a categorical exclusion in accordance with 21 CFR Part 25.31(b). Shire claims that
the Expected Introduction Concentration (EIC) of drug substance(s) at the point of entry in the aquatic environment will be 1 ppb in the fifth year of marketing after approval. Further, Shire claims that to the best of its knowledge no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

Evaluation: Acceptable. Based on 21 CFR 25.31(b) a categorical exclusion is granted since the concentration of the APIs will be less than 1 ppb.

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

/s/

Chhagan Tele
12/23/04 08:27:06 AM
CHEMIST

Thomas Oliver
12/23/04 08:39:57 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-303/S-009
Drug Name:	Adderall XR ® (SLI381)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Shire Laboratories
Date:	9/17/2004
Review Priority:	Priority
Biometrics Division:	I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader James Hung, Ph.D., Acting Deputy Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	June Cai, M.D., Clinical Reviewer Paul Andreason, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Richardae Taylor, Pharm D.

Keywords: ANCOVA, ADHD, Adderall XR

TABLE OF CONTENTS

Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

The conclusion is that the primary analysis for the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the intent-to-treat (ITT) population is significant comparing Adderall XR (10mg/day to 40 mg/day) and placebo in the treatment of adolescents, age 13-17 and weight less than or equal to 75 kg/165 lbs, with Attention Deficit Hyperactivity Disorder (ADHD).

1.2 Brief Overview of Clinical Studies

This was a randomized, double-blind, placebo-controlled trial conducted in 50 centers in USA, evaluating the use of Adderall XR (10mg/day to 40 mg/day) in subjects (age 13-17) with Attention Deficit Hyperactivity Disorder (ADHD). The trial had one 4-week double-blind treatment phase, and followed by a 6-month open-label phase. The primary cohort (designed for the primary objective) consisted of subjects whose weights were less than or equal to 75 kg/165 lbs, and secondary cohort (designed for secondary objective and exploratory analysis) consisted of subjects whose weights were greater than 75 kg/165 lbs. A total of 329 subjects enrolled in the study, and resulted 327 randomized to the double-blind phase. ITT included 287 subjects in the primary cohort, and 40 subjects in the secondary cohort. The primary efficacy endpoint was the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the ITT population. The primary analysis was ANCOVA model with terms for treatment, site, and the corresponding baseline score as the covariate. A closed-testing procedure starting from the highest dose is used to compare each active dose vs. placebo.

1.3 Statistical Issues and Findings

The primary analysis showed that there was a significant difference in favor of Adderall XR, compared to placebo, for the mean change in ADHD-RS-IV from baseline at Week 4 LOCF in the ITT population. Detailed statistics are presented in the following table.

Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	-9.4 (10.6)	-14.9 (12.1)	-20.7 (11.2)	-19.0 (11.1)	-16.5 (11.6)
LS mean difference	--	-5.59	-12.23	-9.23	-8.49
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

2. Introduction

2.1 Overview

Adderall XR is a once-daily, extended-release, single-entity amphetamine produce. Adderall XR was approved by the Agency in 2001 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 and older. Much of the current ADHD literature focuses on school age children (6-12 years old) and there is very limited scientific literature that specifically examines the safety and efficacy of amphetamines in the treatment of adolescents with ADHD.

In this submission, a trial completed was a randomized, double-blind, placebo-controlled conducted in 50 centers in USA, evaluating the use of Adderall XR (10mg/day to 40 mg/day) in subjects (age 13-17) with Attention Deficit Hyperactivity Disorder (ADHD). The trial had one 4-week double-blind treatment phase, and followed by a 6-month open-label phase. The primary cohort (designed for the primary objective) consisted of subjects whose weights were less than or equal to 75 kg/165 lbs, and secondary cohort (designed for secondary objective and exploratory analysis) consisted of subjects whose weights were greater than 75 kg/165 lbs. A total of 329 subjects enrolled in the study, and resulted 327 randomized to the double-blind phase. ITT included 287 subjects in the primary cohort, and 40 subjects in the secondary cohort. The primary efficacy endpoint was the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the ITT population. The primary analysis was ANCOVA model with terms for treatment, site, and the corresponding baseline score as the covariate. A closed-testing procedure starting from the highest dose is used to compare each active dose vs. placebo.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

\\Cdsesub1\n21303\S_009\2004-09-17
\\Cdsesub1\n21303\S_009\2004-10-27
\\Cdsesub1\n21303\S_009\2004-10-29

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Texts, tables, and graphs in Sections 3.1.1 – 3.1.7 are mainly adapted from the Applicant's Study Report.

3.1.1 Objective

The primary objective of this study was to assess, under controlled conditions, the safety and efficacy of ADERALL XR (10mg/day to 40 mg/day) compared to placebo in the treatment of adolescents (age 13-17, weighing less than or equal to 75 kg/165 lbs) with ADHD, based on the clinician administered ADHD-Rating Scale (ADHD-RS-IV).

Secondary objective includes to assess the safety and efficacy of ADERALL XR (50mg/day to 60 mg/day) compared to placebo in the treatment of adolescents (age 13-17, weighing over 75 kg/165 lbs) with ADHD, based on the clinician administered ADHD-Rating Scale (ADHD-RS-IV).

3.1.2 Study Design

This study consisted of two parts, Part A and Part B. Part A was a randomized, double-blind, multicenter, placebo-controlled, forced dose titration phase in which subjects took study drug in a blinded fashion for approximately 4 weeks. Part B was a 6-month open-label extension involving subjects from Part A to continue to assess the safety of various doses. This report describes results of Part A only.

There were 2 cohorts of subjects aged 13-17 years old (inclusive): those weighing less than or equal to 75 kg/165 lbs (primary cohort) and those weighing greater than 75 kg/165 lbs 9secondary cohort). The evaluation of the efficacy and safety in both cohorts will be run in parallel.

Approximately 225 subjects weighing less than or equal to 75 kg/165 lbs were to be randomized in a 1:1:1:1:1 ratio (Adderall XR 10 mg, 20 mg, 30 mg, 40 mg, or placebo). All subjects had 10 mg for Week 1, and increased 10 mg each week until reach their object dose level. Approximately 30 subjects weighing greater than 75 kg/165 lbs were to be randomized in a 1:1:1 ratio (Adderall XR 50 mg, 60 mg, or placebo). Subjects in 50 mg group started 20 mg for Week 1, and increased 10 mg each week. Subjects in 60 mg group started 20 mg for Week 1, 40 mg for Week 2, 50 mg for Week 3, and 60 mg for Week 4. The treatment phase lasted approximately 4 weeks. Visits were scheduled 7 days apart during the treatment phase.

3.1.3 Efficacy Measures

The primary efficacy measure was ADHD-RS-IV total score. This rating scale is based on a clinician administered semi-structured interview with the subject's parent (or primary caregiver) and the subject at each applicable visit, beginning with the baseline visit, to capture the ADHA symptoms within each study week. The ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV criteria. Each item is scored from a range of zero (reflecting no symptoms) to three (reflecting severe symptoms) with total scores ranging from 0 to 54.

The primary endpoint was defined as the change from baseline on the ADHD-RS-IV total score at the last treatment week of double-blind treatment phase.

Secondary efficacy measures included the CGI-I (CGI-improvement) rating scale. Rating was completed with respect to ADHD symptoms relative to the baseline.

3.1.4 Statistical Analysis Plan

The primary analysis was a two-way analysis of covariance (ANCOVA) model with terms for treatment of each active dose vs. placebo, site, and the corresponding baseline score as the covariate, using ITT population. A closed-testing procedure starting from the highest dose is used.

The subject's score on CGI-I was dichotomized into two categories, with "very much improved" and "much improved" going into one category (improved) and the rest into the other category (not improved) prior to analysis. The dichotomized CGI-I was analyzed using a CMH test adjusting for study site between active doses combined vs. placebo. The significant treatment effect of each active dose vs. placebo was based on a closed-testing procedure starting from the highest dose.

3.1.5 Protocol Amendments and Deviations

There was one amendment to the final statistical analysis plan issued on July 14, 2003. The amendment was issued on December 5, 2003 and implemented the following changes: described how sites would be pooled; indicated that the overall test of all active vs. placebo did not need to be significant before each dose was compared to placebo; added efficacy analyses for subjects with low and high baseline ADHD severity both by intended dose and final dose; and added the qualitative, categorized analysis of vital signs and ECG parameters.

3.1.6 Study Population

A total of 329 subjects were enrolled in the study. Two subjects terminated prior to randomization and thus, 327 subjects were randomized. Of these, 287 were in the primary cohort and 40 were in the secondary cohort.

The disposition of all patients randomized in the study for the primary cohort is presented in Table 3.1.6.1.

Table 3.1.6.1 Disposition of Patients (Primary Cohort)

	Placebo	10 mg	20 mg	30 mg	40 mg	Total
Enrolled	54	56	56	58	63	287
Randomized	54	56	56	58	63	287
ITT	52 (96.3%)	54 (96.4%)	53 (94.6%)	58 (100%)	61 (96.8%)	278 (96.9%)
Primary reason for discontinuation						
Adverse event(s)	0	1 (1.8%)	1 (1.8%)	1 (1.7%)	2 (3.2%)	5 (1.7%)
Protocol violation	1 (1.9%)	3 (5.4%)	0	0	1 (1.6%)	5 (1.7%)
Withdrew consent	0	2 (3.6%)	2 (3.6%)	1 (1.7%)	5 (7.9%)	10 (3.5%)
Lost to follow-up	2 (3.7%)	1 (1.8%)	1 (1.8%)	1 (1.7%)	1 (1.6%)	6 (2.1%)
Other	1 (1.9%)	0	1 (1.8%)	0	1 (1.6%)	3 (1.0%)

The demographic and other baseline characteristics for the primary cohort are presented by in Table 3.1.6.2.

Table 3.1.6.2 Demographic and Baseline of the Primary Cohort (All Randomized)

Parameter	Placebo (N=54)	10 mg (N=56)	20 mg (N=56)	30 mg (N=58)	40 mg (N=63)	Total (N=287)
Age (years)						
Mean (SD)	14.5 (1.3)	14.4 (1.2)	14.3 (1.2)	14.2 (1.2)	14.0 (1.2)	14.2 (1.2)
Age category						
13-14	32 (59.3%)	30 (53.6%)	37 (66.1%)	37 (63.8%)	46 (73.0%)	182 (63.4%)
15-17	22 (40.7%)	26 (46.4%)	19 (33.9%)	21 (36.2%)	17 (27.0%)	105 (36.6%)
Gender						
Male	36 (66.7%)	35 (62.5%)	38 (67.9%)	38 (65.5%)	40 (63.5%)	187 (65.2%)
Female	18 (33.3%)	21 (37.5%)	18 (32.1%)	20 (34.5%)	23 (36.5%)	100 (34.8%)
Ethnic origin						
White	40 (74.1%)	40 (71.4%)	42 (75.0%)	43 (74.1%)	49 (77.8%)	214 (74.6%)
Black	11 (20.4%)	10 (17.9%)	9 (16.1%)	8 (13.8%)	6 (9.5%)	44 (15.3%)
Hispanic	3 (5.6%)	2 (3.6%)	3 (5.4%)	5 (8.6%)	6 (9.5%)	19 (6.6%)
Asian or Pacific Islander	0	0	0	0	0	0
Native American	0	2 (3.6%)	0	0	2 (3.2%)	4 (1.4%)
Other	0	2 (3.6%)	2 (3.6%)	2 (3.4%)	0	6 (2.1%)
Weight at baseline (lb)	131.5	125.9	125.3	128.6	125.3	127.2
Mean (SD)	(18.1)	(22.2)	(20.4)	(18.8)	(22.3)	(20.5)
Height at screening (inches)	65.5	64.2	64.5	64.1	64.4	64.5
Mean (SD)	(3.6)	(3.6)	(3.7)	(3.1)	(3.6)	(3.5)
BMI at baseline	21.6	21.4	21.2	22.0	21.1	21.4
Mean (SD)	(2.8)	(2.6)	(2.9)	(2.9)	(2.6)	(2.8)
Type of ADHD						
Inattentive	24 (44.4%)	20 (35.7%)	25 (44.6%)	20 (34.5%)	26 (41.3%)	115 (40.1%)
Hyperactive/Impulsive	0	4 (7.1%)	2 (3.6%)	1 (1.7%)	2 (3.2%)	9 (3.1%)
Combined	30 (55.6%)	32 (57.1%)	29 (63.8%)	37 (63.8%)	35 (55.6%)	163 (56.8%)
Years since ADHD diagnosis: Mean (SD)	4.35 (4.16)	5.44 (3.97)	5.11 (4.41)	4.87 (4.12)	5.76 (4.07)	5.13 (4.14)
Number of subjects with recent prior ADHD treatment	7 (13.0%)	6 (10.7%)	13 (23.2%)	16 (27.6%)	17 (27.0%)	59 (20.6%)

The disposition of all patients randomized in the study for the secondary cohort is presented in Table 3.1.6.3, and the demographic and other baseline characteristics for the secondary cohort are presented by in Table 3.1.6.4, respectively.

Table 3.1.6.3 Disposition of Patients (Secondary Cohort)

	Placebo	50 mg	60 mg	Total
Enrolled	15	15	10	40
Randomized	15	15	10	40
ITT	15 (100%)	15 (100%)	10 (100%)	40 (100%)
Primary reason for discontinuation				
Adverse event(s)	0	2 (13.3%)	1 (10%)	3 (7.5%)
Lost to follow-up	1 (6.7%)	0	0	1 (2.5%)

Table 3.1.6.4 Demographic and Baseline of the Secondary Cohort (ITT)

Parameter	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)	Total (N=40)
Age (years)				
Mean (SD)	15.3 (1.2)	15.4 (1.4)	15.4 (1.2)	15.4 (1.2)
Age category				
13-14	4 (26.7%)	6 (40.0%)	3 (30.0%)	13 (32.5%)
15-17	11 (73.3%)	9 (60.0%)	7 (70.0%)	27 (67.5%)
Gender				
Male	14 (93.3%)	14 (93.3%)	8 (80.9%)	36 (90.0%)
Female	1 (6.7%)	1 (6.7%)	2 (20.0%)	4 (10.0%)
Ethnic origin				
White	9 (60.0%)	11 (73.3%)	6 (60.0%)	26 (65.0%)
Black	4 (26.7%)	1 (6.7%)	2 (20.0%)	7 (17.5%)
Hispanic	2 (13.3%)	2 (13.3%)	2 (20.0%)	6 (15.0%)
Asian or Pacific Islander	0	0	0	0
Native American	0	1 (6.7%)	0	1 (2.5%)
Weight at baseline (lb)	190.5	189.6	191.1	190.3
Mean (SD)	(35.2)	(22.1)	(15.0)	(26.0)
Height at screening (inches)	68.7	71.1	69.3	69.8
Mean (SD)	(3.0)	(2.6)	(3.5)	(3.1)
BMI at baseline	28.4	26.4	28.0	27.5
Mean (SD)	(4.9)	(2.9)	(2.2)	(3.7)
Type of ADHD				
Inattentive	6 (40.0%)	8 (53.3%)	3 (30.0%)	17 (42.5%)
Combined	9 (60.0%)	7 (46.7%)	7 (70.0%)	23 (57.5%)
Years since ADHD diagnosis: Mean (SD)	4.84 (5.19)	8.67 (4.03)	6.34 (4.62)	6.65 (4.83)
Number of subjects with recent prior ADHD treatment	2 (13.3%)	4 (26.7%)	1 (10.0%)	7 (17.5%)

3.1.7 Applicant's Efficacy Results

The primary analysis was a two-way analysis of covariance (ANCOVA) model with terms treatment of each active dose vs. placebo, site, and the corresponding baseline score as the covariate, using ITT population. A closed-testing procedure starting from the highest dose is used.

Table 3.1.7.1 presents the primary analyses results of the primary cohort at Week 4 LOCF.

Table 3.1.7.1 Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	-9.4 (10.6)	-14.9 (12.1)	-20.7 (11.2)	-19.0 (11.1)	-16.5 (11.6)
LS mean difference	--	-5.59	-12.23	-9.23	-8.49
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

P-values in the last row in the above table are for each pair's comparisons with placebo.

Table 3.1.7.2 presents the primary analyses results of the primary cohort at Week 4 OC.

Table 3.1.7.2 Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-OC)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint at Week 4					
N	50	49	50	55	53
Mean (SD)	25.5 (13.2)	19.3 (11.7)	13.1 (10.1)	15.6 (10.9)	15.7 (11.6)
Mean change (SD)	-9.6 (10.2)	-16.0 (12.0)	-20.8 (11.2)	-19.7 (10.8)	-17.3 (11.4)
LS mean difference	--	-6.23	-12.05	-9.21	-8.31
(95% CI)	--	(-10.11, -2.34)	(-15.91, -8.19)	(-13.02, -5.41)	(-12.15, -4.47)
p-value	--	0.0018	<0.0001	<0.0001	<0.0001

Secondary efficacy measures include the dichotomized CGI-I ("improved", or "not improved"). CMH test adjusting for study site between active doses combined vs. placebo was analysis for the dichotomized CGI-I.

Table 3.1.7.3 presents the analyses results of the dichotomized CGI-I at Week 4 LOCF.

Table 3.1.7.3 Analyses of CGI-I in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)	10-40 mg (N=226)
Dichotomized CGI-I						
Improvement	14 (26.9%)	28 (51.9%)	35 (66.0%)	41 (70.7%)	39 (63.9%)	143 (63.3%)
No improvement	38 (73.1%)	26 (48.1%)	18 (34.0%)	17 (29.3%)	22 (36.1%)	83 (36.7%)
Difference in % with improvement in active group vs. placebo	--	24.9%	39.1%	43.8%	37.0%	36.4%
p-value	--	0.0098	0.0002	<0.0001	0.0001	<0.0001

Table 3.1.7.4 presents the analyses results of the dichotomized CGI-I at Week 4 OC.

Table 3.1.7.4 Analyses of CGI-I in the Primary Cohort (ITT-OC)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)	10-40 mg (N=226)
Dichotomized CGI-I						
N	50	49	50	55	53	207
Improvement	13 (26.0%)	28 (57.1%)	35 (70.0%)	39 (70.9%)	36 (67.9%)	138 (66.7%)
No improvement	37 (74.0%)	21 (42.9%)	15 (30.0%)	16 (29.1%)	17 (32.1%)	69 (33.3%)
Difference in % with improvement in active group vs. placebo	--	31.1%	44.0%	44.9%	41.9%	40.7%
p-value	--	0.0043	0.0001	<0.0001	0.0001	<0.0001

The following tables present results for the secondary cohort. Table 3.1.7.5 presents the analyses results of the secondary cohort at Week 4 LOCF.

Table 3.1.7.5 Analyses of ADHD-RS-IV Total Score in the Secondary Cohort (ITT-LOCF)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)
Baseline			
Mean (SD)	35.7 (8.7)	30.4 (10.2)	32.3 (8.6)
Endpoint			
Mean (SD)	23.1 (13.1)	13.5 (8.9)	18.3 (11.5)
Mean change (SD)	-12.5 (10.1)	-16.9 (12.4)	-14.0 (12.5)
LS mean difference	--	-5.63	-1.41
(95% CI)	--	(-17.08, 5.83)	(-13.97, 11.15)
p-value	--	0.3145	0.8156

Table 3.1.7.6 presents the analyses results of the secondary cohort at Week 4 OC.

Table 3.1.7.6 Analyses of ADHD-RS-IV Total Score in the Secondary Cohort (ITT-OC)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)
Baseline			
Mean (SD)	35.7 (8.7)	30.4 (10.2)	32.3 (8.6)
Endpoint at Week 4			
N	14	13	9
Mean (SD)	22.6 (13.4)	14.3 (9.2)	17.3 (11.8)
Mean change (SD)	-12.6 (10.4)	-15.9 (12.8)	-15.8 (11.9)
LS mean difference	--	-3.24	-1.20
(95% CI)	--	(-16.06, 9.58)	(-15.88, 13.48)
p-value	--	0.5943	0.8626

Table 3.1.7.7 presents the analyses results of the dichotomized CGI-I at Week 4 LOCF.

Table 3.1.7.7 Analyses of CGI-I in the Secondary Cohort (ITT-LOCF)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)	50-60 mg (N=25)
Dichotomized CGI-I				
Improvement	7 (46.7%)	11 (73.3%)	6 (60.0%)	17 (68.0%)
No improvement	8 (53.3%)	4 (26.7%)	4 (40.0%)	8 (32.0%)
Difference in % with improvement in active group vs. placebo	--	26.7%	13.3%	21.3%
p-value	--	0.7316	0.4328	0.4072

Table 3.1.7.8 presents the analyses results of the dichotomized CGI-I at Week 4 OC.

Table 3.1.7.8 Analyses of CGI-I in the Secondary Cohort (ITT-OC)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)	50-60 mg (N=25)
Dichotomized CGI-I				
N	14	13	9	22
Improvement	7 (50.0%)	9 (69.2%)	6 (66.7%)	15 (68.2%)
No improvement	7 (50.0%)	4 (30.8%)	3 (33.3%)	7 (31.8%)
Difference in % with improvement in active group vs. placebo	--	19.2%	16.7%	18.2%
p-value	--	1.0000	0.3173	0.6473

3.1.8 Reviewer's Analysis

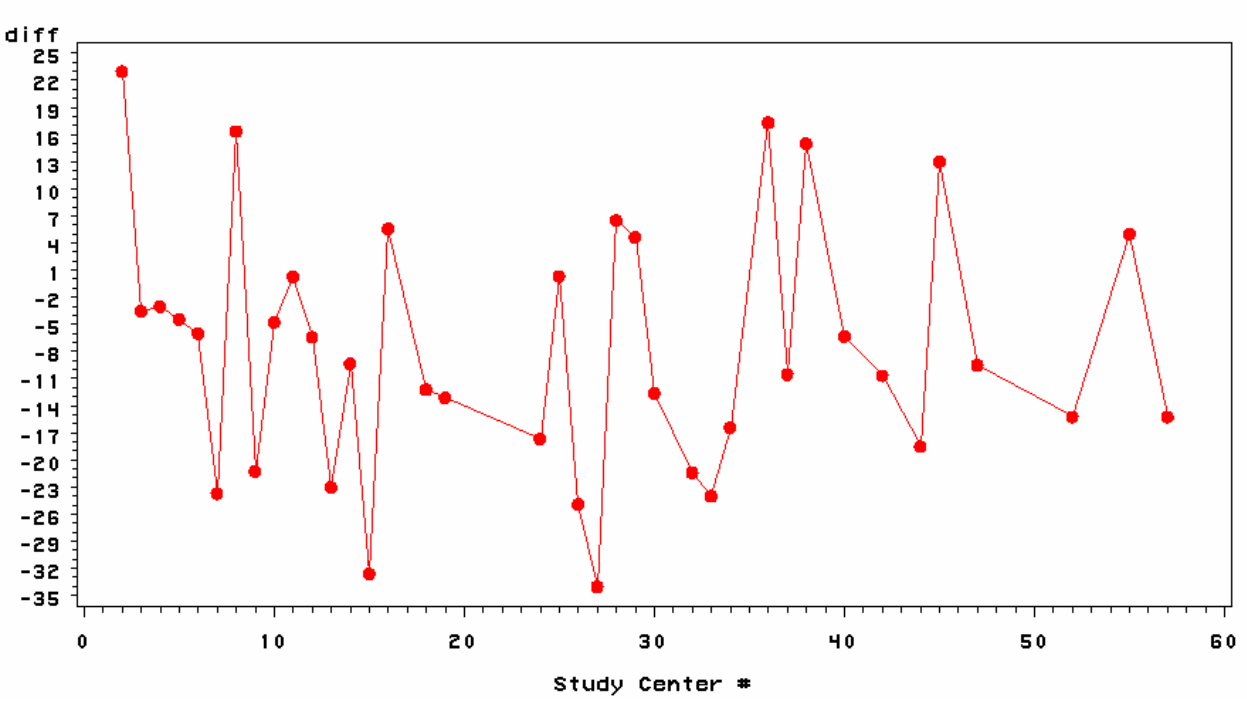
The reviewer validated the sponsor's analysis according to the protocol.

Wilcoxon two-sample test gives p-values .0231 for 10 mg vs. placebo, .0001 for 20 mg vs. placebo, .0001 for 30 mg vs. placebo, and .0018 for 40 mg vs. placebo, respectively.

Table 3.1.8.1 presents difference of the mean change in ADHD-RS-IV at Week 4 LOCF by center.

Table 3.1.8.1 Mean Change of ADHD-RS_IV by Center for Primary Cohort (ITT-LOCF)

Obs	CENTER	n_t	mean_t	n_p	mean_p	diff
1	2	1	-3.0000	1	-26.0000	23.0000
2	3	10	-14.2000	3	-10.6667	-3.5333
3	4	12	-10.3333	3	-7.3333	-3.0000
4	5	7	-9.4286	1	-5.0000	-4.4286
5	6	2	-14.0000	1	-8.0000	-6.0000
6	7	7	-21.7143	1	2.0000	-23.7143
7	8	8	-7.6250	1	-24.0000	16.3750
8	9	4	-18.2500	1	3.0000	-21.2500
9	10	4	-25.7500	1	-21.0000	-4.7500
10	11	7	-27.7143	2	-28.0000	0.2857
11	12	5	-27.4000	1	-21.0000	-6.4000
12	13	1	-27.0000	1	-4.0000	-23.0000
13	14	7	-23.8571	2	-14.5000	-9.3571
14	15	5	-20.6000	1	12.0000	-32.6000
15	16	7	-10.4286	1	-16.0000	5.5714
16	18	7	-16.7143	2	-4.5000	-12.2143
17	19	8	-16.6250	2	-3.5000	-13.1250
18	20	5	-29.0000	.	.	.
19	21	3	-11.3333	.	.	.
20	22	2	-7.5000	.	.	.
21	24	3	-8.6667	1	9.0000	-17.6667
22	25	3	-18.6667	1	-19.0000	0.3333
23	26	12	-25.9167	3	-1.0000	-24.9167
24	27	2	-31.0000	1	3.0000	-34.0000
25	28	2	-12.5000	1	-19.0000	6.5000
26	29	8	-16.3750	2	-21.0000	4.6250
27	30	5	-11.6000	1	1.0000	-12.6000
28	32	5	-22.4000	1	-1.0000	-21.4000
29	33	3	-22.0000	1	2.0000	-24.0000
30	34	5	-18.4000	2	-2.0000	-16.4000
31	36	3	-11.6667	1	-29.0000	17.3333
32	37	13	-15.5385	3	-5.0000	-10.5385
33	38	1	-1.0000	1	-16.0000	15.0000
34	40	3	-13.3333	1	-7.0000	-6.3333
35	41	1	-15.0000	.	.	.
36	42	3	-19.6667	1	-9.0000	-10.6667
37	44	4	-32.5000	1	-14.0000	-18.5000
38	45	4	-19.0000	1	-32.0000	13.0000
39	46	3	-30.6667	.	.	.
40	47	6	-15.5000	1	-6.0000	-9.5000
41	48	2	-20.0000	.	.	.
42	49	5	-13.2000	.	.	.
43	50	1	-8.0000	.	.	.
44	51	3	-19.6667	.	.	.
45	52	4	-13.2500	1	2.0000	-15.2500
46	54	2	-17.5000	.	.	.
47	55	2	-14.0000	1	-19.0000	5.0000
48	56	2	-30.0000	.	.	.
49	57	4	-21.2500	1	-6.0000	-15.2500



After removing both centers 15 and 27, ANCOVA (combined active doses vs. placebo) gives p-value .0001.

3.2 Evaluation of Safety

See Clinical Review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Since the Study was not powered for subgroup analyses, analytical analysis is not performed. Table 4.1.1 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by gender for ITT population.

Table 4.1.1 Mean Change from Baseline in ADHD-RS-IV in the Primary Cohort by Gender

Gender	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Male	35	33	37	38	39
Baseline	35.5	36.7	33.6	36.3	33.9
Endpoint	27.6	18.9	13.2	16.5	16.6

Mean Change	-7.9	-17.8	-20.4	-19.8	-17.3
Female	17	21	16	20	22
Baseline	34.4	32.1	34.7	32.8	30.1
Endpoint	21.9	21.7	13.3	15.3	15.0
Mean Change	-12.4	-10.4	-21.4	-17.5	-15.1

Except for female in 10 mg group, subjects in all other Adderall XR groups had more changes than those in placebo group.

Table 4.1.2 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by age for ITT population. Subjects in all Adderall XR groups had more changes than those in placebo group.

Table 4.1.2 Change from Baseline in ADHD-RS-IV in the Primary Cohort by Age

Age	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
13-14	31	30	37	37	44
Baseline	36.1	36.6	35.9	36.0	32.3
Endpoint	28.1	19.4	14.6	15.9	16.3
Mean Change	-8.0	-17.2	-21.4	-20.1	-16.0
15-17	21	24	16	21	17
Baseline	33.6	32.8	29.3	33.6	33.2
Endpoint	22.3	20.8	10.2	16.4	15.3
Mean Change	-11.3	-12.1	-19.1	-17.2	-17.9

Table 4.1.3 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by race (white vs. non-white) for ITT population. Subjects in all Adderall XR groups had more changes than those in placebo group.

Table 4.1.3 Change from Baseline in ADHD-RS-IV in the Primary Cohort by Race

Race	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
White	38	38	39	43	47
Baseline	33.2	35.5	33.2	35.2	31.4
Endpoint	21.9	19.4	12.6	16.3	15.2
Mean Change	-11.3	-16.1	-20.6	-19.0	-16.2
Non-White	14	16	14	15	14
Baseline	40.1	33.5	35.9	34.7	36.5
Endpoint	36.1	21.5	15.1	15.5	18.9
Mean Change	-4.0	-12.0	-20.9	-19.2	-17.6

4.2 Other Special/Subgroup Populations

Table 4.2.1 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by type of ADHD for ITT population. Since the Study was not powered for subgroup analyses, analytical analysis is not performed. Subjects in all Adderall XR groups had more changes than those in placebo group.

Table 4.2.1 Change from Baseline in ADHD-RS-IV in the Primary Cohort by Type of ADHD

Type of ADHD	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Inattentive	23	20	25	20	26
Baseline	29.7	29.3	29.3	29.4	26.3
Endpoint	18.4	14.9	10.9	14.1	12.5
Mean Change	-11.3	-14.4	-18.4	-15.3	-13.8
Hyperactive/Impulsive or combine	29	34	28	38	35
Baseline	39.3	38.2	38.1	38.1	37.3
Endpoint	31.6	23.0	15.4	17.1	18.7
Mean Change	-7.7	-15.2	-22.7	-21.0	-18.6

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary analysis showed that there was a significant difference in favor of Adderall XR, compared to placebo, for the mean change in ADHD-RS-IV from baseline at Week 4 LOCF in the ITT population, and there was a significant difference in favor of Adderall XR for the proportion of subjects with a score of much improved or very much improved on the CGI-I at Week 4 LOCF. Detailed statistics are presented in the following tables.

Table 5.1.1 Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	-9.4 (10.6)	-14.9 (12.1)	-20.7 (11.2)	-19.0 (11.1)	-16.5 (11.6)
LS mean difference	--	-5.59	-12.23	-9.23	-8.49
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

Table 5.1.2 Analyses of CGI-I in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)	10-40 mg (N=226)
Dichotomized CGI-I						
Improvement	14 (26.9%)	28 (51.9%)	35 (66.0%)	41 (70.7%)	39 (63.9%)	143 (63.3%)
No improvement	38 (73.1%)	26 (48.1%)	18 (34.0%)	17 (29.3%)	22 (36.1%)	83 (36.7%)
Difference in % with improvement in active group vs. placebo	--	24.9%	39.1%	43.8%	37.0%	36.4%
p-value	--	0.0098	0.0002	<0.0001	0.0001	<0.0001

5.2 Conclusions and Recommendations

The conclusion is that the primary analysis for the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the ITT population is significant comparing Adderall XR (10mg/day to 40 mg/day) and placebo in the treatment of adolescents, age 13-17 and weight less than or equal to 75 kg/165 lbs, with Attention Deficit Hyperactivity Disorder (ADHD). The analysis for the dichotomized CGI-I is also significant in favor of Adderall XR for the proportion of subjects with a score of much improved or very much improved at Week 4 LOCF.

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/s/

Kun He
2/17/05 10:02:04 AM
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Kun Jin
2/17/05 02:44:28 PM
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James Hung
2/17/05 02:55:48 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Supplemental New Drug Application
Efficacy Supplement – Response to Approvable Letter
OCPB Review

NDA:	21-303
Serial Number:	SE5-009
Type of Submission:	Response to Approvable Letter
Generic Name:	Mixed Salts of a Single-Entity Amphetamine Product Extended Release Capsules
Brand Name:	Adderall XR
Formulation(s); Strength(s); Route(s)	Capsules 5, 10, 15, 20, 25, 30 mg po
Sponsor:	Shire Laboratories Rockville, MD
Submission Dates:	May 27, 2005
Consult Request Date:	June 14, 2005
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Team Leader	Raman Baweja, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
ORM Division	Division of Neuro-psychiatric Drug Products (DNPDP) HFD-120
Indication:	ADHD in Adolescents (13 – 17 years old)

1 BACKGROUND

This submission is a response to an approvable letter for the treatment of ADHD in Adolescents dated March 15, 2005.This letter outlined a number of deficiencies that had to be addressed prior to approval. For Clinical Pharmacology and Biopharmaceutics the following single deficiency was listed:

> **Clinical Pharmacology & Biopharmaceutics**
>
> The metabolic pathways of amphetamine are not described in the labeling of Adderall. Although there appears to be a role for CYP2D6, amphetamine metabolism has not been well characterized in the literature. We recommend that in *vitro* studies be performed to characterize the metabolic pathways and specific enzymes involved in the metabolism of Adderall. This type of information will determine the importance of specific pathways and the potential for drug interactions mediated by these pathways and will help determine the necessity for *in vivo* evaluation. Similarly, it would be useful to characterize the effect of Adderall on drug metabolizing enzymes. For guidance, you can refer to the Draft Preliminary Concept Paper "Drug Interaction Studies – Study design, data Analysis, and Implications for Dosing and Labeling" (http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1_04_Topic2-TabA.pdf).

The present submission responds to this deficiency.

2 OCPB REVIEW AND FINDINGS

The sponsor submitted a copy of the November 2004 draft report entitled: **'NTP-CERHR EXPERT PANEL REPORT on the REPRODUCTIVE and DEVELOPMENTAL TOXICITY of AMPHETAMINE AND METHAMPHETAMINE'** from the US Department of Health and Human Services National Toxicology Program as well as

In addition, the sponsor submitted the results of two sets of *in vitro* experiments to

a) Examine whether *l*- and *d*-amphetamine is metabolized by human and rat hepatic microsomes.

b) Examine the inhibitory potential of *l-, d-,* and *d,l*-amphetamine on CYP1A2, 2C9, 2C19, 2D6, and 3A4/5.

2.1 REVIEW OF HUMAN MICROSOMAL INCUBATIONS

For human microsomal incubations both *d*- and *l*- amphetamine were incubated at concentrations of 10 μM, which is several fold greater than the *in vivo* peak concentrations of 1.5 μM. Under these conditions approximately 12% of *l*- and *d*-amphetamine was metabolized, and enzyme activity decreased after 15 minutes.

The results of these experiments indicate that amphetamine is metabolized by P450s although the short duration of enzyme activity indicates the possibility of auto-inhibition probably by a metabolite. This might also be exacerbated by the high concentrations used. In addition, the similar extent of metabolism in the presence of active glucuronidases is not surprising as amphetamine would need to be oxidized prior to glucuronidation. Thus no conclusions regarding the extent of oxidation by P450s or metabolism by glucuronidases can be made from these experiments.

2.2 REVIEW OF CYP ISOZYME INHIBITORY POTENTIAL

Table 1 shows the results of *in vitro* CYP isozyme inhibition experiment with amphetamine for 5 CYP isozymes. These experiments were carried out using probe substrate concentrations equal to the substrate's Km and amphetamine concentrations approximately 100 fold greater than *in vivo* peak concentrations.

CYP2D6 was inhibited 13.1% by amphetamine under these conditions. Estimations based on expected *in vivo* concentrations suggest that the degree of inhibition for each of these isozymes is less than 1% by amphetamine itself.

Pre-incubation with amphetamine resulted in inhibition of CYP1A2, 2D6 and 3A4/5 indicating that one or more metabolites of amphetamine might inhibit these isozymes. Although inhibition in the possible presence of metabolites did not result in much greater inhibition, since we don't know the concentration of these metabolites under these experimental conditions compared with *in vivo* conditions and since auto-inhibition is a distinct possibility based on the microsomal experiments, the degree of inhibition *in vivo* for any of these isozymes cannot be predicted.

Table 1 Summary of In Vitro P450 Inhibition Studies Estimated Extent of In Vivo Inhibition by OCPB Reviewer

Inhibitor	% Inhibition					
	1A2	2C9	2C19	2D6	3A4/5	
					6β-hydroxylase	Midazolam 1-hydroxylase
***In Vitro* with No Pre-Incubation**						
d-amphetamine	0	0	0	10.2	0	0
l-amphetamine	0	0	0	0	0	0
d,l- amphetamine	0	0	7.5	**13.1**	0	0
***In Vitro* Inhibition After Metabolic Activation**						
d-amphetamine	12.6	0	0	12.5	6.9	6.2
l-amphetamine	9.1	0	0	3.5	2	4.4
d,l- amphetamine	9.6	0	0	***17.6***	3.3	3.1
Estimated *In Vivo* Inhibition						
Inhibition by amphetamine itself at *in vivo peak concentrations with inhibited drug's concentrations <Km*	0	0	<1	**0.4 ?**	0	0
Inhibition by amphetamine metabolites *with inhibited drug's concentrations <Km*	**a**	a	a	**a**	**a**	**a**
Total Inhibition	**a**					

a unable to predict based on available information

3 OCPB RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed the response to the approvable letter to NDA 21-303 Supplement SE5-009 dated March 15, 2005 that was submitted May 27, 2005 and has determined that the information submitted was sufficient for labeling purposes. Therefore this particular deficiency has been adequately addressed.

The medical officer is requested to review OCPB's labeling comments for drug metabolism and elimination labeling and labeling changes should be forwarded to the sponsor as appropriate.

4 LABELING COMMENTS

The sponsor has not proposed any new labeling for drug metabolism. However OCPB has proposed additional labeling based on the sponsor's submission, (see § 4.1).

Labeling proposals may be found on the next page with OCPB proposed additions indicated by a single underline.

The labeling that is not underlined is from the March 15th approvable letter:

2 Page(s) of Draft Labeling have been Withheld in Full immediately following this page.

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

5 SIGNATURES

_____ _____

Ronald E. Kavanagh, BS Pharm, Pharm.D., Ph.D., OCPB/DPE-1 **Date**

_____ _____

Raman Baweja, Ph.D., Team Leader, OCPB/DPE-1 **Date**

CC:

NDA 21-303 SE5-009	(orig., 1 copy)
HFD-120	(TaylorR, AndreasonP, LaughrenT, KatzR)
HFD-860	(Baweja, KavanaghR, RahmanA, MehtaM)
CDR	(B.Murphy)

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/s/

Ron Kavanagh
7/11/05 12:31:07 PM
BIOPHARMACEUTICS

Raman Baweja
7/11/05 02:06:18 PM
BIOPHARMACEUTICS

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

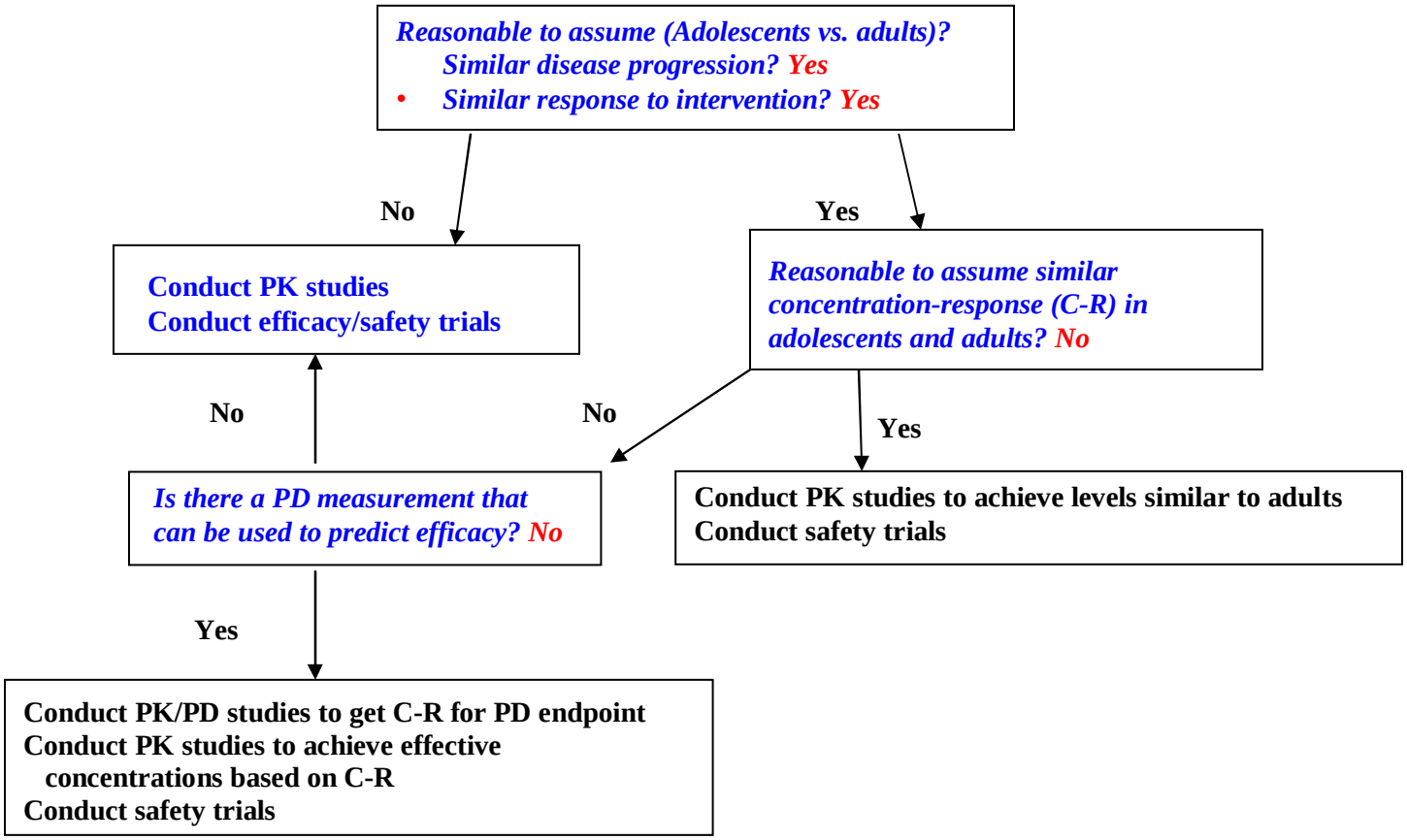
[1]p-value for the indicated effect from an analysis of variance

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 in a ratio of 3:1. 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. The capsules contain two types of pellets: immediate release pellets that release the first half of the dose of mixed amphetamine salts in a similar mechanism to Adderall IR, and delayed-release pellets that release the second half of the dose of mixed amphetamines salts 4 to 6 hours later.

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?

(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.

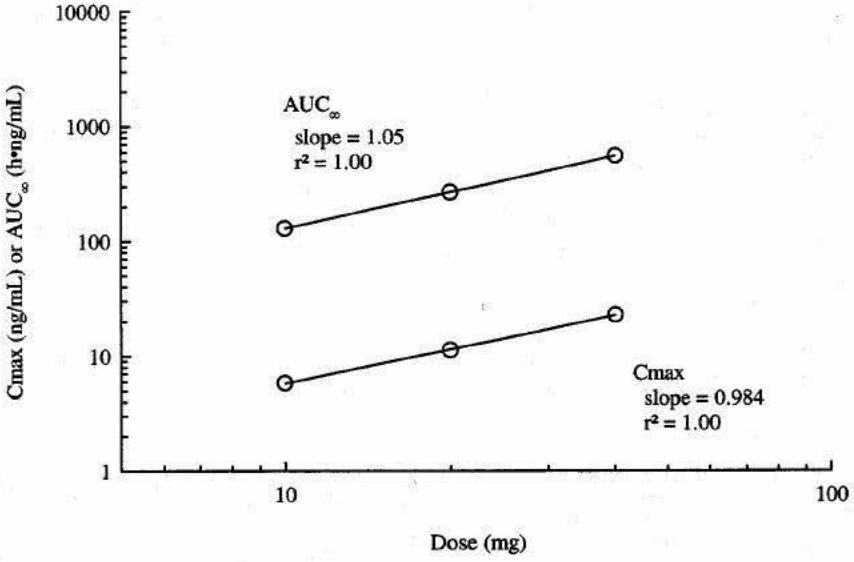


Figure 2 (above)

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.

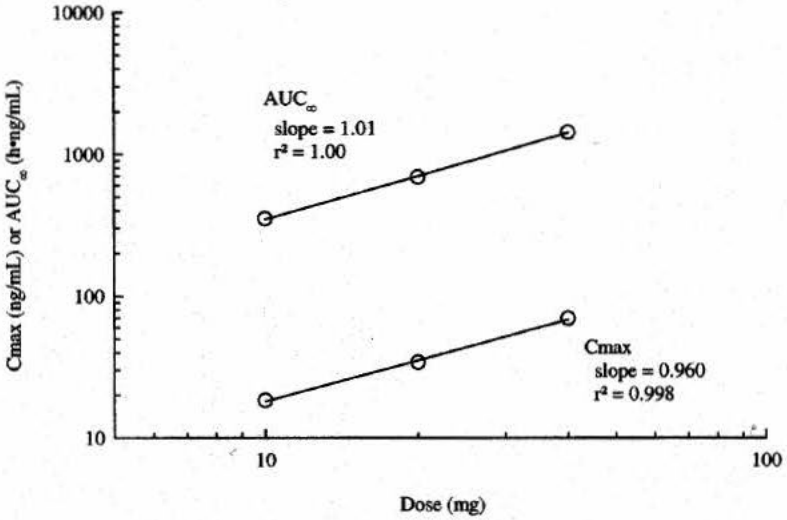


Figure 3

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®.

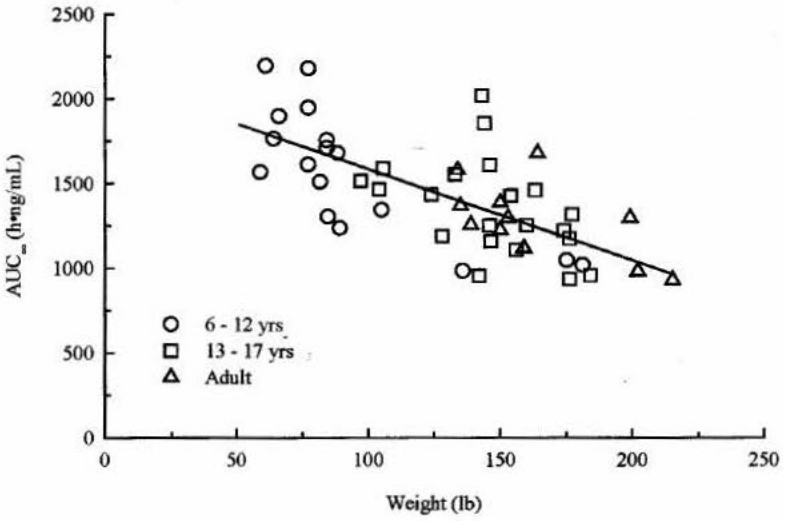


Figure 2: Relationship between AUC_∞ and weight for l-amphetamine after oral administration of ADDERALL XR®.

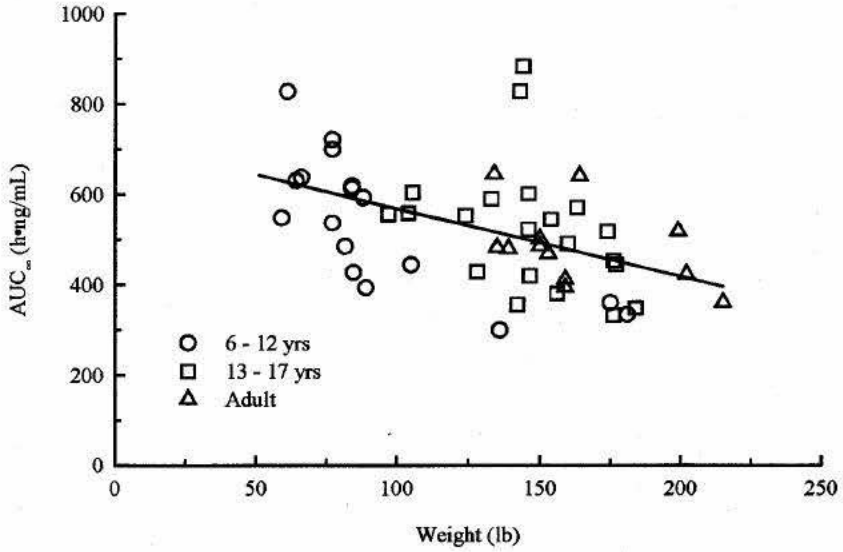
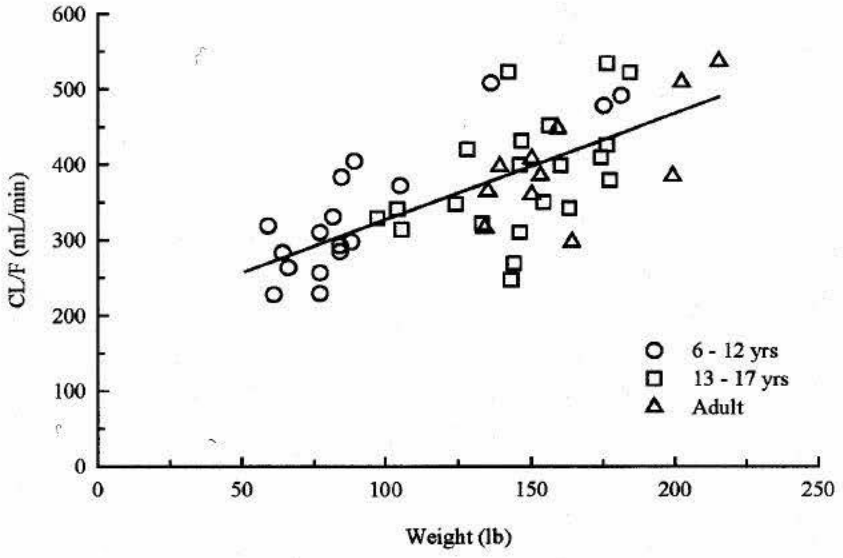


Figure 3: Relationship between CL/F and weight for d-amphetamine after oral administration of ADDERALL XR®.



Figs 5 (above) and 6 (below)

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

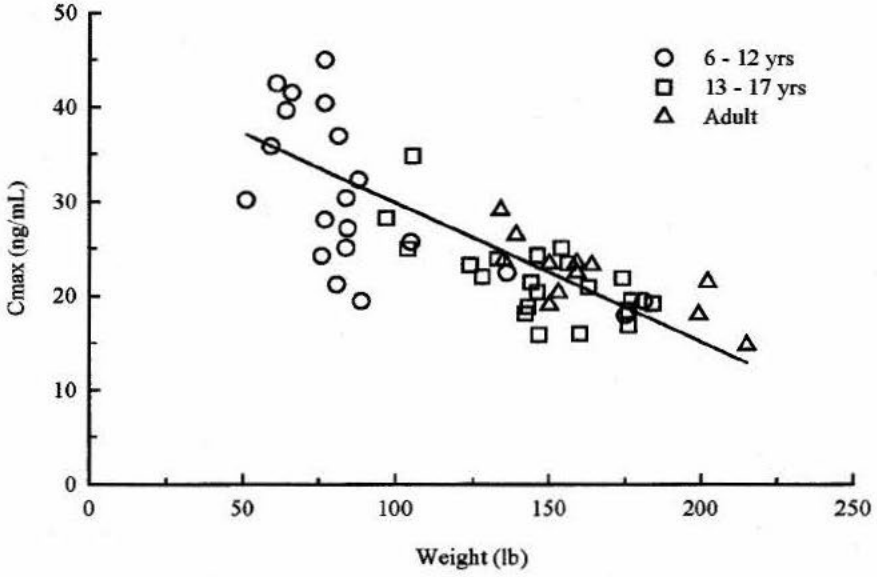
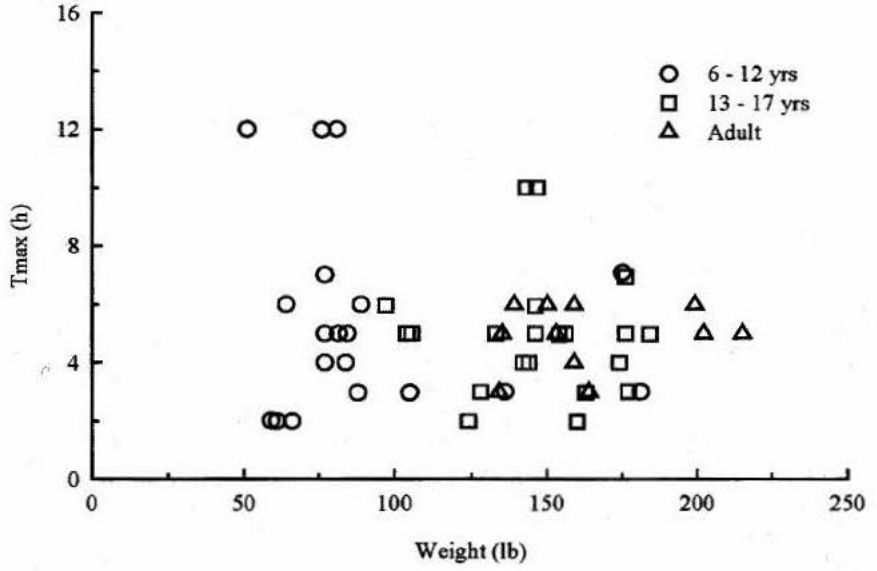


Figure 11: Relationship between Tmax and weight for d-amphetamine after oral administration of ADDERALL XR®.



Figs 7 (above) and 8 (below)

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

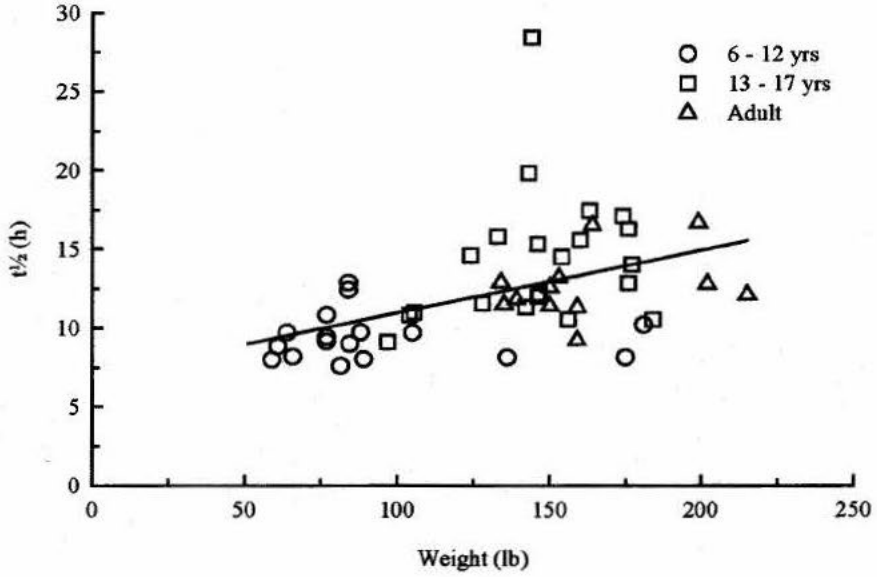
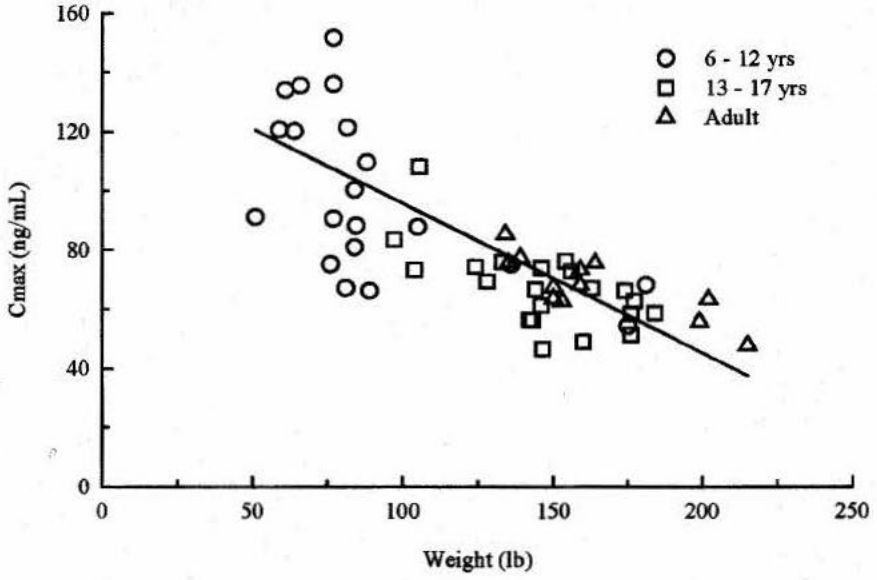


Figure 9: Relationship between Cmax and weight for d-amphetamine after oral administration of ADDERALL XR®.



Figs 9 (above) and 10 (below)

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

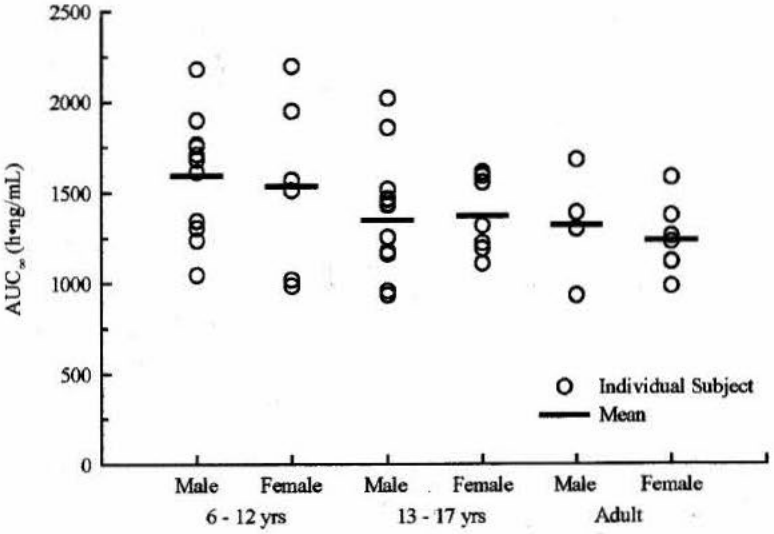
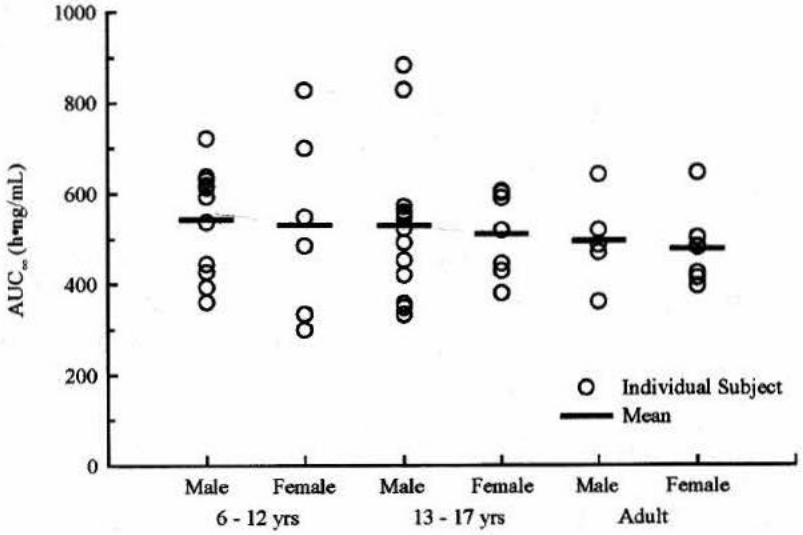


Figure 26: Relationship between AUC_∞ and gender for l-amphetamine after oral administration of ADDERALL XR®.



Figures 11 (above) and 12 (below)

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

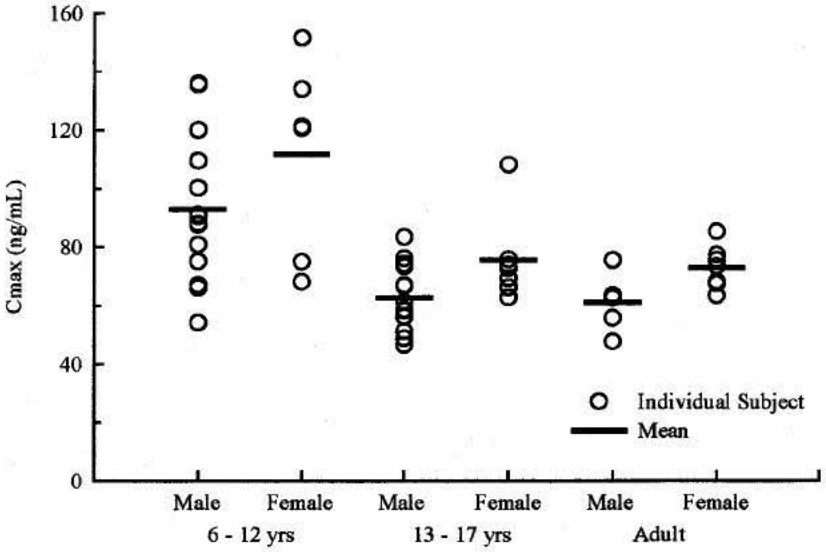
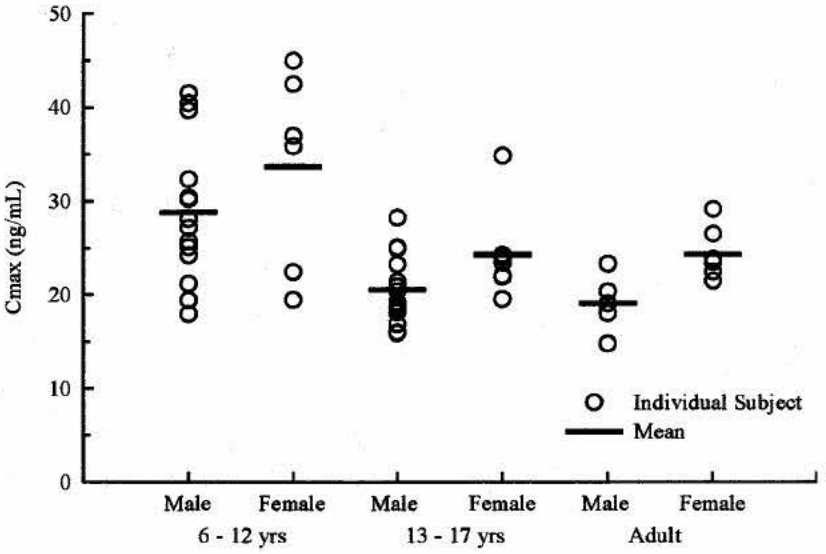


Figure 34: Relationship between Cmax and gender for l-amphetamine after oral administration of ADDERALL XR®.



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. (b) (4) (b) (4) 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: This was moved out of the section on Gender)

Pediatric Population

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

Children (b) (4) eliminated amphetamine faster than adults. Children had (b) (4) higher systemic exposure to amphetamine (Cmax and AUC) than adults for a given dose of Adderall XR, which was attributed to the higher dose administered to children on mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults. (b) (4) .

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

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

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.

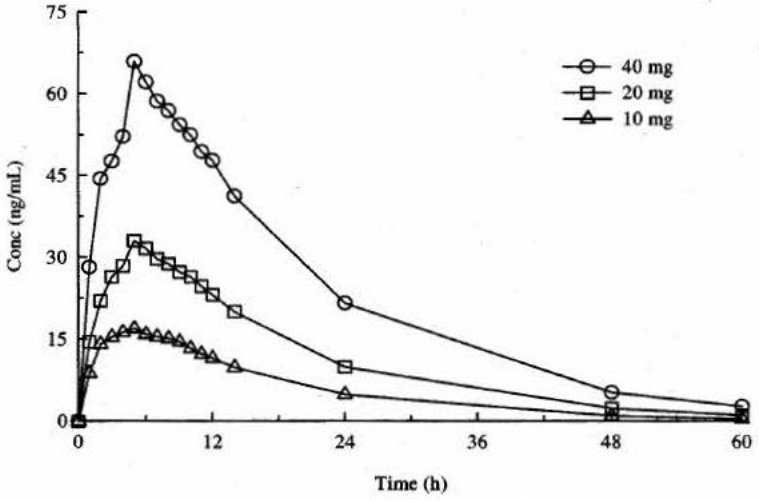


Figure 2: Mean plasma concentrations of d-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb — semi-logarithmic axes.

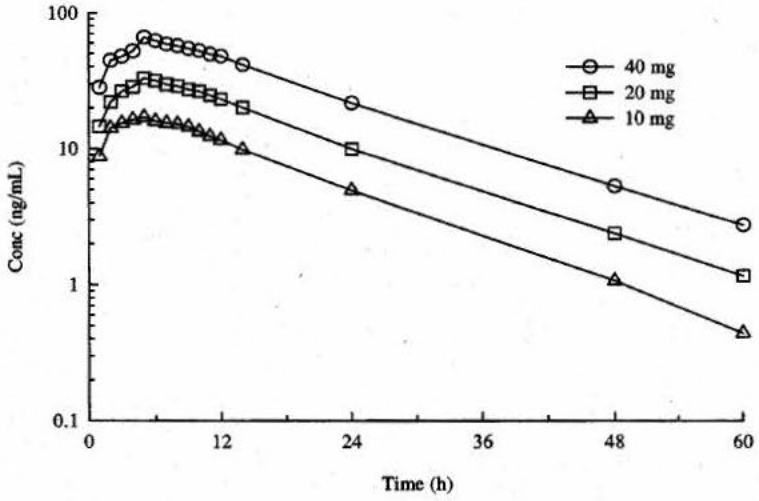


Figure 3: Mean plasma concentrations of l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb — linear axes.

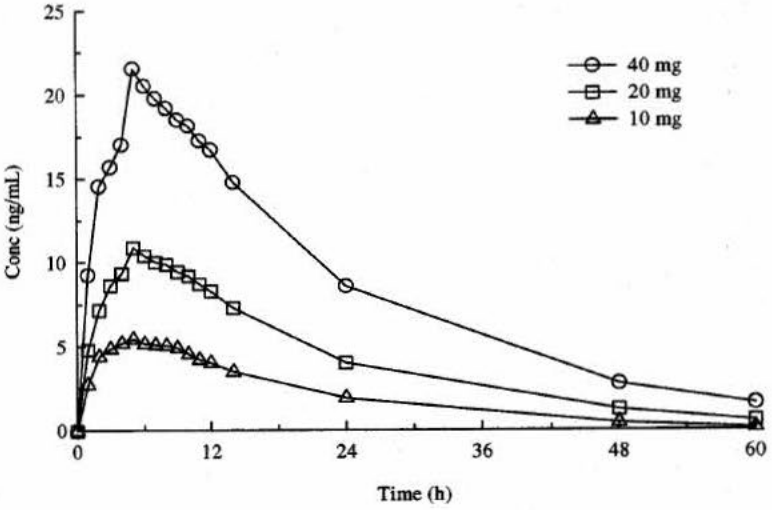


Figure 4: Mean plasma concentrations of l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb — semi-logarithmic axes.

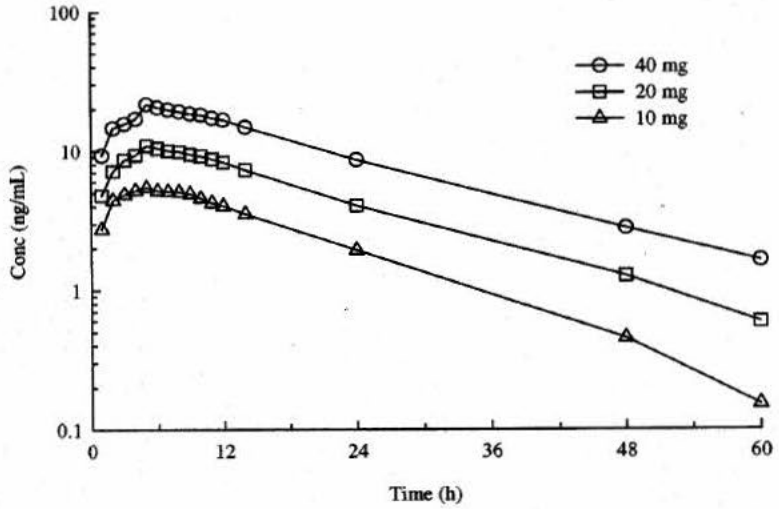


Table 3: Statistical comparison of Tmax and t½ for d- and l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb.

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.

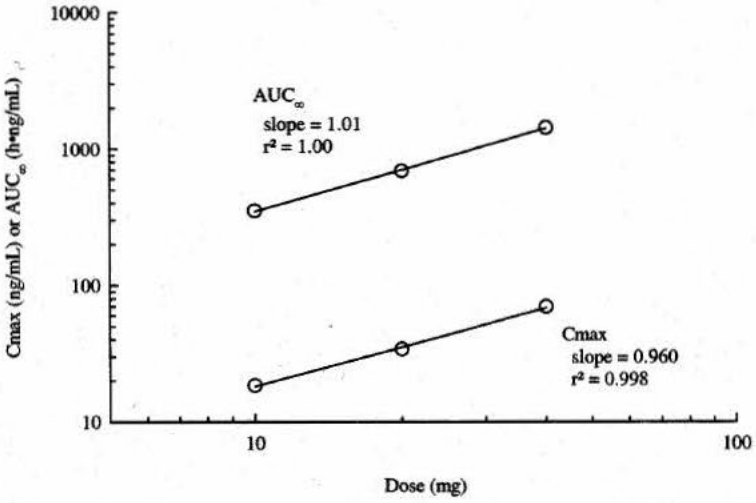


Figure 6: Relationships between Cmax and AUC_∞ and dose of l-amphetamine after oral administration of 10 mg, 20 mg, and 40 mg of ADDERALL XR® to adolescent subjects weighing ≤ 75 kg/ 165 lb.

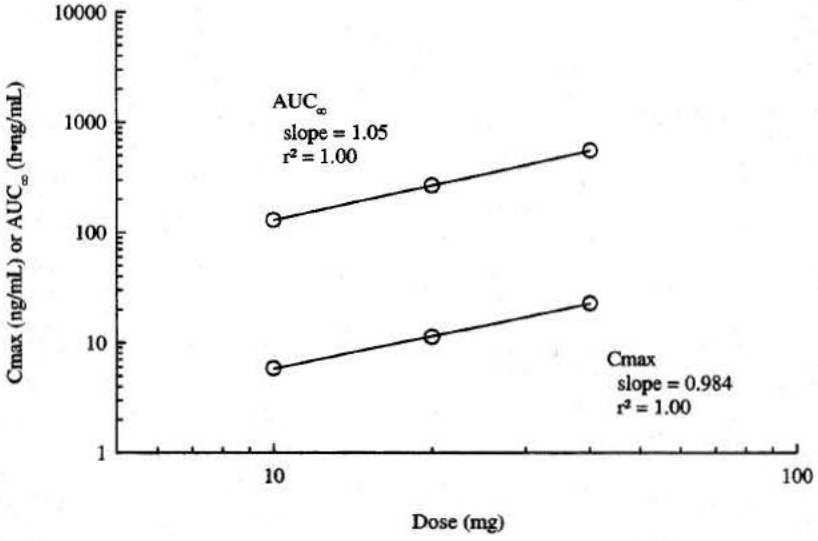


Figure 7: Mean plasma concentrations of d-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — linear axes.

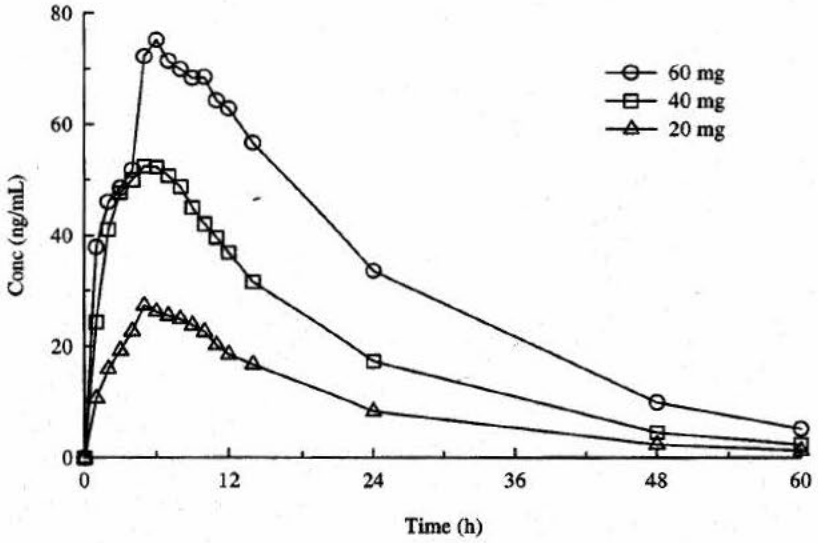


Figure 8: Mean plasma concentrations of d-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — semi-logarithmic axes.

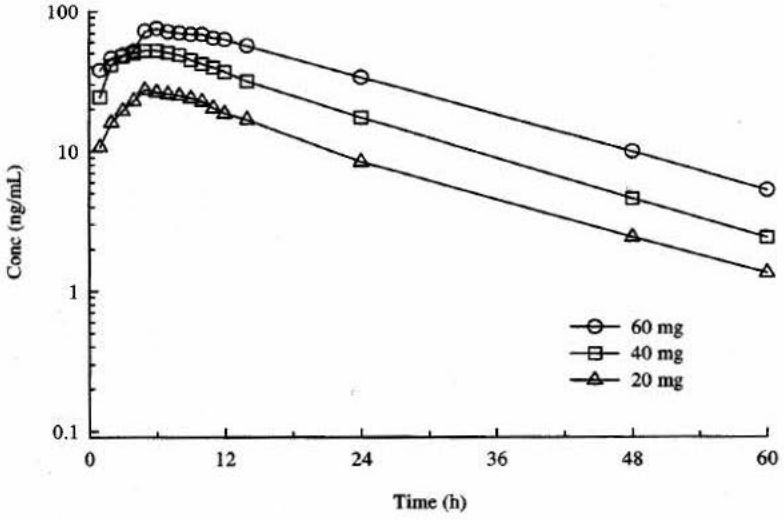


Figure 9: Mean plasma concentrations of l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — linear axes.

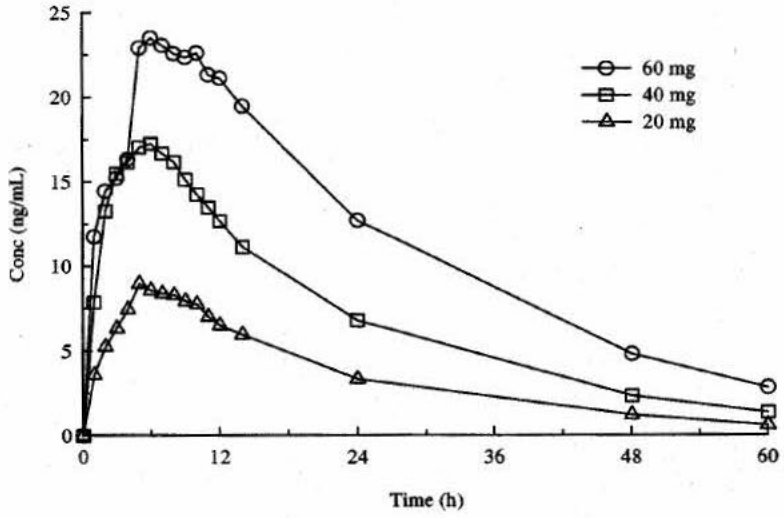


Figure 10: Mean plasma concentrations of l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb — semi-logarithmic axes.

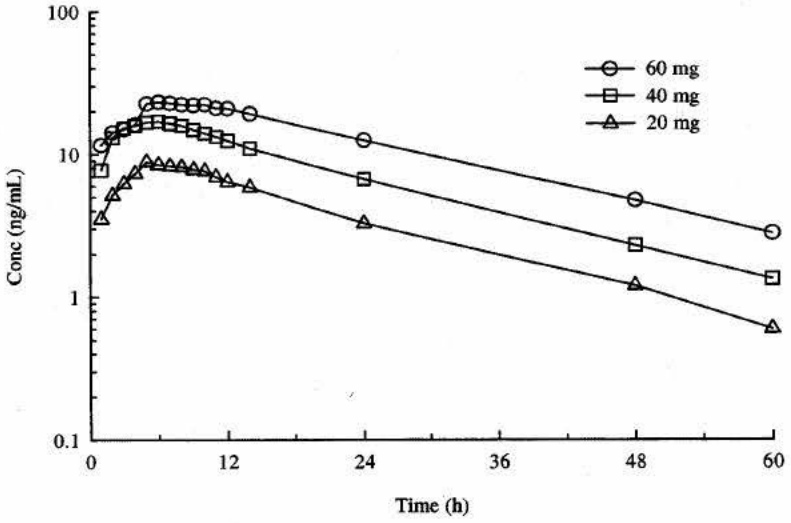


Table 4: Summary of pharmacokinetic parameters for d- and l-amphetamine after oral administration of 20 mg, 40 mg, and 60 mg of ADDERALL XR® to adolescent subjects weighing > 75 kg/ 165 lb.

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.

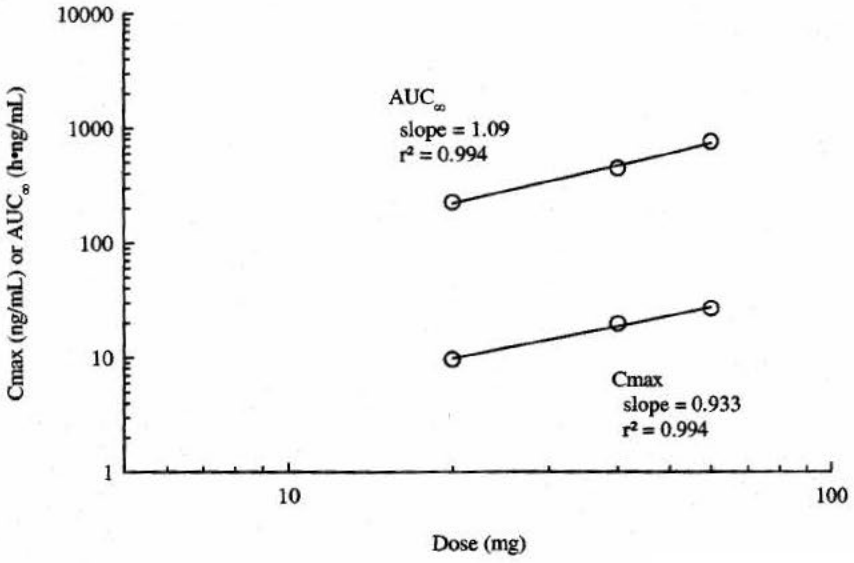


Figure 13: Relationship between dose-normalized Cmax and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

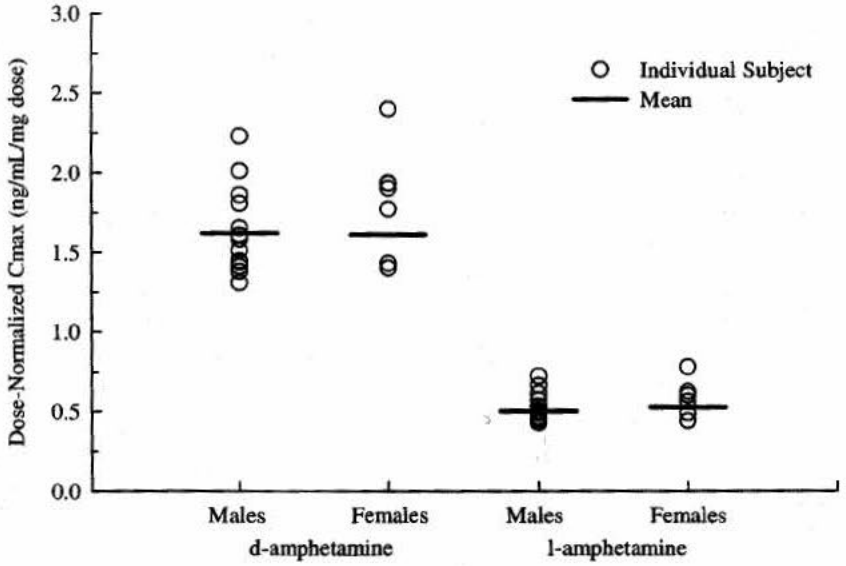


Figure 14: Relationship between dose-normalized AUC_∞ and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

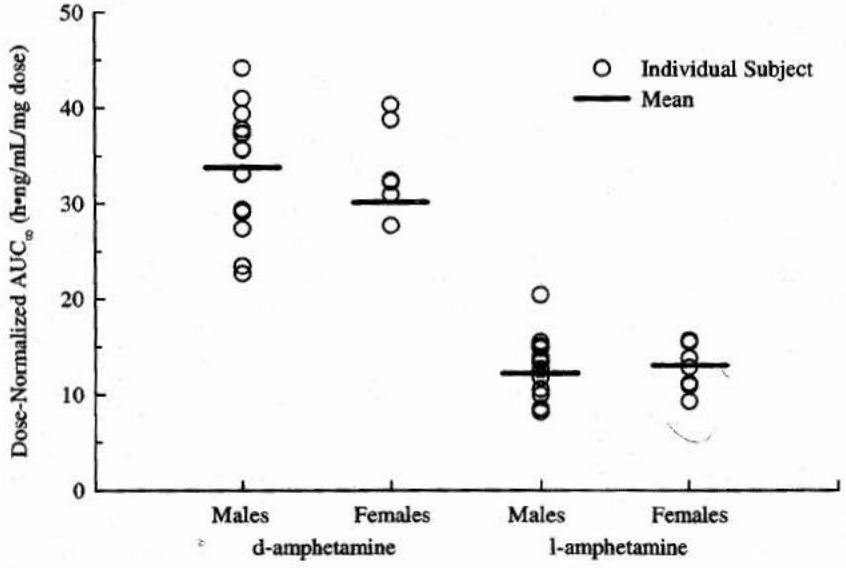


Figure 15: Relationship between t½ and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

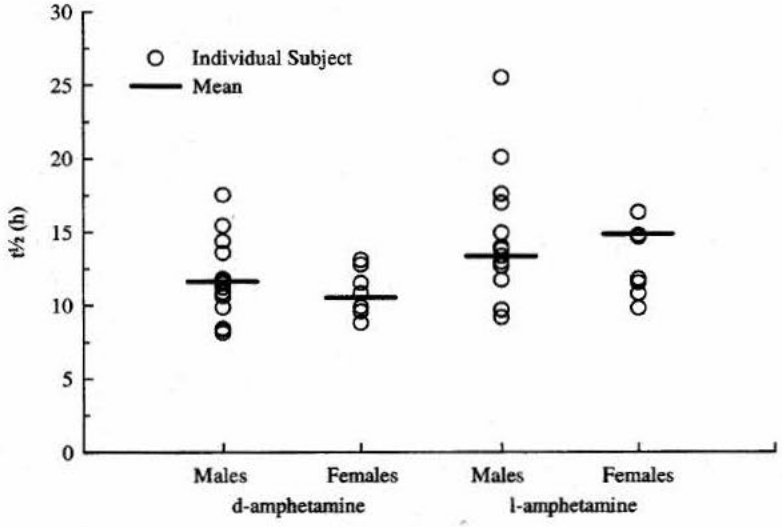


Figure 16: Relationship between CL/F and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

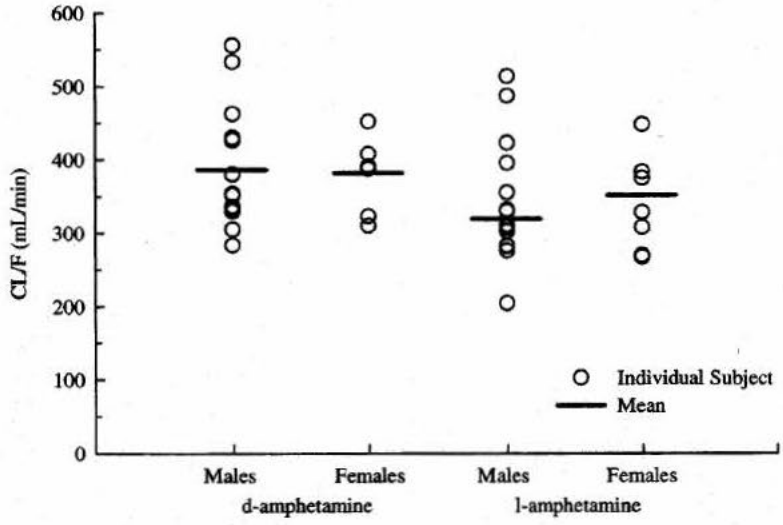


Figure 17: Relationship between Vz/F and gender for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

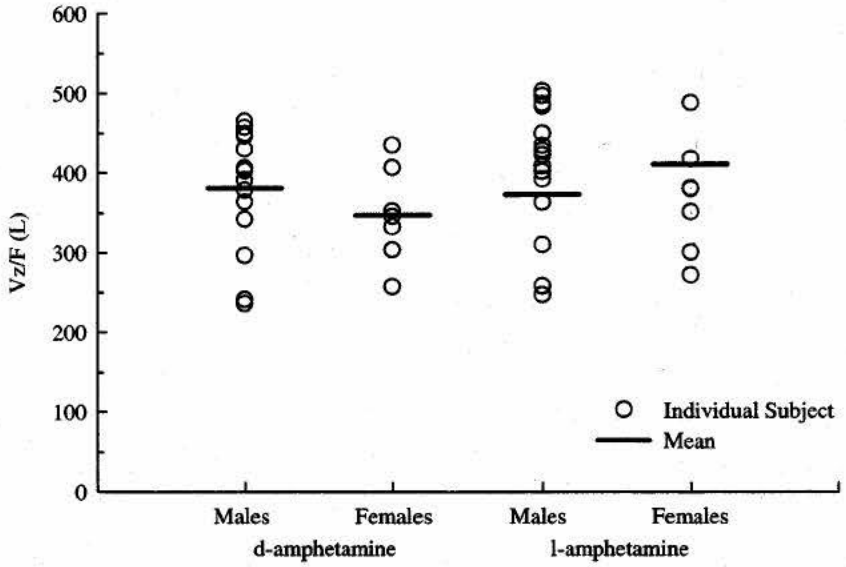


Table 7: Statistical comparison of Cmax, AUC_{∞}, t½, CL/F, and Vz/F for d- and l-amphetamine by gender after oral administration of ADDERALL XR® to adolescent subjects.

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.

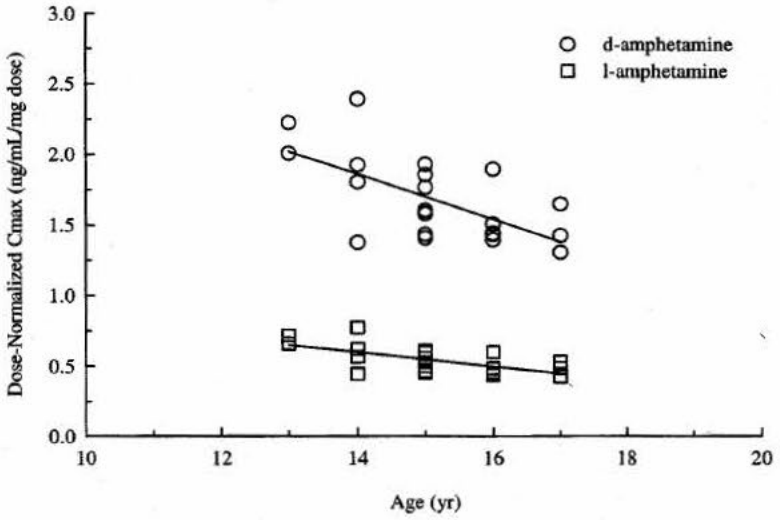


Table 8: Statistical comparison of Cmax, AUC_{∞}, t½, CL/F, and Vz/F for d- and l-amphetamine with age after oral administration of ADDERALL XR® to adolescent subjects.

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.

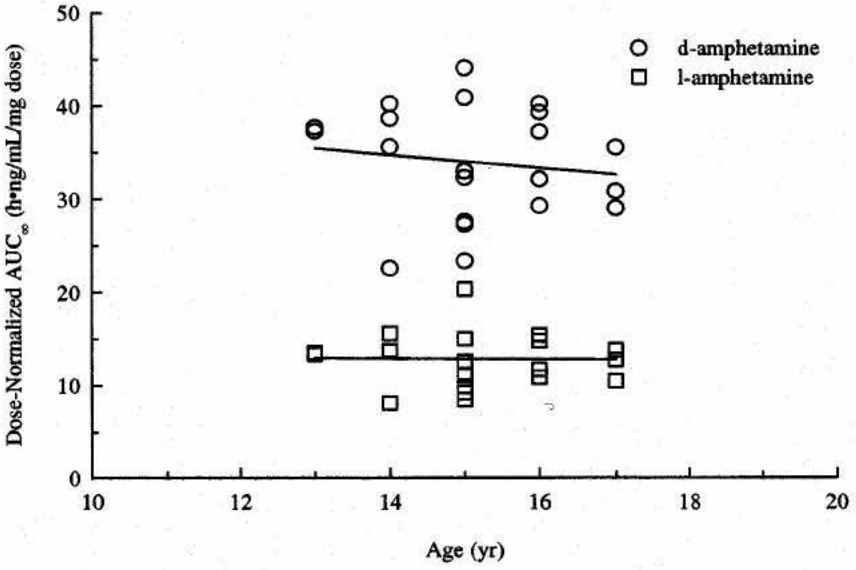


Figure 20: Relationship between t½ and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

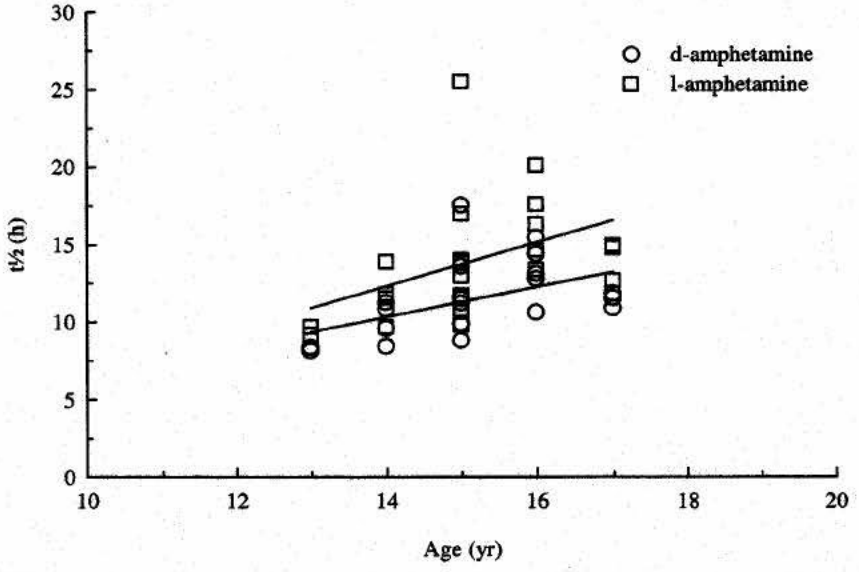


Figure 21: Relationship between CL/F and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

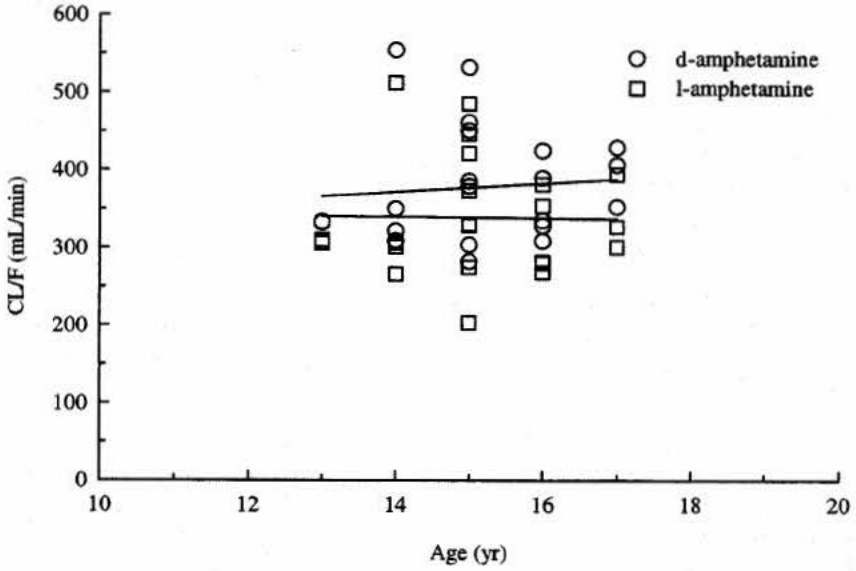


Figure 22: Relationship between Vz/F and age for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

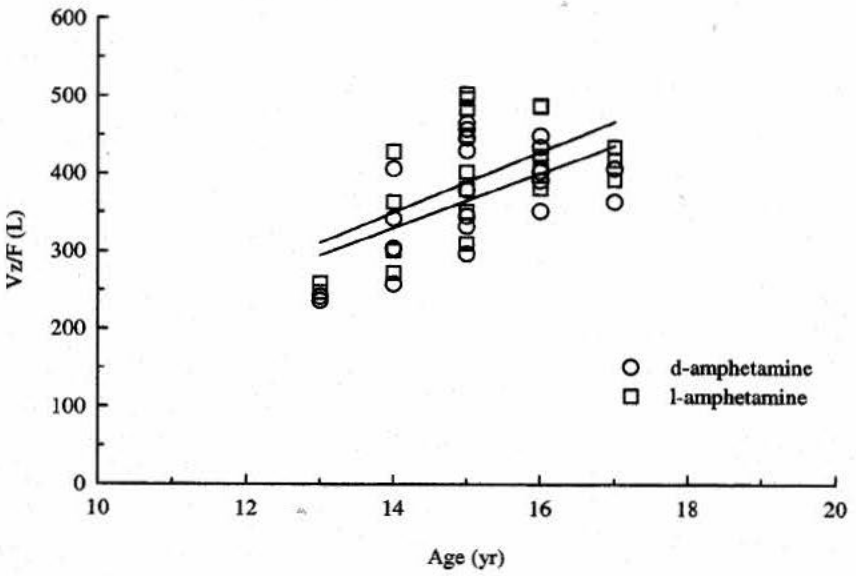


Figure 23: Relationship between dose-normalized Cmax and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

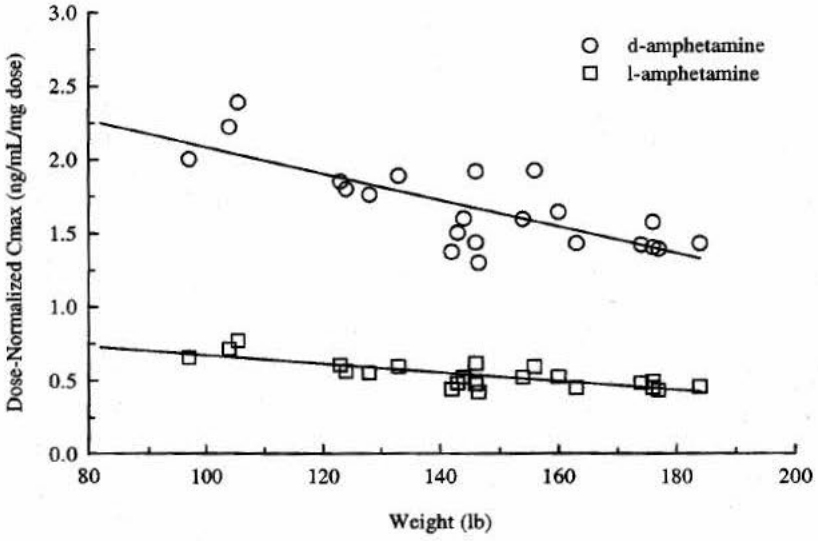


Figure 24: Relationship between dose-normalized AUC_∞ and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

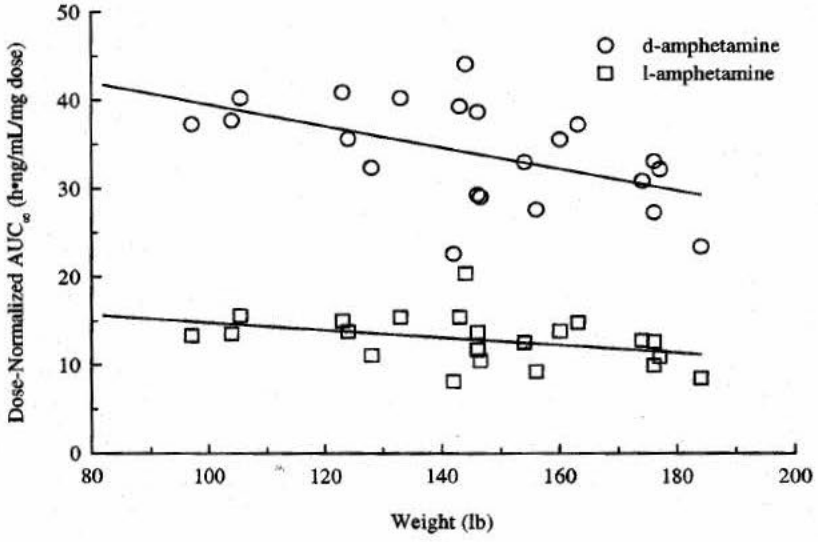


Figure 25: Relationship between t½ and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

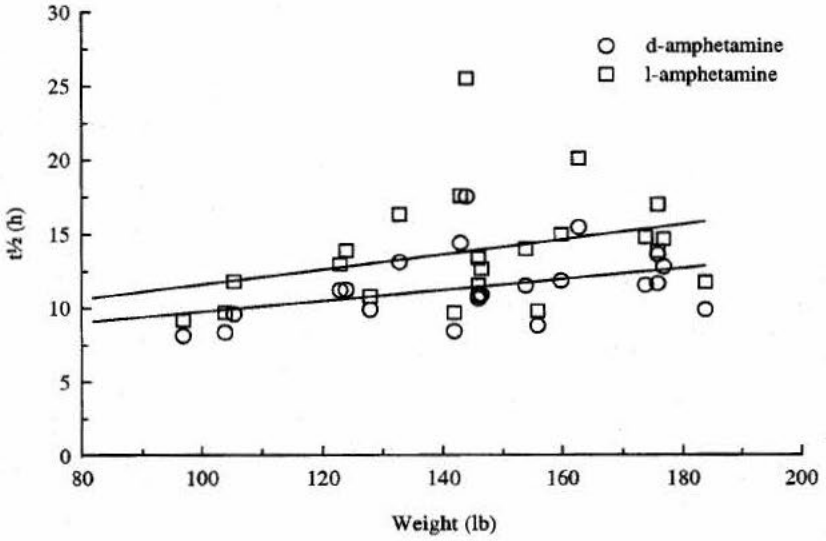


Figure 26: Relationship between CL/F and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

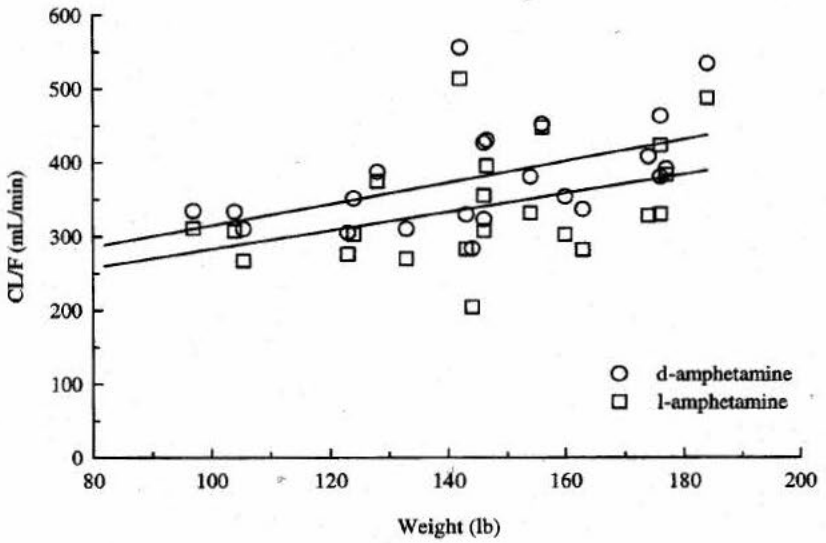


Figure 27: Relationship between Vz/F and weight for d- and l-amphetamine after oral administration of ADDERALL XR® to adolescent subjects.

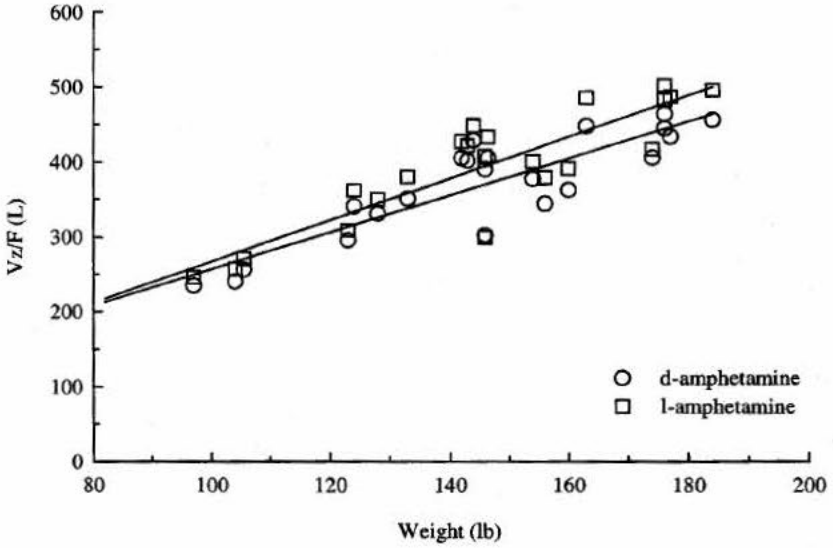


Table 9: Statistical comparison of Cmax, AUC_∞, t½, CL/F, and Vz/F for d- and l-amphetamine with weight after oral administration of ADDERALL XR® to adolescent subjects.

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	20.42
			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 (b) (4) *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®.

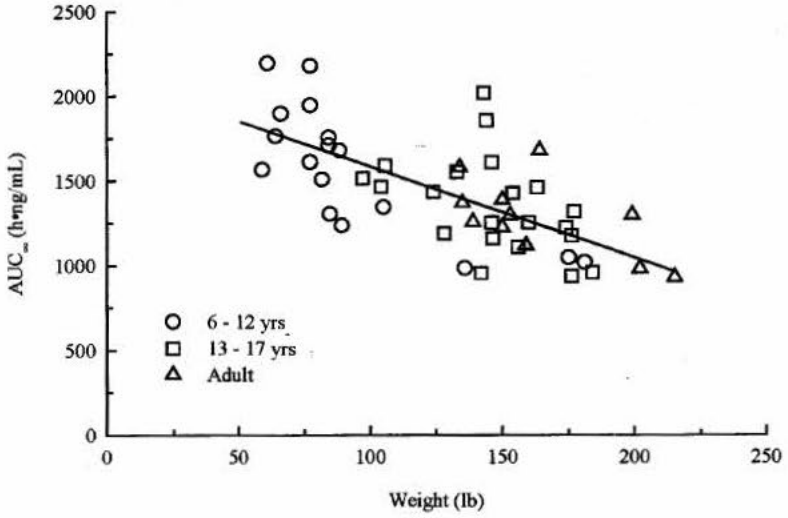


Figure 2: Relationship between AUC_∞ and weight for l-amphetamine after oral administration of ADDERALL XR®.

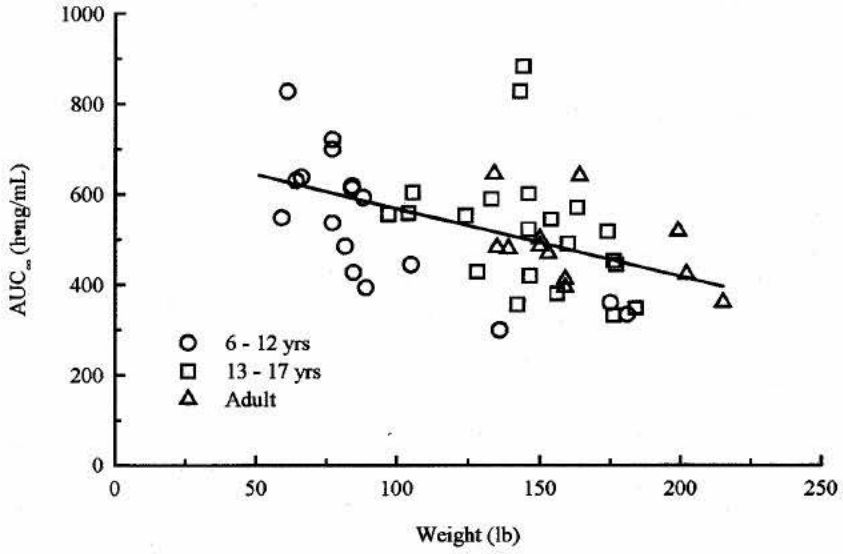


Figure 3: Relationship between CL/F and weight for d-amphetamine after oral administration of ADDERALL XR®.

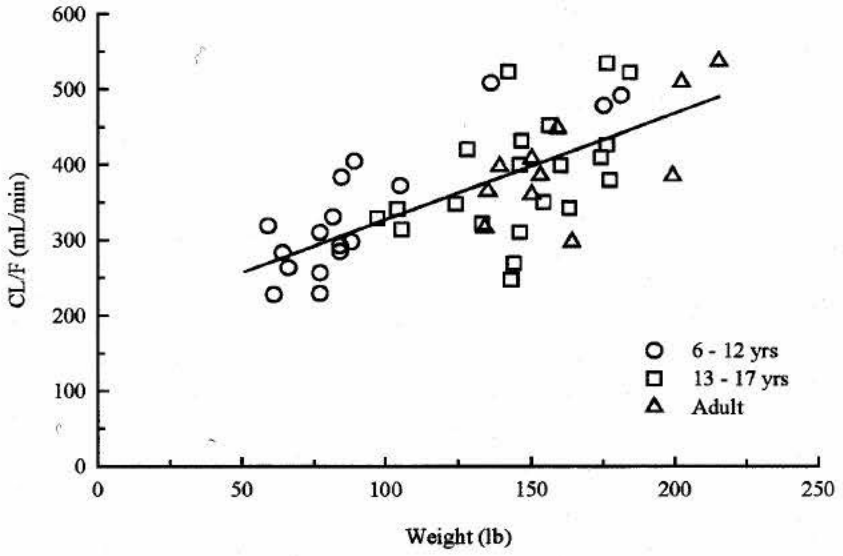


Figure 4: Relationship between CL/F and weight for l-amphetamine after oral administration of ADDERALL XR®.

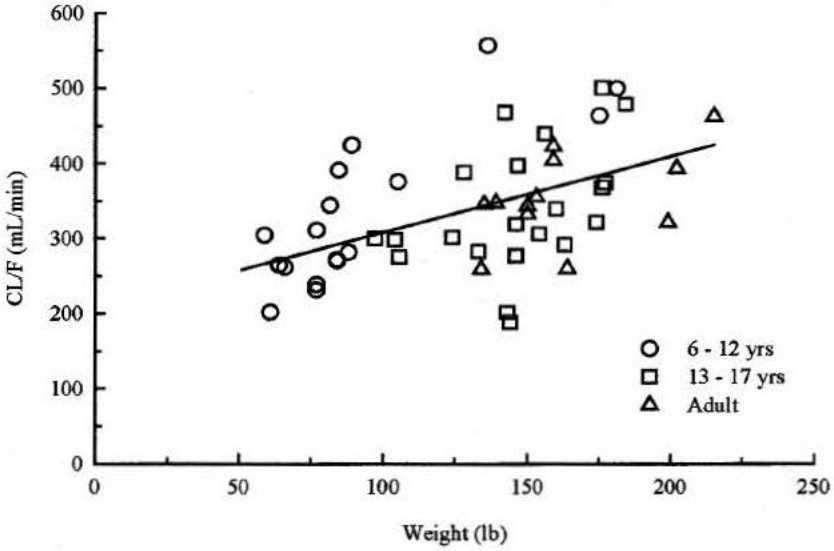


Figure 5: Relationship between Vz/F and weight for d-amphetamine after oral administration of ADDERALL XR®.

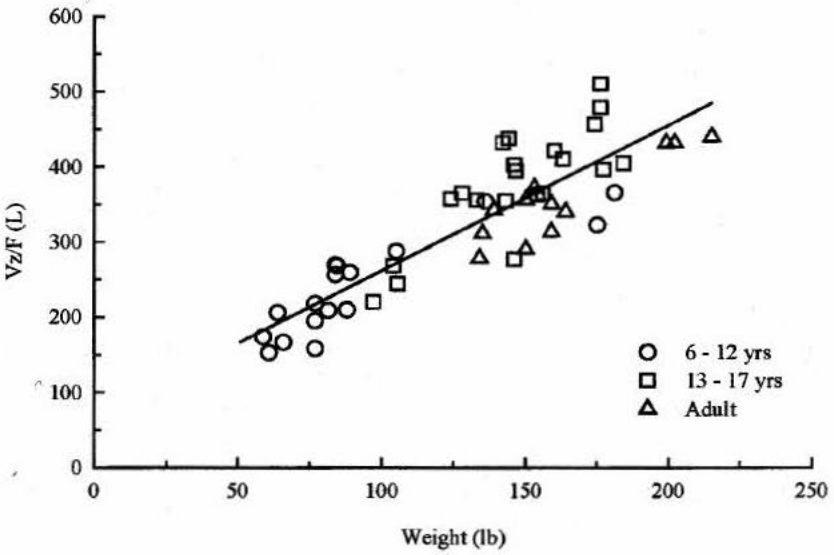


Figure 6: Relationship between Vz/F and weight for l-amphetamine after oral administration of ADDERALL XR®.

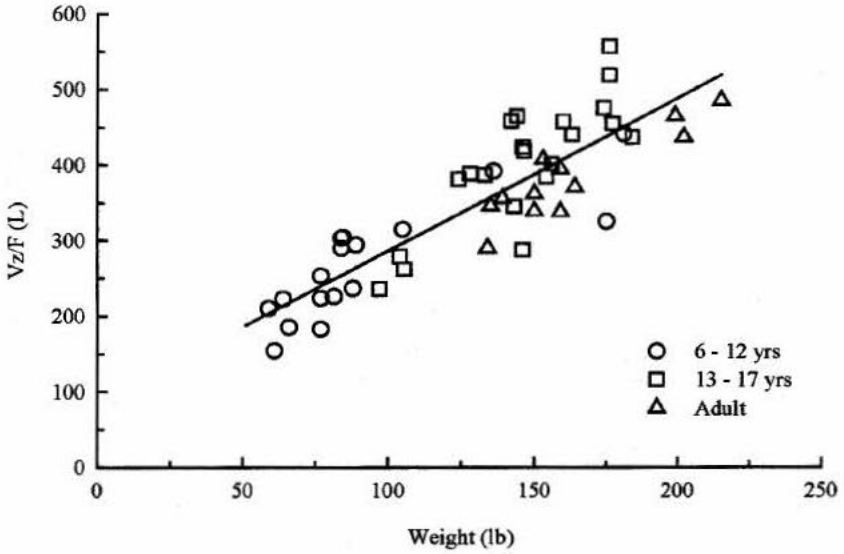


Figure 7: Relationship between t½ and weight for d-amphetamine after oral administration of ADDERALL XR®.

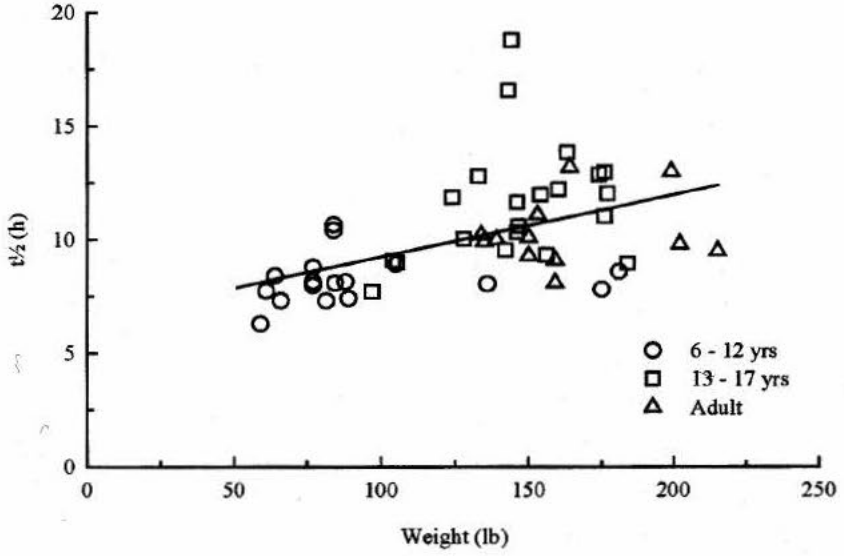


Figure 8: Relationship between t½ and weight for l-amphetamine after oral administration of ADDERALL XR®.

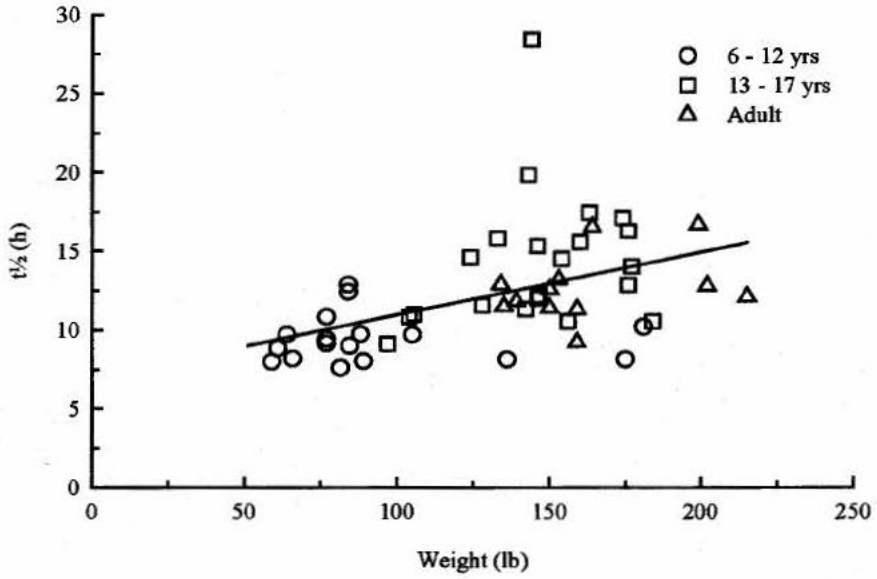


Figure 9: Relationship between Cmax and weight for d-amphetamine after oral administration of ADDERALL XR®.

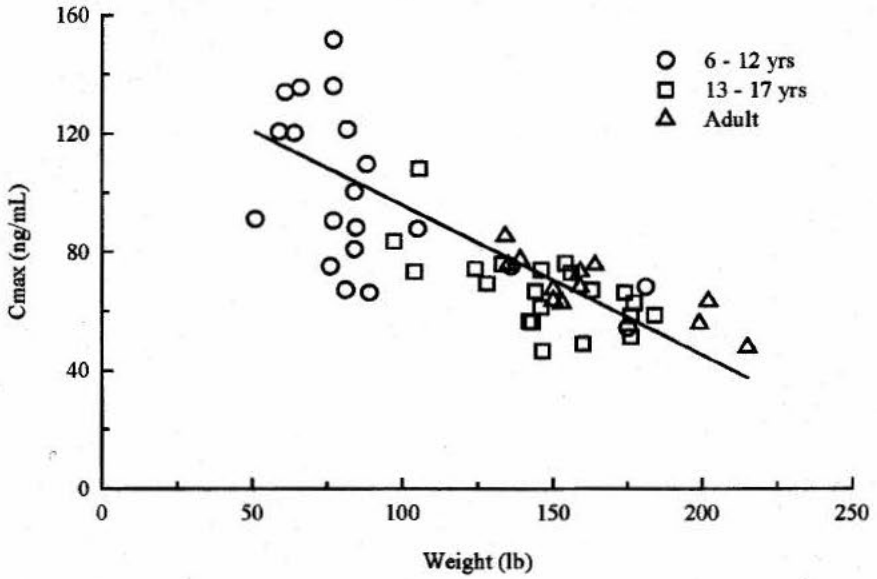


Figure 10: Relationship between Cmax and weight for l-amphetamine after oral administration of ADDERALL XR®.

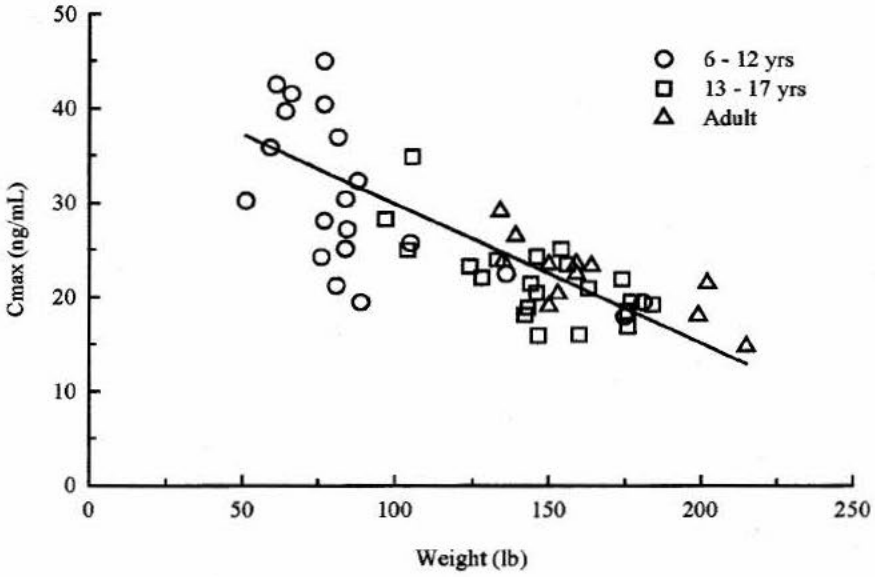


Figure 11: Relationship between Tmax and weight for d-amphetamine after oral administration of ADDERALL XR®.

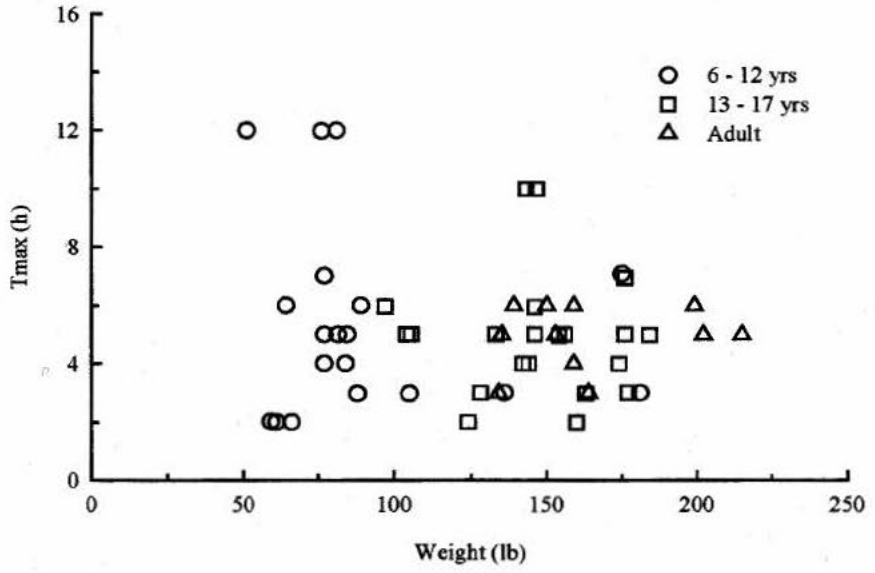


Figure 12: Relationship between Tmax and weight for l-amphetamine after oral administration of ADDERALL XR®.

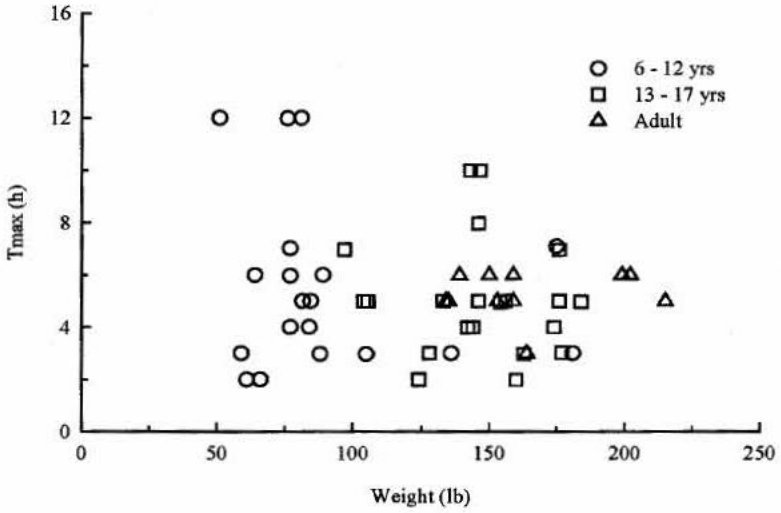


Table 5: Statistical evaluation of the effect of body weight on the pharmacokinetic parameters for d- and l-amphetamine after oral administration of ADDERALL XR®.

	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®.

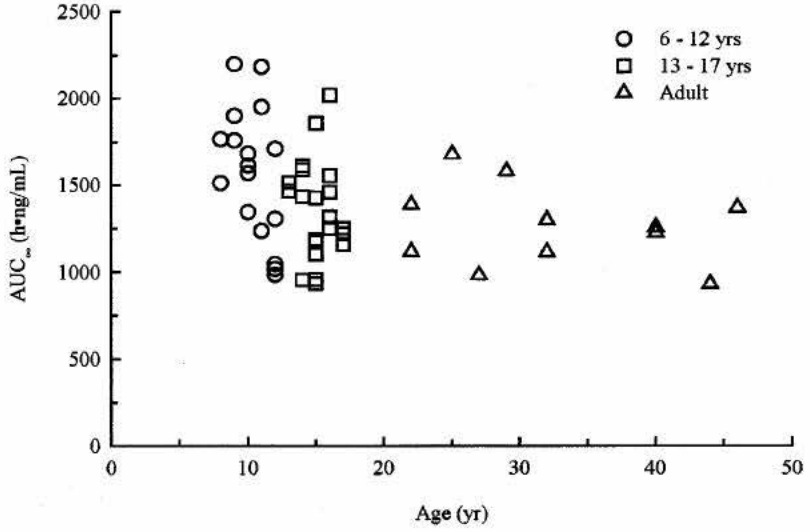


Figure 14: Relationship between AUC_∞ and age for l-amphetamine after oral administration of ADDERALL XR®.

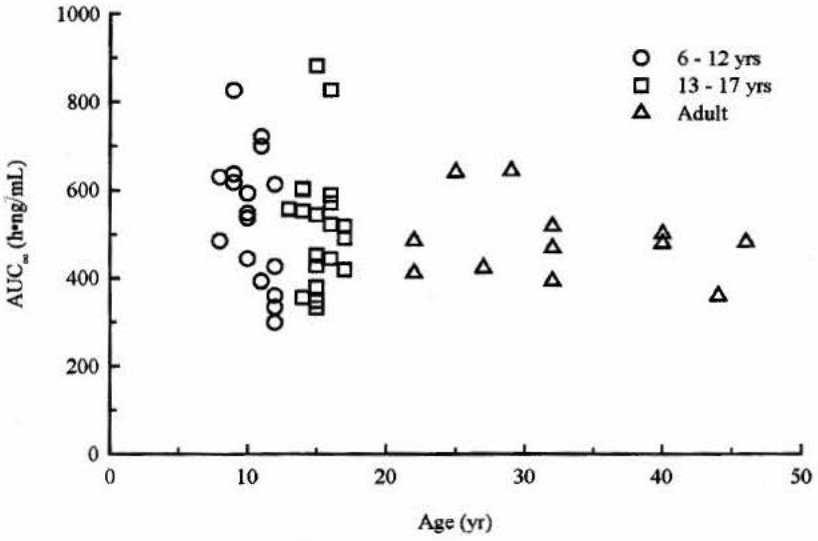


Figure 15: Relationship between CL/F and age for d-amphetamine after oral administration of ADDERALL XR®.

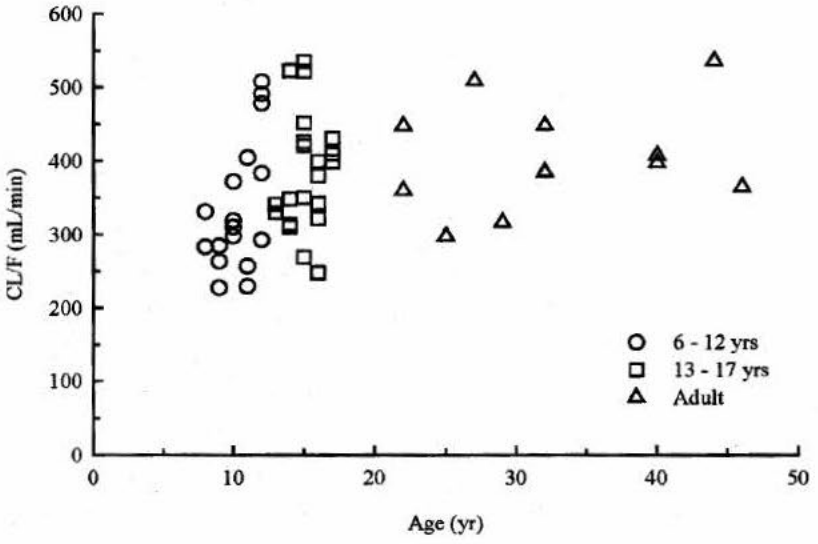


Figure 16: Relationship between CL/F and age for l-amphetamine after oral administration of ADDERALL XR®.

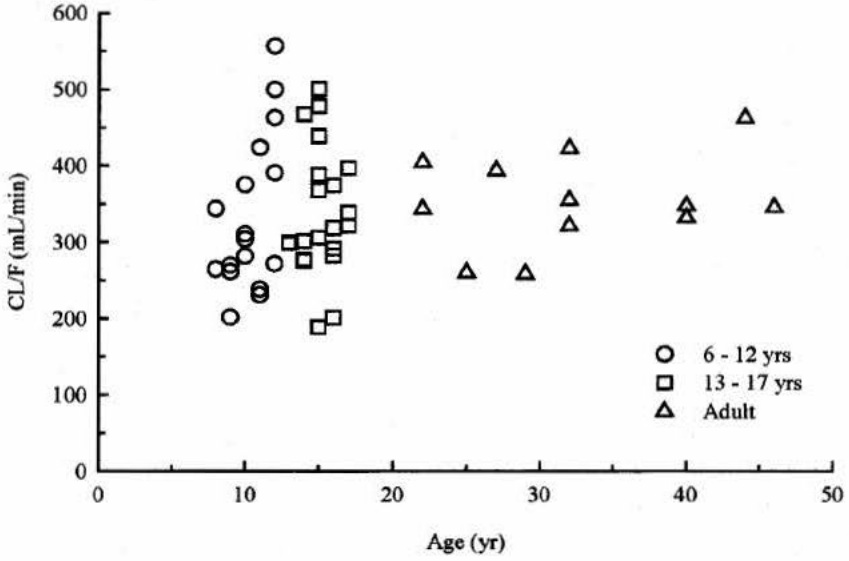


Figure 17: Relationship between Vz/F and age for d-amphetamine after oral administration of ADDERALL XR®.

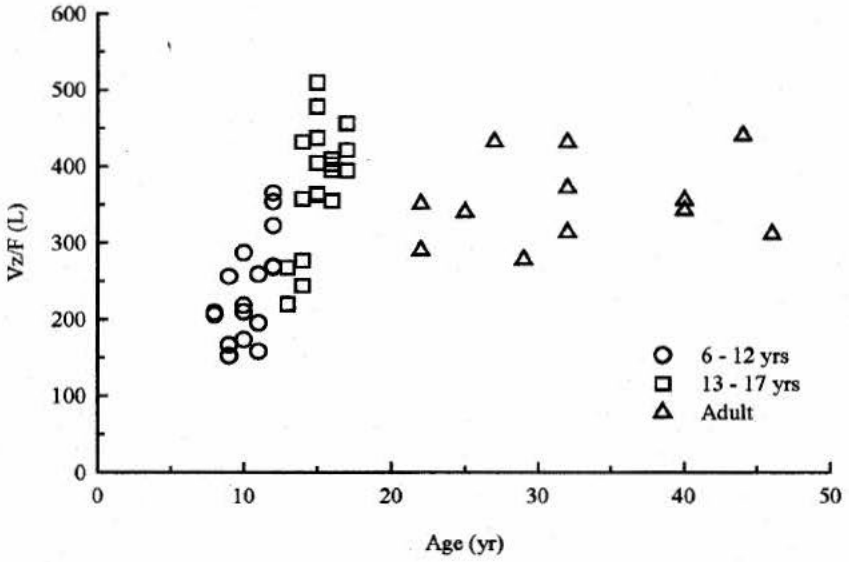


Figure 18: Relationship between Vz/F and age for l-amphetamine after oral administration of ADDERALL XR®.

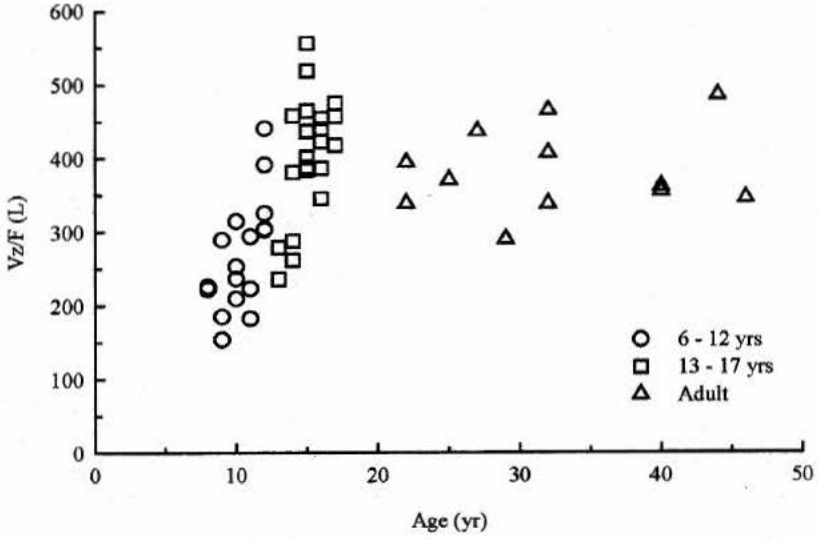


Figure 19: Relationship between t½ and age for d-amphetamine after oral administration of ADDERALL XR®.

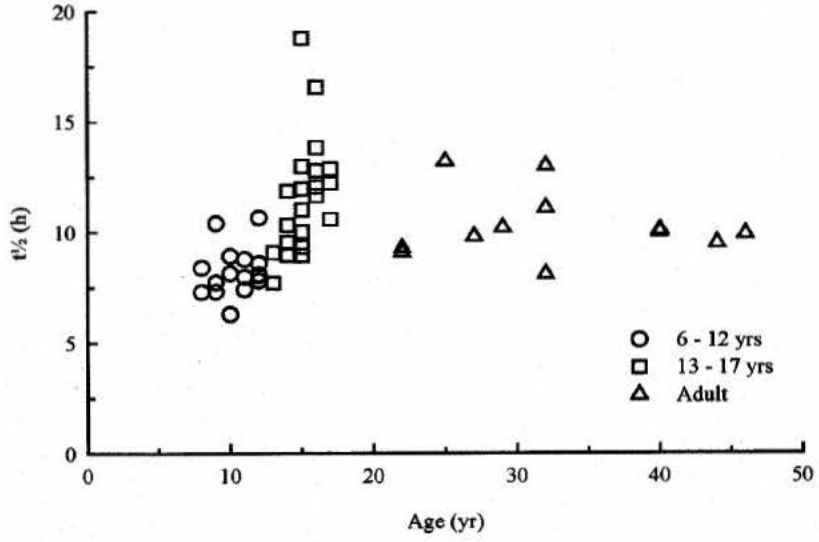


Figure 20: Relationship between t½ and age for l-amphetamine after oral administration of ADDERALL XR®.

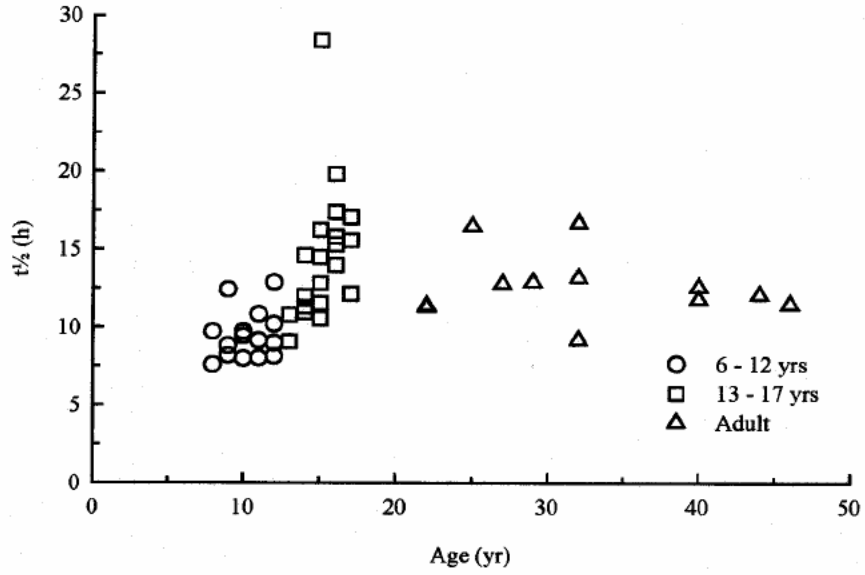


Figure 21: Relationship between Cmax and age for d-amphetamine after oral administration of ADDERALL XR®.

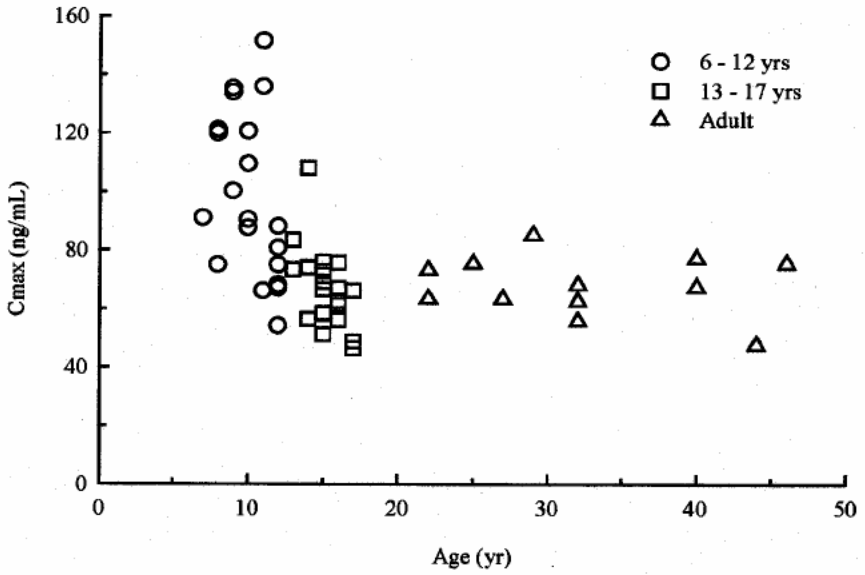


Figure 22: Relationship between Cmax and age for l-amphetamine after oral administration of ADDERALL XR®.

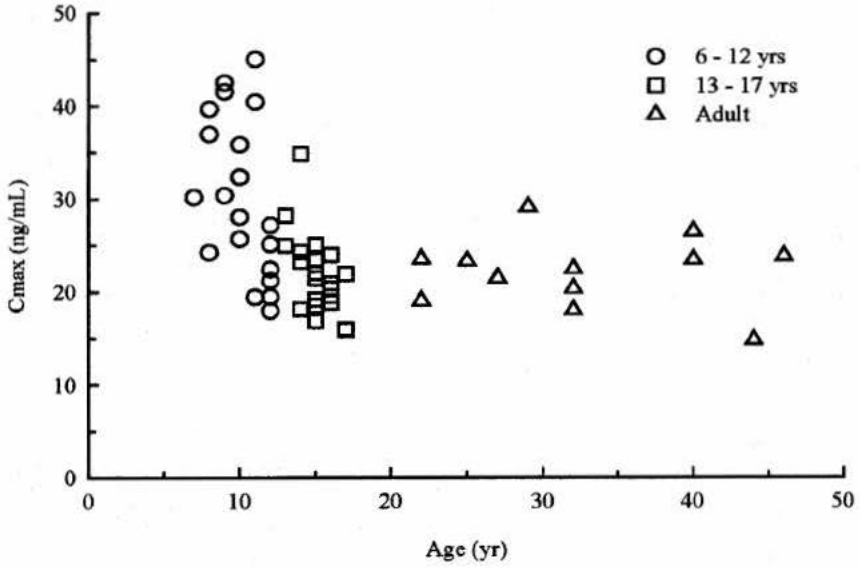


Figure 23: Relationship between Tmax and age for d-amphetamine after oral administration of ADDERALL XR®.

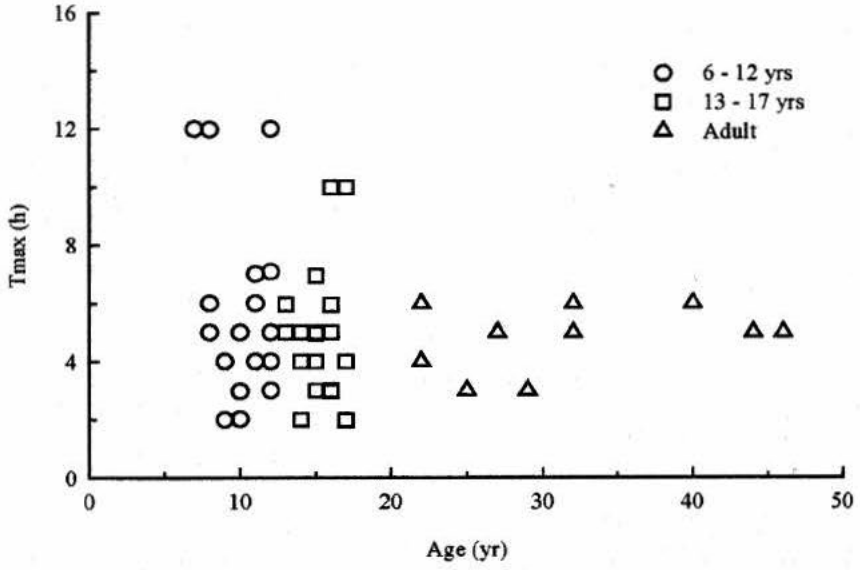


Figure 25: Relationship between AUC_∞ and gender for d-amphetamine after oral administration of ADDERALL XR®.

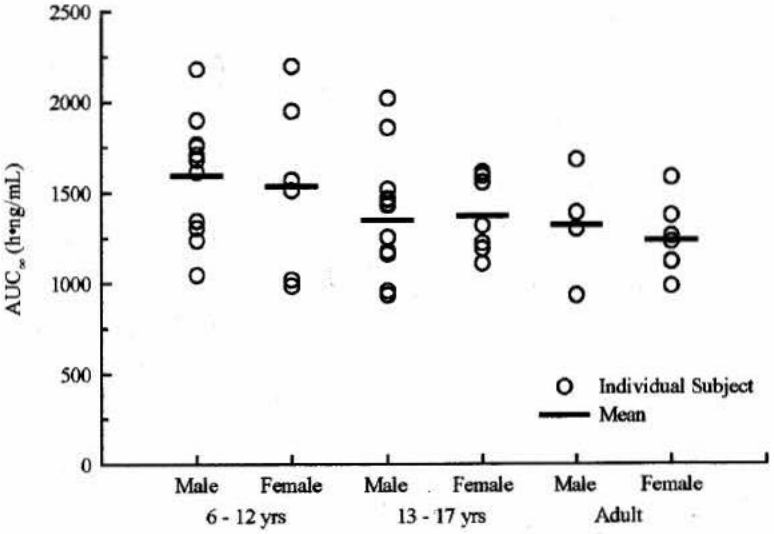


Figure 26: Relationship between AUC_∞ and gender for l-amphetamine after oral administration of ADDERALL XR®.

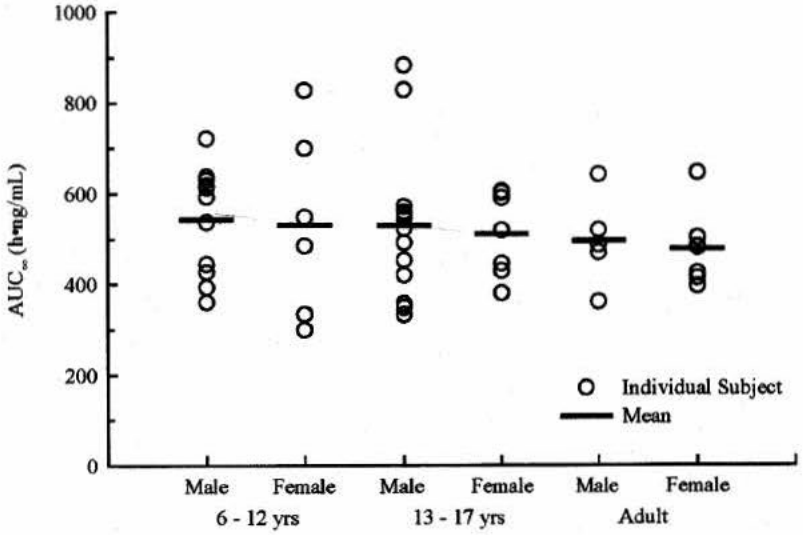


Figure 27: Relationship between CL/F and gender for d-amphetamine after oral administration of ADDERALL XR®.

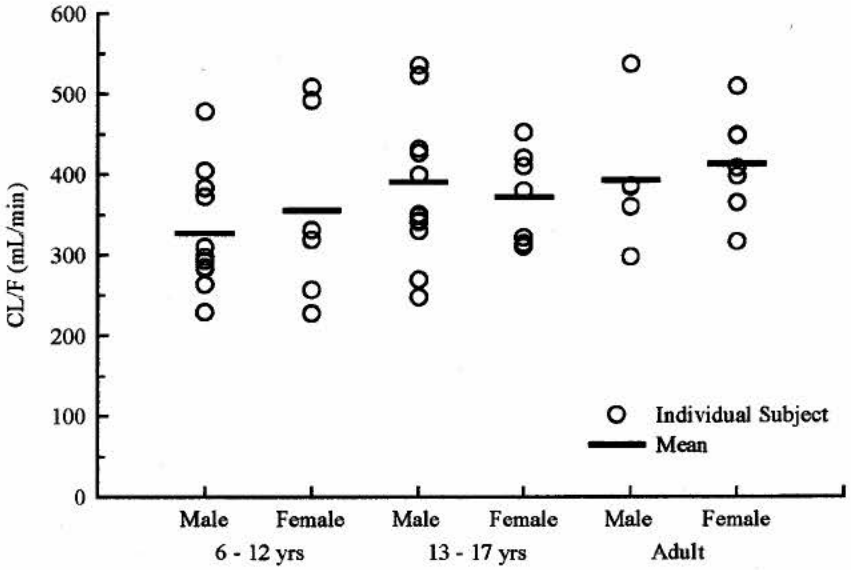


Figure 28: Relationship between CL/F and gender for l-amphetamine after oral administration of ADDERALL XR®.

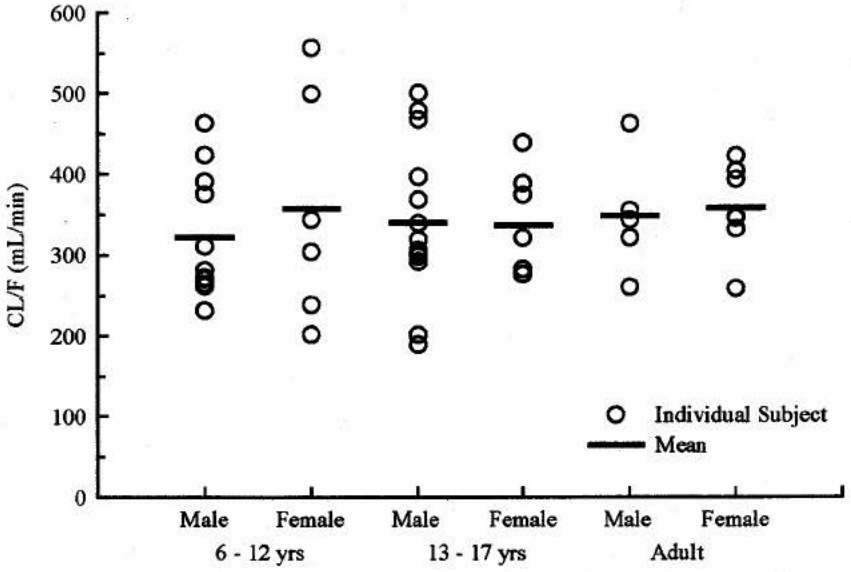


Figure 29: Relationship between Vz/F and gender for d-amphetamine after oral administration of ADDERALL XR®.

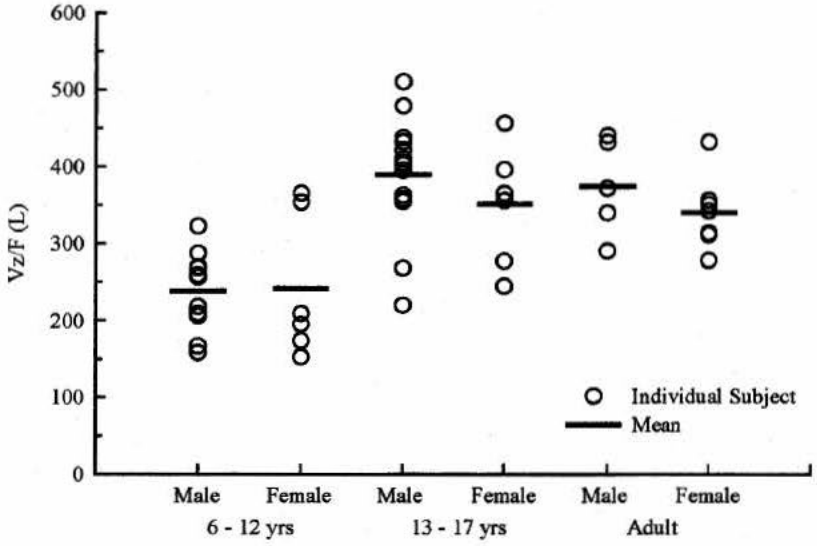


Figure 30: Relationship between Vz/F and gender for l-amphetamine after oral administration of ADDERALL XR®.

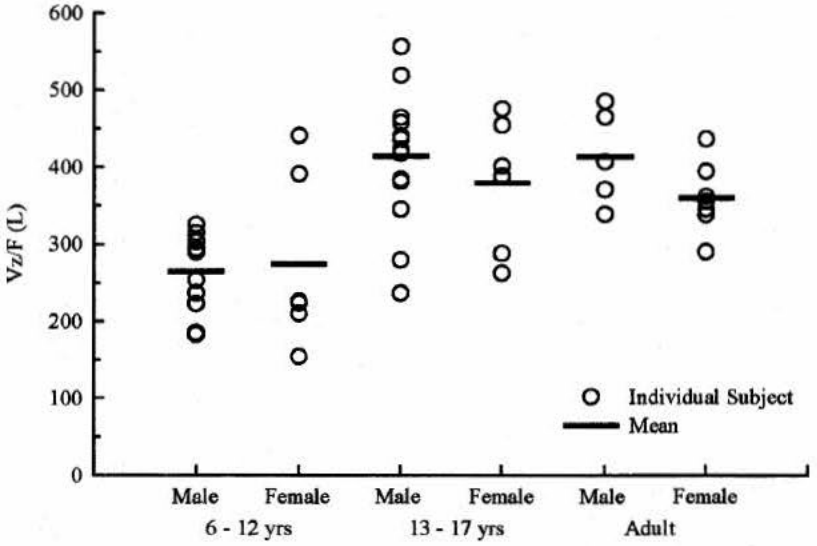


Figure 31: Relationship between t½ and gender for d-amphetamine after oral administration of ADDERALL XR®.

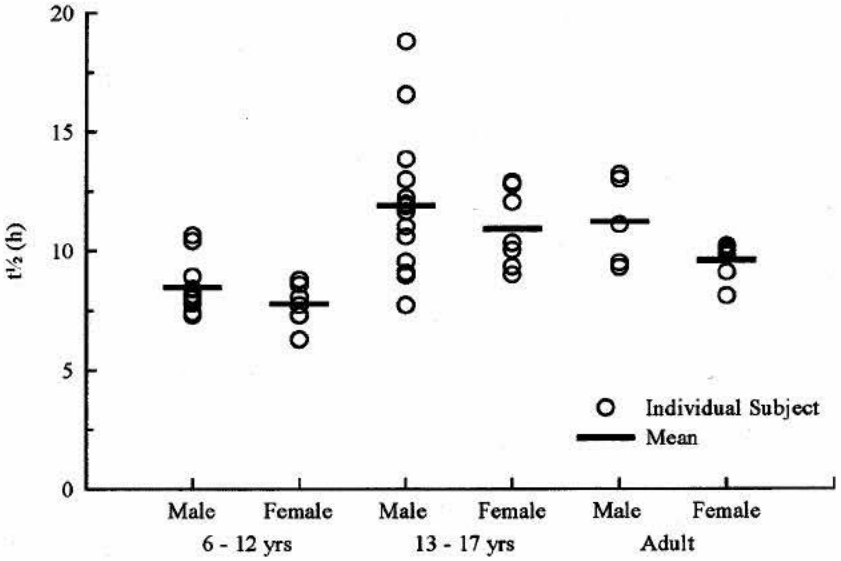


Figure 32: Relationship between t½ and gender for l-amphetamine after oral administration of ADDERALL XR®.

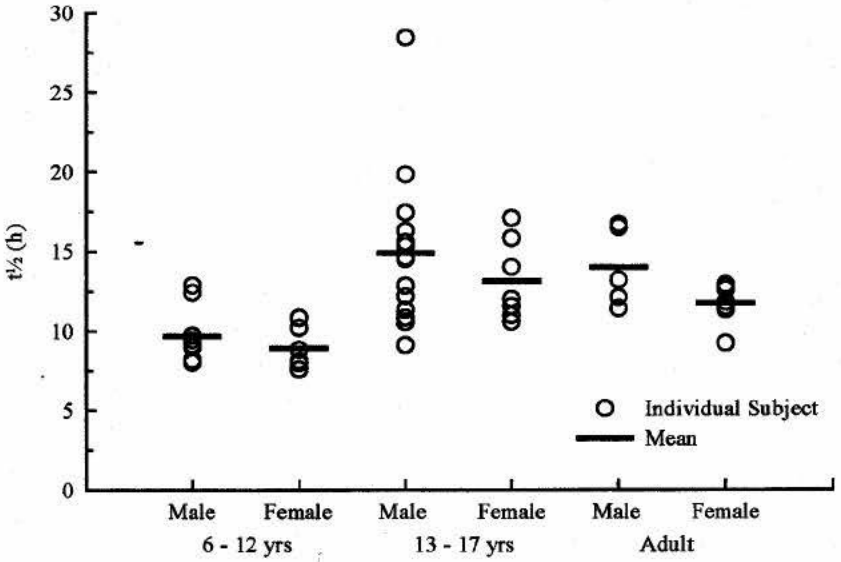


Figure 33: Relationship between Cmax and gender for d-amphetamine after oral administration of ADDERALL XR®.

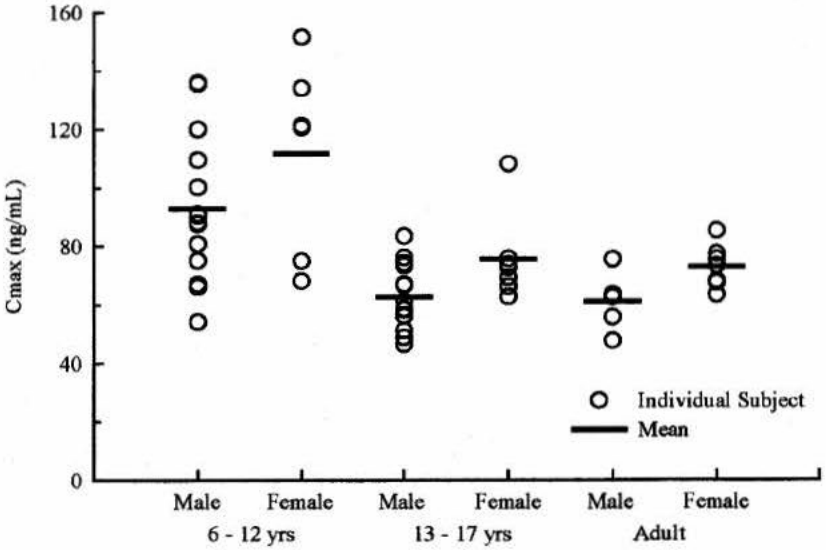


Figure 34: Relationship between Cmax and gender for l-amphetamine after oral administration of ADDERALL XR®.

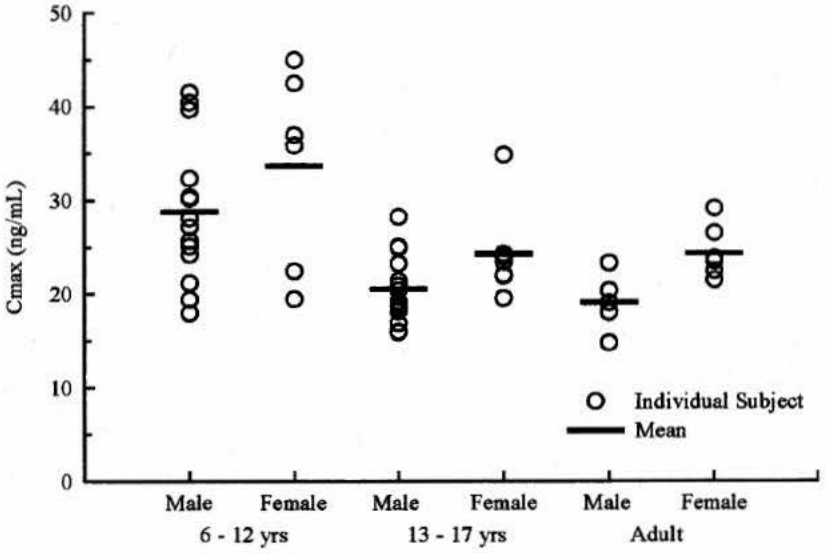


Figure 33: Relationship between Cmax and gender for d-amphetamine after oral administration of ADDERALL XR®.

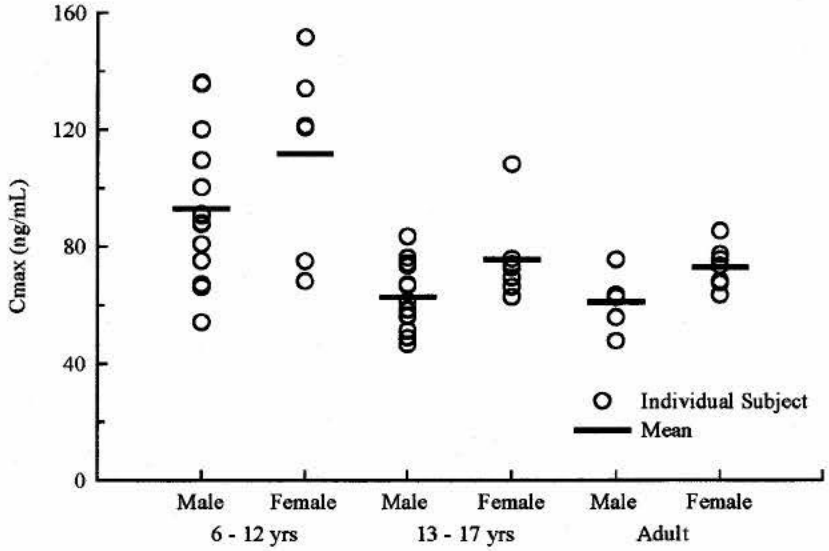


Figure 34: Relationship between Cmax and gender for l-amphetamine after oral administration of ADDERALL XR®.

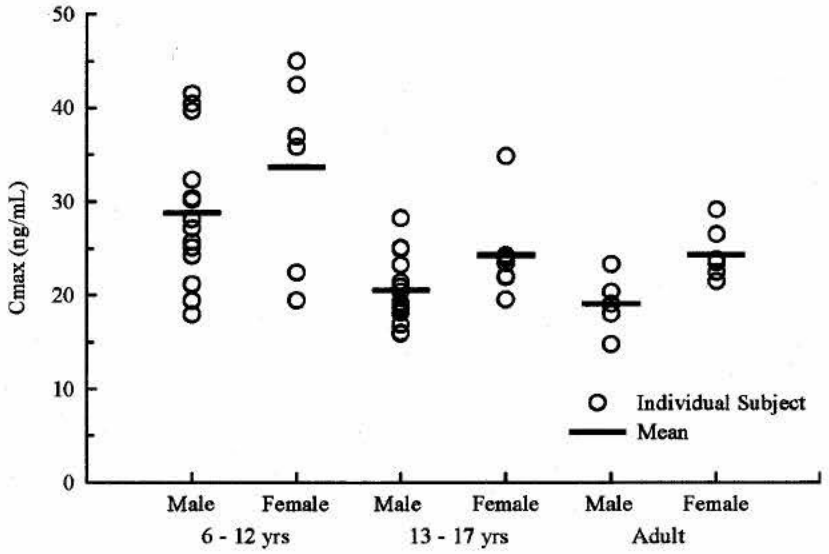


Figure 35: Relationship between Tmax and gender for d-amphetamine after oral administration of ADDERALL XR®.

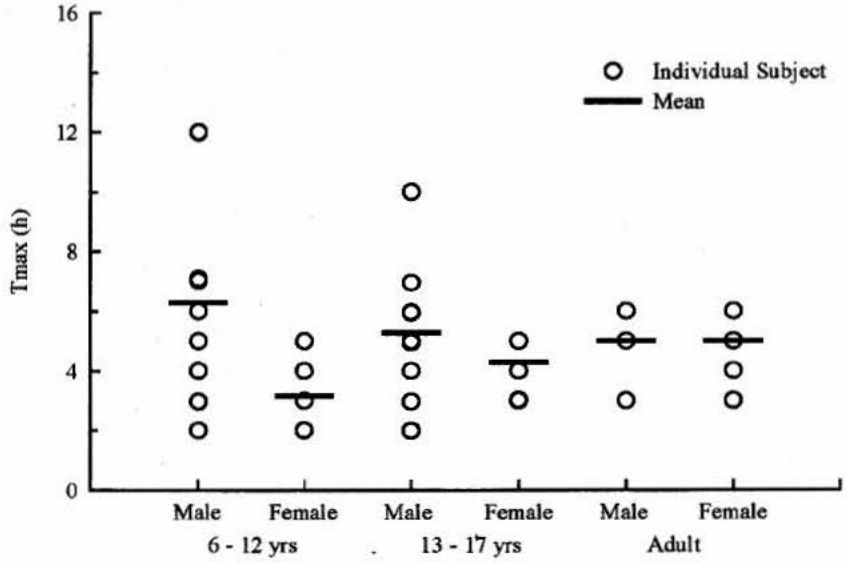


Figure 36: Relationship between Tmax and gender for l-amphetamine after oral administration of ADDERALL XR®.

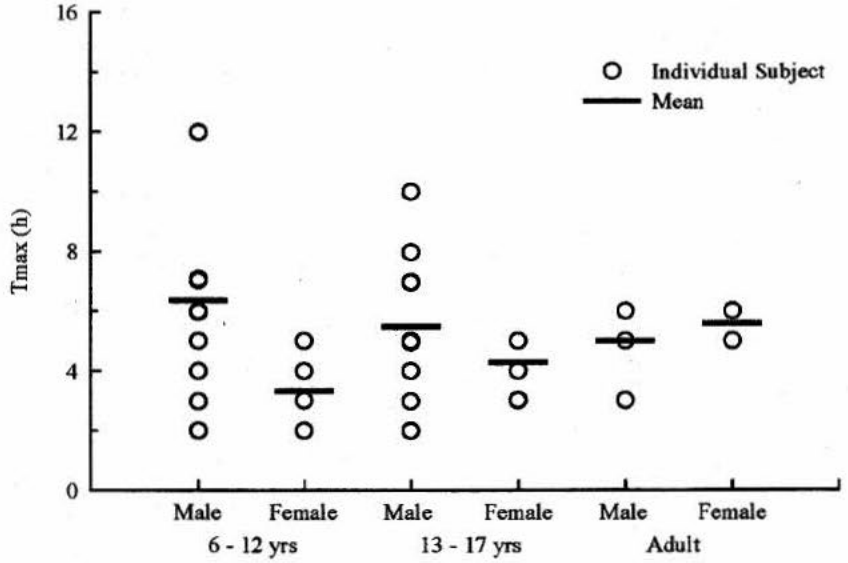


Table 6: Statistical comparison of pharmacokinetic parameters for d- and l-amphetamine by gender after oral administration of ADDERALL XR®.

	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	91.0	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)

APPEARS THIS WAY ON THE ORIGINAL

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

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		**1**		
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	**NA**			
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/

Andre Jackson
10/13/04 08:11:32 AM
BIOPHARMACEUTICS

Sally Yasuda
10/18/04 04:56:31 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-303 SUPPL # 009 HFD # 130

Trade Name Adderall XR Extended-Release Capsules

Generic Name mixed salts of a single-entity amphetamine product

Applicant Name Shire Development, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-303

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study SLI381.110 and Study SLI381.314

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study SLI381.110 and Study SLI381.314

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 58,037	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 58,037	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Richardae Taylor, Pharm.D.
Title: Project Manager
Date: 7/19/05

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Acting Division Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Thomas Laughren
7/22/05 09:06:47 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-303 **Supplement Type (e.g. SE5):** SE5 **Supplement Number:** 009

Stamp Date: September 17, 2004 **Action Date:** July 31, 2005

HFD 130

Trade and generic names/dosage form: Adderall XR (mixed salts of a single-entity amphetamine product) Extended-Release Capsules

Applicant: Shire Development, Inc. **Therapeutic Class:** Amphetamine Product

Indication(s) previously approved: ADHD

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: adolescent ADHD

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver ____Deferred __X__Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

❑ **Products in this class for this indication have been studied/labeled for pediatric population**
❑ **Disease/condition does not exist in children**
❑ **Too few children with disease to study**
❑ **There are safety concerns**
❑ **Adult studies ready for approval**
❑ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies: Original NDA approved in pediatric population, children with ADHD aged 6-12 years. This supplement provided for the adolescent population.

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-303/S-009
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Thomas Laughren

7/22/05 09:11:09 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 2 2005

Bradley Vince, DO
Vince and Associates Clinical Research
6600 College Blvd., Suite 330
Qverland Park, Kansas 66211

Dear Dr. Vince:

On January 18 and January 19, 2005, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation:

> Protocol SLI381.314 entitled "A Phase III, Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Safety and Efficacy Study of ADDERALL XR® in Adolescents with Attention Deficient Hyperactivity Disorder" of the investigational drug ADDERALL XR®, performed for Shire.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN/FEI: #3004857432

Field Classification:NAI
Headquarters Classification:
__x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:

HFA-224
HFD-120 Doc.Rm. NDA#21-303/SE1-009
HFD-120/Katz
HFD-120/Cai
HFD-120/Taylor
HFD-46/c/r/s/ GCP File #11397
HFD-46/Stasko
HFR-SW350/DIB/Thorsky
HFR-SW350/Bimo Monitor and Field Investigator/Montgomery
GCF-1 Seth Ray

r/d: (Stasko): (2/28/05)
reviewed:NK:(3/1/05)
f/t:
o:\Stasko\GCP Letters\Vince, Brad NAI LTR AdderallXR PWR NDA21802 21303.s009 2 05.doc

Reviewer Note to Rev. Div. M.O.

- A total of 18 subjects were enrolled for protocol SLI381-314 and 18 subjects did complete the randomized portion of the study. Five subjects discontinued in the taper portion of the study. There are no details provided as to why these subjects discontinued. For the taper portion of trial SL1381.314B, a total of thirteen patients completed this arm. An in-depth audit of 1/3 of the subjects' records was conducted.

- All subjects signed the informed consent. No significant discrepancies noted between the source documents, CRF and data listings. No underreporting of adverse events noted.

- Overall, data appeared acceptable.

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/s/

Ni Aye Khin

3/13/05 06:20:48 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-303/S-009

Shire Pharmaceutical Development, Inc.
Attention: Stephen W. Sherman, JD
Senior Director, Regulatory Affairs
U.S. Research and Development
1801 Research Blvd., Suite 600
Rockville, MD 20850

Dear Mr. Sherman:

Please refer to your September 17, 2004 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall XR (mixed salts of a single-entity amphetamine product) Extended-Release Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 16, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Details on the foreign postmarketing surveillance reports were not provided in the submission. Please provide this information.
2. Provide information regarding who conducted the review of the literature search and what information was actually reviewed. In addition, please provide an explanation for the conclusions.
3. Please provide tables for the outliers in the laboratory analysis.
4. We note that the "alpha level 0.50" is mentioned throughout your submission. Please clarify if this is the correct value or a typographical error.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}
Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

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