CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11-522/S-030

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I

NDA:	11,522 [SCF-030(AZ)]
Brand Name:	Adderall®
Generic Name	Mixed salts of single-entity amphetamine product
Dosage form and Strength:	IR Tablets (5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, and 30mg)
Route of administration:	Oral
Indication:	Attention Deficit Disorder with Hyperactivity (ADHD) and narcolepsy
Sponsor:	Shire Pharmaceutical Development Inc.
Type of submission:	Supplement amendment-Full response to Approvable letter
Clinical Division:	HFD-120/Neuropharmacological Drug Products
OCPB Division:	HFD-860/DPEI
Priority:	Standard
Submission date:	07/08/02
OCPB Consult date:	07/12/02
Reviewer:	Wen-Hwei Chou, Pharm.D., Ph.D.
Team leader:	Ramana Uppoor, Ph.D.

1 Executive summary

This review evaluates a supplement amendment in response to the approvable letter dated March 20, 2002 for a prior-approval supplement of NDA11,522. The prior-approval supplement was for the 7 marketed strengths (5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, and 30mg) of Adderall® tablets. In the approvable letter, the sponsor was requested to address comments from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) regarding issues on bioanalytical assay and revision of labeling from the available sources.

Overall, the sponsor's responses to OCPB comments are found to be satisfactory. In addition, OCPB proposes minor changes to the labeling text.

Additionally, the sponsor proposed a level 1 revision of commercial batch sizes and validation protocol. Additional dissolution data will be required for this level 1 scale-down change in batch size.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed this supplement amendment: Full response to approvable letter to the NDA11-522 and finds it acceptable to support approval of this CMC supplement. Comments (1) (general labeling) and (2) (level 1 batch size change) can be addressed separately. Please forward comments (1) and (2) to the sponsor.

1.2 Comments to the sponsor:

(1) The proposed labeling text is generally acceptable. Several minor changes are recommended (bold font indicates added text, strikethrough indicates deletion):
   (a) In the "Pediatric Patients" subsection, label text of (age 7-12 years) should be added: Children **(age 7-12 years)** eliminated amphetamine faster than adults.
   (b) In the "Metabolism & Elimination" subsection: **A minor metabolite formed via** ring hydroxylation of amphetamine has been shown to be mediated in vitro by cytochrome P450 2D6.
   (c) In the "Gender" subsection: Systemic exposure to amphetamine was 20-30% higher in women (N=19) than in men (N= 17)~~.~~ due to the higher dose administered to women on a mg/kg body weight basis~~)~~.

(2) The sponsor is requested to submit dissolution data (application/compendial medium and specification) for all seven strengths including different batch sizes that are being proposed. This should be submitted in the same manner as outlined in SUPAC-IR level 1 batch size change (annual report).

Wen-Hwei Chou, Pharm.D., Ph.D. _____

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

cc: NDA11-522 Adderall®, HFD-120, HFD-860 (Mehta, Sahajwalla, Uppoor, Oliver, Chou), Central Documents Room (Biopharm-CDR)

APPEARS THIS WAY
ON ORIGINAL

2 Table of contents

3 Summary of clinical pharmacology and biopharmaceutics findings

The sponsor submitted this amendment in response to the approvable letter issued on March 20, 2002 to NDA 11,522 (S-030). In current submission, the sponsor incorporated responses to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) comments regarding issues on bioanalytical assay and revision of labeling from the available sources. The sponsor proposed revision of labeling text based on the two BE studies submitted in S-030, seven literature references, one study report from children with attention deficit hyperactivity disorder, and label text of Adderall XR (extended release tablet). In addition, the sponsor proposed a level 1 revision of commercial batch sizes and validation protocol. Additional dissolution data will be required for this level 1 scale-down changes in batch size (to be submitted as annual report).

Overall, the sponsor's responses to OCPB comments are found to be satisfactory. In addition, OCPB proposes minor changes to the labeling text.

4 Question based review

4.1 Basics of Adderall

Adderall is an amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate. ADDERALL® (immediate-release) tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Adderall is indicated for the treatment of Attention Deficit Disorder with Hyperactivity (ADHD) and narcolepsy. The daily dose for ADHD in children from 3 to 5 years of age is 2.5 mg daily; raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In children 6 years of age and older, treatment should start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. The usual daily dose for narcolepsy is 5 mg to 60 mg per day in divided doses. Adverse reactions that may result from amphetamine use include palpitations, tachycardia, elevation of blood pressure, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances, anorexia and weight loss, urticaria, impotence, and changes in libido.

4.2 Did the sponsor adequately address the comments from the Office of Clinical Pharmacology and Biopharmaceutics?

Overall, the sponsor's responses to the three comments from the Office of Clinical Pharmacology and Biopharmaceutics are found to be satisfactory.

Briefly summarized below are sponsor's responses to three comments from OCPB:

(1) Based on information from current submission, the following relevant PK information should be added to the "Clinical Pharmacology" section of the label:

Pharmacokinetics

ADDERALL® (immediate-release) tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of a single dose 10 or 30mg of ADDERALL® (immediate-release) to healthy volunteers under fasted conditions, peak plasma concentrations occurred approximately 3 hours post-dose for both d-amphetamine and l-amphetamine. The mean elimination half-life (t1/2) for l-amphetamine was longer than the t1/2 of d-isomer (11.5-13.8 hours vs 9.77-11hours). The PK parameters (Cmax, AUC0-inf) of d- and l-amphetamine increased approximately from 10 mg to 30mg indicating dose-proportional pharmacokinetics.

Sponsor's response:

Agreed to the addition of this paragraph with minor modification and has amended the draft package insert accordingly. The proposed non-substantive minor revisions to the paragraph are listed below:

(a) They removed the parenthetical references to "immediate-release" after the use of ADDERALL for consistency with the rest of the package insert.

(b) In the third sentence that begins "The mean elimination half-life. .," The sponsor revised the sentence so that d-amphetamine is listed before l-amphetamine for consistency with the rest of the package insert.

(c) They have subscripted the "max" in Cmax and the "O-inf" in AUCO-inf.

Agency: Acceptable.

(2) We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the PK of amphetamine is lacking in current label. You are requested to update labeling to incorporate the above information from literature and/or other available resources.

Sponsor's response: Described below are the sponsor proposed labeling text including "Pharmacokinetics" discussed in (1) above. The supportive materials include (a) review of literature regarding the metabolism, and excretion of amphetamine, (b) reanalyzing results (gender-effect) from two studies submitted (under SCF-030, 371.101 & 371.302), (c) newly submitted study report of a study in pediatric ADHD, and (d) label from XR (extended release tablet) race-effect):

Agency:

- Overall, the sponsor proposed revision of label is acceptable. See appendices for individual review of the material submitted to support these revision. In addition, briefly described below are the three labeling issues that are not discussed in the appendices:
  - We consider the following acceptable:
    (a) Gender-effect: the data analysis on gender-effect on PK from the 2 studies submitted in S-030 (see discussion below):

    Gender-effect: Based upon the combined data for both formulations within each study, the female-to-male ratios of Cmax and AUC0-inf ranged from 1.18 to 1.35 and those for t1/2 from 0.86 to 1.03. Ratios for the dose normalized Cmax and AUC0-inf ranged from 0.86 to 1.16. [Ratios are tabulated in tables below]

Study	Males	Females
307.101	7	11
307.102	10	8
Total	17	19

Female-to-Male Ratios

Study	Assay	Parameter*	Female	Male	Ratio (Female/Male)
371.101	d-amphetamine	AUC	990.40	751.81	1.32
		AUC(DN)	2,137.21	1,898.24	1.13
		CMAX	58.61	43.38	1.35
		CMAX(DN)	126.80	110.65	1.15
		THALF	10.00	9.66	1.03
	l-amphetamine	AUC	372.53	280.04	1.33
		AUC(DN)	802.91	707.27	1.14
		CMAX	18.93	13.85	1.37
		CMAX(DN)	40.94	35.30	1.16
		THALF	11.73	11.71	1.00
371.102	d-amphetamine	AUC	311.16	261.16	1.19
		AUC(DN)	1,945.00	2,189.04	0.89
		CMAX	18.36	13.75	1.34
		CMAX(DN)	115.07	115.05	1.00
		THALF	9.98	11.65	0.86
	l-amphetamine	AUC	119.94	101.93	1.18
		AUC(DN)	747.87	851.95	0.88
		CMAX	5.82	4.40	1.32
		CMAX(DN)	36.46	36.84	0.99
		THALF	12.45	14.59	0.85

    (b) Race: The sponsor indicated that since the majority of the subjects in studies 371.101 &311.102 were Caucasians and any effects of race should be related to drug entity rather than the formulation, they proposed using the same statement in the draft labeling for ADDERALL XR (note: separate labels are proposed for ADDERALL & ADDERALL XR);.
    (c) Drug-interaction, The sponsor did not proposed any revision to the "Drug Interaction" section since they indicated that the current label for ADDERALL has an extensive section on Drug Interactions in the section entitled PRECAUTIONS.

- In conclusion, OCPB finds the sponsor proposed labeling text acceptable. Several minor changes are recommended (bold font & underlining indicates added text, strikethrough indicates deletion):
  (a) In the "Pediatric Patients" subsection, label text of (age 7-12 years) should be added: Children **(age 7-12 years)** eliminated amphetamine faster than adults.
  (b) In the "Metabolism & Elimination" subsection: **A minor metabolite formed via** ring hydroxylation of amphetamine has been shown to be mediated in vitro by cytochrome P450 2D6.

(c) In the "Gender" subsection: Systemic exposure to amphetamine was 20-30% higher in women (N=19) than in men (N= 17) due to the higher dose administered to women on a mg/kg body weight basis).

(3) We request that you address the issue regarding procedure for bioanalysis of plasma samples for which concentration values were outside of the linear range defined by the bioanalytical method. We note that nearly 100 out of the 648 concentration values for d-amphetamine in human plasma samples in study#371.101 were outside of the linear range ng/ml) as defined by the bioanalytical method.

Sponsor's response: Plasma samples with a concentration above the upper limit of quantitation (AQL; 50 ng/ml) were reanalyzed after a 2-fold dilution (DF = 2) in a subsequent analytical run that included a dilution quality control (QC) sample.

Agency: Acceptable

4.3 What additional change has the sponsor proposed in this amendment? What additional supportive data is required ?

Sponsor: In current amendment, the sponsor has proposed revisions to its proposed manufacturing batch sizes and validation protocol contained in the Prior-Approval Supplement (S-30) submitted to the Agency on November 20,2001 (page 1-168 and Attachment 1.2.8.1 CMC Briefing Packet for SLI 371 Tablets, page 1-409) for commercial considerations. The manufacturing blend batch size originally listed in Table 1-18, page 1-168 has been changed from kg for all strengths to kg for the 5 mg tablet and kg for the remaining strengths (see Revised Table 1-18 below). The proposed tableting batch sizes have also been adjusted from that described in the original Table 25 (page 1-409) to Revised Table 25, below. Note that two tableting batch sizes are proposed for the 10 mg, 20 mg, and 30 mg strengths.

Agency:

- The sponsor had proposed a level 1 change in batch size, which will need to meet application/compendial release requirements.
- The sponsor is requested to submit this data using application/compendial medium for all strengths including different batch sizes according to SUPAC-IR in the annual report.

5 Appendices: Individual study review including literature references

5.1 Markowitz JS & Patrick KS. PK & PD drug interactions in the treatment of ADHD. Clin Pharmacokinet 2001:40:753-772

Study design	Reviews of literature: Medline & current contents (1966-2000)
Objective	Review of literature on drug-drug interactions pertinent to the ADHD patient
Result	Metabolism of amphetamine primarily involves oxidative deamination to form the inactive metabolites benzoic acid and its glycine conjugate, hippuric acid. Aromatic hydroxylation occurred to a lesser extent.

5.2 Dring LG et al. The metabolite fate of amphetamine in man and other species. Biochem J 1970;116:425-435

Study design	Mass balance study in 3 male volunteers; ^{14}C Amphetamine(±, +,-) 5mg (0.07mg/kg) given orally
Analytical Method	^{14}C in urine and feces was determined with scintillation spectrometer. Amphetamine and its metabolites in urine were determined by the isotope-dilution procedure.
Result	• The ^{14}C excreted mainly (90%) in the urine in 3-4 days. Approximately 60-65% of the dose was excreted in the first 24 hours, about one-half (30% of dose) as unchanged drug, followed by benzoic acid (total, 21%), hippuric acid (16%), 1-phenylpropan-2-one (3.4%) and 4-hydroxyamphetamine (1-6%). • There was little difference in ^{14}C excretion after administration of the three optical forms of amphetamine (±, +,-).

5.3 Caldwell J et al. Comparative metabolism of the amphetamine drugs of dependence in man and monkeys. J med Primatol 1977, 6:367-375

Study design	Mass balance study in 3 male volunteers; ^{14}C Amphetamine(±, +,-) (0.29 mg/kg) given orally
Result	• The ^{14}C excreted mainly (82%) in the urine in 48 hours, about one-half (30% of dose) as unchanged drug, followed by hippuric acid (21%) arising from deamination and side-chain degradation , and 4-hydroxyamphetamine (3%) arising from aromatic hydroxylation.

5.4 Rowland M, Amphetamine blood and urine levels in man. J Pharm Sci 1969:58:508-509

Study design	Dextroamphetamine 10mg in 50-100ml was given to 3 male subjects, blood sample was drawn over 48 hours, while urine was collected usually at 12hour intervals for 6 days and volume and pH recorded.
Results	All subjects gave peak blood levels around 2 hours, after which they declined exponentially over the next 48 hours with a t1/2 around 12 hours. Mean total urinary recovery of unchanged amphetamine was 45% of the ingested dose, which is higher than the 32% previously found.

5.5 Davis JM et al. Effects of urinary pH on amphetamine metabolism. Ann NY Acad Sci 1971;179:493-501

Study design	4 healthy adults (3 female, 1male); 50 microcuries of ^{3}H- Amphetamine(8.6curies/mM) IV and blood samples were drawn at 2, 6, 12, 24 and 48 hours. Studied in 2 occasions, once under a condition (an acidic diet) that would lead to the production of acid urine (pH 5.5-6.0) and once during the production of an alkaline urine (pH 7.5-8.0), which was induced by the oral administration of 2-3 g of sodium bicarbonate four times a day.
Analytical Method	^{3}H in urine was determined with scintillation spectrometer. Amphetamine and its metabolites in urine were determined by the paper and thin-layer chromatography.
Result	• In all 4 subjects, amphetamine was cleared from the blood plasma at a much faster rate during the "acid-ash" diet (when urinary pH was less than 6.0) than during the administration of sodium bicarbonate (urinary pH greater than 7.5).

	• During the production of acidic urine, the t1/2 of amphetamine ranged from 8 to 10.5 hours, whereas during alkaline urine production the t1/2 of plasma amphetamine ranged from 16-31 hours. • The marked differences in rate of disappearance of amphetamine from plasma was reflected in the rate of appearance of amphetamine and of total radioactivity in the urine. During acid urine production, about 70% of the injected radioactivity was excreted in the first 24 hours and 90% during the first 4 days, whereas under alkaline urine production only about 45% was excreted in the first 24 hours and 70-80% during the first 5 days. • Disappearance of amphetamine from the blood is the result of both excretion in the urine and conversion to metabolites. During acid urine production, the excretion of unchanged amphetamine was approximately 4 times as great as the excretion of the deaminated metabolites (hippuric and benzoic acids), whereas during alkaline urine production, deaminated metabolite excretion was almost equal to that of unchanged amphetamine.

5.6 Bechett AH et al. The relation between blood levels and urinary pH values using [14C] amphetamine. J Pharm Pharmacol 1969;21:251-258

Study design	2 healthy male adults, 45 microcuries of S-(+)-[^{14}C]- Amphetamine sulfate in aqueous solution by mouth. Urine samples were collected at 30 minutes interval for 4 hours and then at 60 min intervals for a further 8 hours, finally 24 h sample was collected. Blood samples were taken at times midway between those of urine samples. Two trials were conducted: (a) the urinary pH was not modified, (b) an acid urinary pH (5.0±0.2).
Method	^{14}C was determined with scintillation spectrometer. Amphetamine and its metabolites in urine were determined by the thin-layer chromatography.
Result	• The rate of excretion of amphetamine in urine showed urinary pH dependent fluctuations which agreed with earlier studies made under conditions of fluctuating urinary pH. • Under acid but not under fluctuating urinary conditions the rate or urinary excretion of amphetamine is directly proportional to its plasma concentration.

5.7 Bach MV et al. Involvement of CYP2D6 in the in vitro metabolism of amphetamine, two N-alkylamphetamines, and their 4-hydroxylated derivatives. Xenobiotica 1999:719-732

Study design	In vitro microsomal preparations from cells expressing human CYP2D6
Objective	Determine whether CYP2D6 was capable of catalyzing the direct ring oxidation of amphetamine
Method	The human CYP2D6 microsomal product used in this study was derived from a human AHH-1TK+/- cell line transfected with complementary DNA that encoded human CYP2D6. Total protein content was 10mg/ml in 100mM potassium phosphate (pH7.4) and CYP2D6 content was 170pmol/mg protein. GC assay was used to detect parent and metabolites.
Data analysis	Apparent Michaelis-Menten parameters Km and Vmax were calculated using michaelis-Menten equation by a least square regression analysis of reaction velocities versus substrate concentration curves.
Result	The only metabolite produced from amphetamine was ring-4-hydroxylated compound, and the rates of formation was low relative to other related compounds.

5.8 Reviewer's comments on literature references

- The majority of the studies were old studies, or in a small number of subjects.
- The bioanalytical method used in Davis et al & Beckett et al (i.e. paper or thin layer chromatography) was not considered specific assay.
- Benzoic acid, and its glycine conjugate, hippuric acid, are the primary metabolites of amphetamine, both of which are inactive. After oral administration, 30% to 48% of the dose is recovered unchanged in the urine, the extent dependent upon urine pH. Minor but active metabolites are p-hydroxyamphetamine, phenylpropanolamine, and p-hydroxynorephedrine. The ring hydroxylation of

amphetamine to 4-hydroxyamphetamine, a minor metabolite, has been shown to be mediated in vitro by cytochrome P450 2D6.

5.9 A PK/PD study comparing a single dose of Adderall to twice-daily dosing in children with attention deficit hyperactivity disorder (study 371.403).

(Synopsis is a direct excerpt from the submission)

2. SYNOPSIS

Name of Study Drug:	IND#:	Protocol No.	Phase:	Country:
Adderall®		371.403	IV	USA

Title:
A Pharmacokinetic/Pharmacodynamic Study Comparing a Single Dose of Adderall to Twice-Daily Dosing in children with Attention Deficit Hyperactivity Disorder

Principal Investigator/Affiliation:	No. of Study Centers:	Study Period:
	2	First enrollment date: March 29, 1999 Last completion date: May 23, 1999

Objectives: To determine the pharmacokinetics of Adderall in children with ADHD, following once- and twice-a-day single 10 mg dose; to determine the pharmacodynamics and pharmacokinetic/pharmacodynamic correlations of Adderall.

Methodology: This was a randomized, double-blind, two-way cross-over study, at two study sites, to determine the pharmacokinetics and pharmacodynamics of Adderall following once or twice single daily dosing of 10 mg to children with ADHD. There was a one-week washout period prior to treatment and between treatments.

Number of Subjects (planned and analyzed): Twelve children (11 males and one female), between the ages of 7 and 12 years, were enrolled in the study, as required by the protocol. All subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Eligible subjects met the DSM-IV criteria for ADHD, and had a history of significant response to stimulant medication needed as divided daily dosing.

Test Product, Dose and Mode of Administration, Batch Number: Study drug was supplied in hard gelatin capsules, containing 10 mg Adderall (Lot Number: GUS00328.04). Identical capsules were filled with inactive ingredient for the placebo capsules (Lot Number: GUS00328.03). Each child received two doses of study medication, 4 hours apart, either two 10 mg capsules of Adderall, or a single 10 mg capsule of Adderall and a single capsule of placebo.

Duration of Treatment: One day for each of two treatment phases with a 7-day interval

Reference Therapy, Dose and Mode of Administration, Batch Number: There was no active reference therapy in this study. Placebo doses described above were used as dummies in the Adderall one 10 mg dose regimen so that the blinded protocol could be maintained.

Author:	Signature: /S/	Date: 6/5/2000
Statistician:	Signature: /S/	Date: 6-6-2000
Approved by: SVP, Sponsor's Medical Officer	Signature: /S/	Date: 6/12/2000

Name of Study Drug:	IND#:	Protocol No.	Phase:	Country:
Adderall		371.403	IV	USA

Criteria for Evaluation:

Pharmacokinetics: The pharmacokinetic profile of Adderall was based on the following parameters: AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, C_{max}, and T_{max}. Blood samples were drawn pre-dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post dose for assay of d- and l-amphetamine levels, upon which the calculations for the pharmacokinetic parameters was based.

Pharmacodynamics: Improvement in ADHD was based on subjective measures (rating scale for attention and deportation) and an objective measure (number of math problems attempted and solved). The assessments were performed during each of the 10 class periods on the two dosing days.

Safety: Blood pressure was monitored to ensure it was maintained with in prescribed limits. Subjects were monitored for adverse events on each treatment day by questioning and observation.

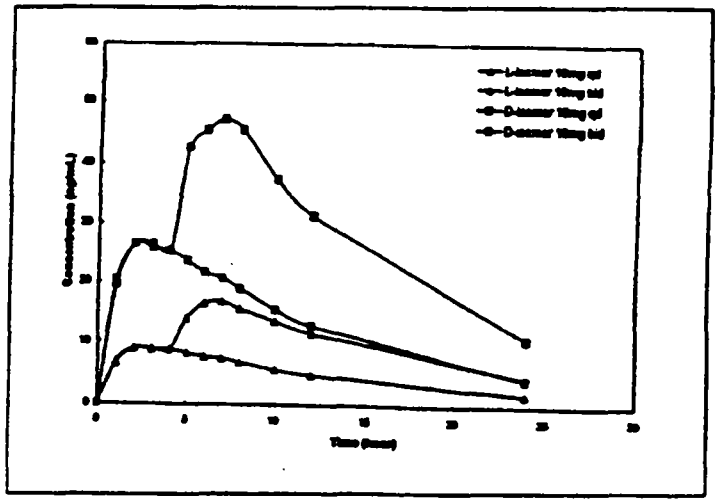
Statistical Methods:

Pharmacokinetics: Pharmacokinetic parameters were not analyzed using the planned analysis of variance since the differences between the two doses were so graphically apparent for all of the parameters except $t_{1/2}$. Descriptive statistics for pharmacokinetic parameters and plasma drug concentration are presented. The differences between the treatment groups were tested at each time point using paired t-test; the analyses were performed for the d- and l-isomers of amphetamine.

Pharmacodynamics: As the study design was not expected to show inter-group differences over the first four hours, the planned analysis of variance was performed only on the data obtained following administration of the second dose, using a 2x4 randomized block design. Descriptive statistics are presented for performance scores on math problems and on rating scales. Inter-group differences between each of these measures following the second dose of study drug were tested by ANOVA (utilizing a 2x4 randomized block design, and including the following factors: center, subject-within-center, treatment and post-2nd-dose-time and an interaction of treatment by post-2nd-dose-time term).

Results:

Pharmacokinetics: The pharmacokinetic analysis showed that after the first dose of Adderall the mean T_{max} for both the l- and the d- isomers of amphetamine was 2.45 hours. A second dose of Adderall, administered 4 hours after the first dose, was absorbed when the plasma concentrations of the d- and l- amphetamines from the first dose were just past their C_{max} values. The plasma concentrations of the amphetamine isomers increased rapidly following the second dose. The C_{max} concentrations after the second dose were approximately twice the C_{max} concentration following the first dose and occurred about 2.45 hours after the second dose (see figure below).



Name of Study Drug: Adderall	IND#:	Protocol No. 371.403	Phase: IV	Country: USA

The other dose-dependant pharmacokinetic parameters for each isomer, AUC_{0-t} and $AUC_{0-\infty}$, following BID dosing, were approximately twice that following QD dosing. Thus, the two 1x10 mg dosing regimen provided each subject with approximately twice the exposure to the amphetamine isomers, as compared to the one 1x10 mg doing regimen, and the Q4H dosing schedule resulted in a longer T_{max} of about 6 to 7 hours.

Pharmacodynamics: For both treatment regimens, the improvements in both the objective and subjective assessments, which were present at 4 hours post dose, were similar following the first Adderall dose. After the second dose of Adderall BID treatment, administered 4 hours after the first dose, the improvements in these parameters were maintained for an additional 6 hours ($p<0.05$ for math test and [redacted] deportment), in comparison to the Adderall QD treatment. The data show that the Adderall 10 mg BID dosing schedule, with a four-hour interval between doses, resulted in additive values for the pharmacokinetic parameters and showed, in children with ADHD, cognitive and behavioral improvement of up to 10 hours as measured by the [redacted] rating scale and math test.

Safety: The adverse events that occurred during the dosing phases were mild and transient. All AEs resolved within the same day. There was no pattern to the type of adverse events that occurred.

CONCLUSIONS: Adderall 10 mg BID regimen with a 4-hour dosing interval provides each subject with approximately twice the exposure to the amphetamine isomers and longer T_{max} of about 6 to 7 hours, as compared to 10 mg QD regimen, which has a T_{max} of about 2.5 hours. Adderall 10 mg administered as a BID dosing schedule is more effective than a single daily dose of 10 mg Adderall with respect to the cognitive and behavioral improvement in children with ADHD. The duration of drug action is about 10 hours for Adderall 10 mg BID given 4 hours apart, compared to a duration of about 6 hours for Adderall 10 mg QD. Adderall shows a clear dose-response relationship for ADHD. Both dosage schedules were safe and well tolerated.

5.9.1 Reviewer's Comments

PK measures

- Age-effect: The 10 mg dose is common to Studies 371.403 (pediatric) and 371.102 (adult) and the mean values for d- and l-amphetamine for Cmax and AUC0-inf (original and dose-normalized) and t1/2 are compared below.
- Children eliminated amphetamine faster than adults. The elimination t1/2 is approximately 4 hours shorter for d-amphetamine and 6 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (AUC) than adults for a given dose of ADDERALL, 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 35% less systemic exposure compared to adults.

Comparison of d- and l-Amphetamine Pharmacokinetic Parameters in Pediatric and Adult Patients after Administration of 10 mg of ADDERALL®

Parameter[1]	Pediatric[2]	Adult[3]
d-amphetamine		
Cmax (ng/mL)	28.4 ± 6.50	13.8 ± 1.35
Cmax (Dose-Normalized)	106 ± 23.7	115 ± 13.3
AUC_∞ (h•ng/mL)	384 ± 109	261 ± 53.6
AUC_∞ (Dose-Normalized)	1447 ± 316	2189 ± 469
t½ (h)	7.47 ± 0.97	11.7 ± 1.49
l-amphetamine		
Cmax (ng/mL)	9.64 ± 2.35	4.40 ± 0.42
Cmax (Dose-Normalized)	36.0 ± 7.71	36.8 ± 4.06
AUC_∞ (h•ng/mL)	146 ± 51.6	104 ± 22.8
AUC_∞ (Dose-Normalized)	542 ± 122	852 ± 187
t½ (h)	8.55 ± 1.57	14.6 ± 1.93

[1]Mean ± standard deviation
[2]Study 371.403, Treatment A (10 mg single dose)
[3]Study 371.102, male subjects, both formulations combined. Data for males were since the majority of the pediatric subjects, 11 of 12, were male.

Demographic and other baseline characteristics:

- Ninety-one percent (11/12) of subjects enrolled were male and 8% (1/12) were female. Race distribution was primarily Caucasian (75%, 9/12), with three Hispanic subjects (25%).

Table 2 Demographic Data

Characteristic	All Subjects
N	12
Age (years)	9.8 ± 1.8*
Weight (lbs)	83.3 ± 28.23*
Height (in)	54.8 ± 3.4*
Sex	
Male	11 (91.7%)
Female	1 (8.3%)
Race:	
Caucasian	9 (75.0%)
Hispanic	3 (25.0%)

*mean ± SD

Bioanalytical method and assay validation:

- We consider the bioanalytical assay used this study acceptable since it is a validated method and has been used for the existing Adderall tablet product.
- Overall the analytical method for d- or l-amphetamine in EDTA treated human plasma was found to be specific, reproducible, sensitive and adequate to characterize the PK of d- and l-amphetamine.
- Method:

- A weighted [(1/x) where x=the concentration of the compound] linear regression was used to determine slopes, intercepts, and correlation coefficients.
- This reviewer has summarized within-study assay validation

Within-study assay performance for d- and l-amphetamine in EDTA human plasma		
	Study #371.403	
Parameters	Quality control samples (d-/l-amphetamine)	standard curve samples (d-/l-amphetamine)
concentration (ng/ml)		
Intra-day precision (%CV)		
Intra-day accuracy (% accuracy)		
Inter-day precision (%CV)		
Inter-day accuracy (% accuracy)		
correlation (range of R2 values)		
Linear range (ng/ml)		
Sensitivity/LLOQ		

Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I

NDA:	11,522 [SCF-030, SCF-30(BB), SCF-30(BC)]
Brand Name:	Adderall®CII
Generic Name	Mixed salts of single-entity amphetamine product
Dosage form and Strength:	IR Tablets (5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, and 30mg)
Route of administration:	Oral
Indication:	Attention Deficit Disorder with Hyperactivity (ADHD) and narcolepsy
Sponsor:	Shire Pharmaceutical Development Inc.
Type of submission:	Prior Approval CMC Supplement
Clinical Division:	HFD-120/Neuropharmacological Drug Products
OCPB Division:	HFD-860/DPEI
Priority:	Standard
Submission date:	11/20/01 01/17/02 [SCF-30(BB), electronic submission of biostudies] 02/12/02 [SCF-30(BC), dissolution data]
OCPB Consult date:	12/07/01
Reviewer:	Wen-Hwei Chou, Pharm.D., Ph.D.
Team leader:	Ramana Uppoor, Ph.D.
Acting Team leader:	Vanitha Sekar, Ph.D.

Executive summary

The sponsor submitted a CMC supplement to the NDA11-522 for multiple postapproval changes in all 7 marketed strengths (5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, and 30mg) of Adderall®CII tablets. Overall, in-vivo bioequivalence (BE) studies are required to adopt these multiple postapproval changes in manufacturing site, manufacturing equipment, and manufacturing process made in this submission. Demonstration of bioequivalence for the highest tablet strength along with the comparative dissolution profiles in the approved medium for other strengths will be sufficient to support the waivers on BE studies of lower strengths. Based on the procedure for tablet compression, the seven strengths can be separated into 2 formulation groups (5, 7.5, and 10mg as one group, and 12.5, 15, 20 and 30mg as another group) where there is compositional proportionality within each formulation group.

The sponsor has submitted two BE studies performed on the 10 and 30 mg tablet strengths along with dissolution profiles in the approved medium for all strengths and has requested biowaivers for the remaining strengths. Overall, the sponsor has submitted sufficient information to support these multiple postapproval changes in all 7 strengths of Adderall. This approval is based on the bioequivalence of the 10mg and 30 mg tablets manufactured before and after the changes were made, and granting of biowaivers for the remaining strengths (5mg, 7.5mg, 12.5mg, 15mg, and 20mg) based on the similar dissolution profiles, compositional proportionality and dose-proportional pharmacokinetics.

The sponsor did not propose labeling changes, however, since relevant clinical pharmacology information is lacking in current label, the sponsor will be requested to update label from available sources.

Recommendation:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed this CMC supplement to the NDA11-522 for multiple postapproval changes and finds it acceptable. Please forward comments (1)–(3) to the sponsor.

Comments to the sponsor:
Labeling:

1. We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the PK of amphetamine is lacking in current label. You are requested to update labeling to incorporate the above information from literature and/or other available resources.

2. Based on information from current submission, the following relevant PK information should be added to the "Clinical Pharmacology" section of the label:

   Pharmacokinetics
   ADDERALL® (immediate-release) tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of a single dose 10 or 30mg of ADDERALL® (immediate-release) to healthy volunteers under fasted conditions, peak plasma concentrations occurred approximately 3 hours post-dose for both d-amphetamine and l-

amphetamine. The mean elimination half-life (t1/2) for l-amphetamine was longer than the t1/2 of d-isomer (11.5-13.8 hours vs 9.77-11hours). The PK parameters (Cmax, AUC0-inf) of d- and l-amphetamine increased approximately three-fold from 10 mg to 30mg indicating dose-proportional pharmacokinetics.

General Comment:

3. We request that you address the issue regarding procedure for bioanalysis of plasma samples for which concentration values were outside of the linear range defined by the bioanalytical method. We note that nearly 100 out of the 648 concentration values for d-amphetamine in human plasma samples in study#371.101 were outside of the linear range ng/ml) as defined by the bioanalytical method.

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT Initialed by Vanitha Sekar, Ph.D. _____

cc: NDA11-522 Adderall®CII, HFD-120, HFD-860 (Mehta, Marroum, Uppoor, Sekar, Chou), Central Documents Room (Biopharm-CDR)

Table of contents

Summary of clinical pharmacology and biopharmaceutics findings

Adderall is a single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate. ADDERALL® (immediate-release) tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Adderall is indicated for the treatment of Attention Deficit Disorder with Hyperactivity (ADHD) and narcolepsy. The daily dose for ADHD in children from 3 to 5 years of age is 2.5 mg daily; raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In children 6 years of age and older, treatment should start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. The usual daily dose for narcolepsy is 5 mg to 60 mg per day in divided doses. Adverse reactions that may result from amphetamine use include palpitations, tachycardia, elevation of blood pressure, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances, anorexia and weight loss, urticaria, impotence, and changes in libido.

The approved dissolution method and specification for all 7 strengths are as follow: USP Apparatus I, 900ml water, 100rpm, Q % in 30 minutes, detection at nm. The sponsor submitted a CMC supplement to the NDA11-522 for multiple postapproval changes in all 7 marketed strengths (5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, and 30mg) of Adderall®CII tablets. Based on the postapproval changes made, the regulatory requirement in order to adopt these changes for Adderall required the sponsor to submit two BE studies on the highest strengths (10mg and 30mg) from each formulation group. BE studies on 5, 7.5, 12.5, 15, and 20 mg tablets would be waived provided that dissolution profiles are similar in application/compendial medium for all strengths for the new and reference products, pharmacokinetics are dose proportional and there is proportionality in composition.

In the initial submission, the sponsor submitted two BE studies performed on highest strengths (10 and 30mg) from two common blends and requested biowaivers for the remaining strengths without providing any dissolution profiles. Later, upon Agency's request the sponsor submitted dissolution profiles in application/compendial medium (water) for all 7 strengths from the batches manufactured before and after the changes were made, and the bio-batches used for the 2 BE studies (10 and 30 mg). In addition, the sponsor also submitted a dissolution profile for the 5mg new tablet in 0.1NHCl medium for consideration since the new 5mg tablet failed to demonstrate the similarity in approved medium based on the f2 test, when compared to the existing 5 mg tablet.

Question based review

(1) What are the postapproval changes made to this product and submitted in this supplement?

In the current submission, the sponsor has submitted multiple postapproval changes including changes in the manufacturing site, equipment and process

for all 7 marketed strengths (5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, and 30mg) of Adderall®CII tablets (Table 1).

Table 1 OCPB's summary of postapproval changes and overall requirement for approval

Category of Changes	Level of change	What SUPAC IR Guidance recommends	What the Sponsor initially submitted	Regulatory requirement
Manufacturing site	3	Case B dissolution: Multiple-point dissolution profile performed in the application/compendial medium	None	In addition to the 2 in-vivo BE studies performed on the highest strength (10 or 30mg) of each common blend, a Case B dissolution profiles in application/ compendial medium for all 7 strengths (5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, and 30mg) are required in order to grant the waiver of BE studies for the remaining strengths.
Manufacturing equipment	2	Case C dissolution: Multiple-point dissolution profiles performed in 5 different media	None	
Manufacturing process	3	In vivo bioequivalence (BE) study	2 BE studies performed on 10 and 30 mg	

The 7.5 and 10mg tablets are compressed from a common blend and 12.5, 15, 20 and 30mg are compressed from a different common blend. Although 5mg tablets were manufactured separately, the composition of the 5 mg tablet is considered quantitatively proportional to the 7.5mg and 10 mg tablet composition. Following differences between 5mg tablet and 7.5/10mg are noted: (1) higher content % individually) for 4 active ingredients, (2) the absence of the colorant, and (3) minor adjustment in other excipients to replace the colorant in the formulation. (Tables 2, 3, 4, 5)

Table 2

Table 1-17 Batch Formula for SLI 371 Tablets (Batch Size Used in Clinical and Stability Studies)

Component	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	20 mg	30 mg
Amphetamine Aspartate Monohydrate							
Amphetamine Sulfate, USP							
Dextroamphetamine Saccharate							
Dextroamphetamine Sulfate, USP							
Magnesium Stearate, NF							
FD&C Aluminum Lake Blue #1 [redacted]							
FD&C Aluminum Lake Yellow #6							
Total[1]	74.90	74.89	74.89	74.88	74.88	74.88	74.88

[1]Totals have been rounded to nearest hundredth.
[2]Used for 7.5 mg and 10 mg tablets only
[3]Used for 12.5 mg, 15 mg, 20 mg, and 30 mg tablets only.

Table 3

Table 19 Quantitative Composition of SLI 371 Tablets

Component	Quantity (%)		
	5 mg	7.5 mg and 10 mg	12.5 mg, 15 mg, 20 mg, and 30 mg
Dextroamphetamine Sulfate, USP			
Amphetamine Aspartate			
Dextroamphetamine Saccharate			
Amphetamine Sulfate, USP			
Magnesium Stearate, NF			
FD&C Aluminum Lake Yellow #6			
FD&C Aluminum Lake Blue #1			

Table 4

Table 1-15 Theoretical Milligram/Tablet of Components in SLI 371 Tablets, 5 mg, 7.5 mg, and 10 mg

Component	5 mg[1] (mg/tablet)	7.5 mg[1] (mg/tablet)	10 mg[1] (mg/tablet)
Amphetamine Aspartate Monohydrate			
Amphetamine Sulfate, USP			
Dextroamphetamine Saccharate			
Dextroamphetamine Sulfate, USP			
Magnesium Stearate, NF			
FD&C Aluminum Lake Blue #1 [redacted]			
Total[1]			

[1]All values, including the totals have been rounded to nearest hundredth.
[2]Used for 7.5 mg and 10 mg tablets only.

Table 5

Table 1-16 Theoretical Milligram/Tablet of Components in SLI 371 Tablets, 12.5 mg, 15 mg, 20 mg and 30 mg

Component	12.5 mg[1] (mg/tablet)	15 mg[1] (mg/tablet)	20 mg[1] (mg/tablet)	30 mg[1] (mg/tablet)
Amphetamine Aspartate Monohydrate				
Amphetamine Sulfate, USP				
Dextroamphetamine Saccharate				
Dextroamphetamine Sulfate, USP				
Magnesium Stearate, NF				
FD&C Aluminum Lake Yellow #6 [redacted]				
Total				

[1]All values, including the totals have been rounded to nearest hundredth.

(2) Has the sponsor submitted sufficient supportive information for the multiple postapproval changes?

The sponsor has conducted two BE studies on the highest strengths (10 and 30 mg) from each common blend. Results from the BE studies are discussed below. The test products of Adderall (10mg and 30mg) are bioequivalent to the marketed products of Adderall. The 90% CI of test-to-reference ratio fell within the recommended 0.80-1.25 goal-post for the log transformed PK parameters (Cmax and AUC0-inf) and the elimination half-lives and tmax were comparable for test and marketed products of both isomers (Tables 6-8, Fig 1-2)

Table 6

Table 2-4 Pharmacokinetic Parameters and Bioequivalence Comparison for after oral administration of single 30 mg doses of the new and marketed ADDERALL tablet formulations to healthy volunteers (Study 371.101)

Parameter[2]	Formulation		Ratio[1]	
	New	Marketed	Point Estimate	90% Confidence Interval
d-Amphetamine				
C_{max} (ng/mL)	53.1 ± 10.7	52.2 ± 10.9	1.02	0.99 → 1.05
AUC_{0t} (h•ng/mL)	891 ± 227	865 ± 231	1.03	0.99 → 1.08
AUC_{∞} (h•ng/mL)	911 ± 238	884 ± 242	1.03	0.99 → 1.08
l-Amphetamine				
C_{max} (ng/mL)	17.0 ± 3.72	16.9 ± 3.63	1.01	0.98 → 1.03
AUC_{0t} (h•ng/mL)	323 ± 88.6	318 ± 92.3	1.02	0.97 → 1.07
AUC_{∞} (h•ng/mL)	339 ± 92.7	334 ± 97.7	1.02	0.97 → 1.08

[1]Ratio of the new to the marketed formulation Analysis of natural log-transformed data
[2]Mean ± standard deviation

Table 7

Table 2-5 Pharmacokinetic Parameters and Bioequivalence Comparison after oral administration of single 10 mg doses of the new and marketed ADDERALL tablet formulations to healthy volunteers (Study 371.102).

Parameter[2]	Formulation		Ratio[1]	
	New	Marketed	Point Estimate	90% Confidence Interval
d-Amphetamine				
C_{max} (ng/mL)	15.7 ± 3.01	15.8 ± 3.02	0.98	0.96 → 1.01
AUC_{0t} (h•ng/mL)	263 ± 61.8	277 ± 74.1	0.95	0.92 → 0.99
AUC_{∞} (h•ng/mL)	276 ± 62.3	290 ± 76.4	0.96	0.93 → 1.00
l-Amphetamine				
C_{max} (ng/mL)	5.02 ± 0.89	5.00 ± 0.95	1.00	0.97 → 1.02
AUC_{0t} (h•ng/mL)	92.1 ± 24.5	97.4 ± 29.6	0.96	0.92 → 1.00
AUC_{∞} (h•ng/mL)	107 ± 26.5	112 ± 31.5	0.97	0.93 → 1.01

[1]Ratio of the new to the marketed formulation Analysis of natural log-transformed data
[2]Mean ± standard deviation

Table 8 Terminal t1/2 and tmax of d- and l-amphetamine:

	d-amphetamine				l-amphetamine			
	10mg tablet (study# 371.102)		30mg tablet (study# 371.101)		10mg tablet (study# 371.102)		30mg tablet (study# 371.101)	
	t1/2 (hr)	tmax (hr)	t1/2 (hr)	tmax (hr)	t1/2 (hr)	tmax (hr)	t1/2 (hr)	tmax (hr)
test product	10.9±1.67	2.72	9.77±1.93	2.50	13.5±2.46	2.89	11.5±2.48	3.03
marketed product	11.0±1.96	2.62	9.97±1.80	2.58	13.8±2.37	2.80	11.9±2.26	2.94

Fig 1

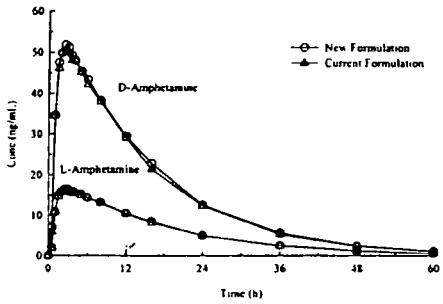


Figure 2-1 Mean plasma concentrations of d-amphetamine and l-amphetamine after oral administration of single 30 mg doses of the new and marketed ADDERALL tablet formulations to healthy volunteers (Study 371.101).

Fig 2

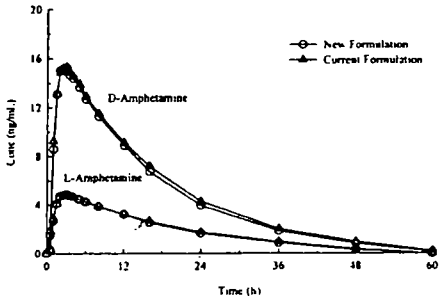


Figure 2-2 Mean plasma concentrations of d-amphetamine and l-amphetamine after oral administration of single 10 mg doses of the new and marketed ADDERALL tablet formulations to healthy volunteers (Study 371.102).

The sponsor has also submitted dissolution profiles in the compendial/application medium for all strengths. The proposed bioanalytical assay and product dissolution method and specification for the test product (SLI371) are acceptable since the sponsor adopted them from the existing Adderall tablet product for all 7 strengths (Table 9).

Table 9

Table 2-10 Proposed Product Dissolution Method and Specification

1	**Dosage Form:**	Tablet	Tablet
2	**Strength:**	10 mg	30 mg
3	**Apparatus Type:**		
4	**Media:**		
5	**Volume:**		
6	**Speed of Rotation (Rate of Flow for Flow-Through Apparatus):**		
7	**Sampling Time(s):**		
8	**Brief Description of the Dissolution Analytical Method:**		
9	**Recommended Dissolution Specification:**		

As noted by Dr. Christy John in his chemistry review dated August 31, 2000, the original approved dissolution specification was "Not Less Than" (NLT) % (Q) of label claim in 45 minutes (500ml Water, USP I, basket at 100rpm, 37°C ± 0.5°C). Later, in a general correspondence dated January 20, 2000, this specification was tightened to NLT % (Q) of label claim in 30 minutes. In addition, as noted by Agency letter to the sponsor dated January 29, 1997, an alternative method may be used for routine batch release.

Both the currently approved and the test products including biobatches have similar dissolution profiles in the application medium (water) for all tablet strengths except for the 5mg tablet for which similarity factor (f2) was (less than the recommended value of or greater) (Table10, 11 and Fig 3-9) However, the dissolution profile obtained in 0.1N HCl for the 5mg strength demonstrates that at 15 minutes, the tablets were % dissolved indicating a rapidly dissolving drug product, and suggests that dissolution is probably not the rate limiting step for in-vivo bioavailability (Table 12). In addition, tmax for d- and l-amphetamine were approximately 3 hours post-dose respectively, suggesting that the differences observed in the dissolution profiles at the early time points (10 and 15 minutes) for the 5 mg strength may not be clinically relevant.

Table 10: Dissolution profile comparisons: SLI37 (tested product) vs Adderall IR (approved product) in application/compendial medium (water) including biobatches [10mg (0I2775, 30mg (0C2780, B5306)]

Tablet Strength	f2 similarity Factor
5mg	37
7.5mg	81
10mg	50
12.5mg	71
15mg	71
20mg	61
30mg	79

Table 11: Dissolution profile for **Adderall IR tablets, 10mg in water (biobatch 0H5157)**

Time (minutes)	Bio-batch 0H5157 % dissolved	Average	Std Dev
10		97	3.9
20		101	1.7
30		101	1.4
40		103	1.2

Table 12: SLI371 tablets, 5mg in 0.1NHCl

Batch	% dissolved at 15 minutes	Average	Std Dev
0F6012		96	3.2
0F6022		103	3.6
0J6023		102	2.9

Fig 3

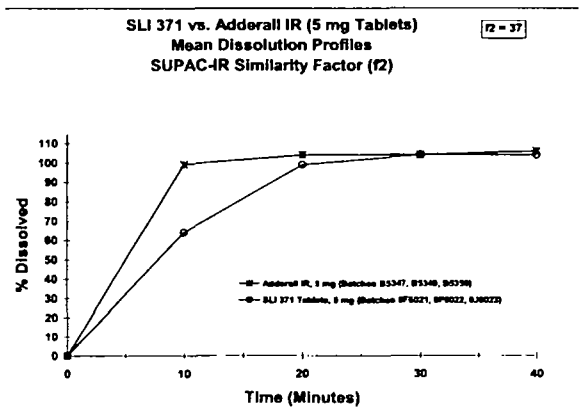


Fig 4

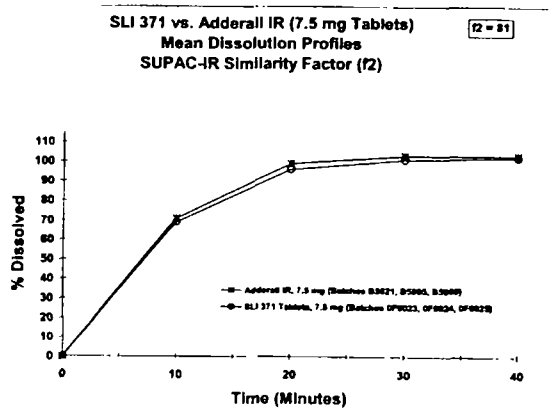
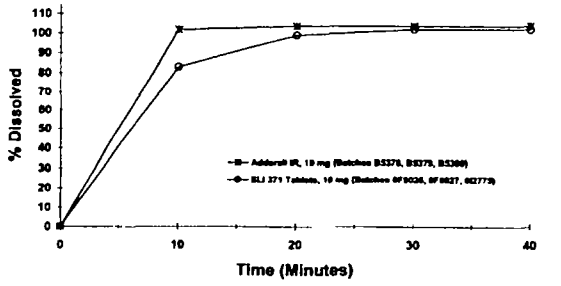


Fig 5

Fig 6



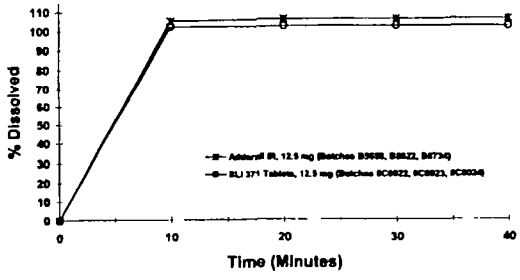
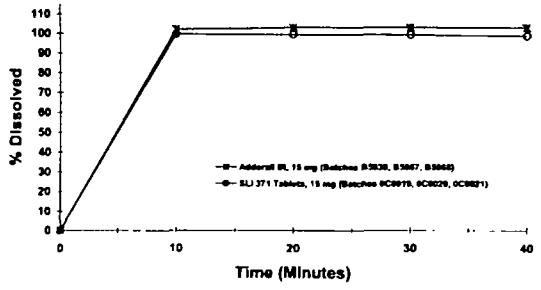


Fig 7

Fig 8



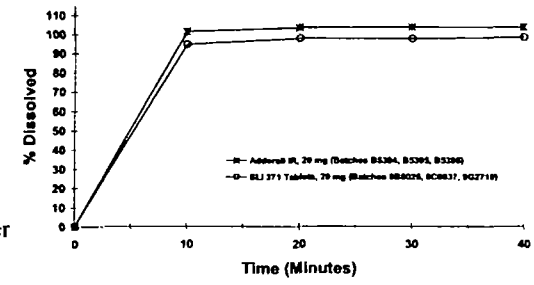
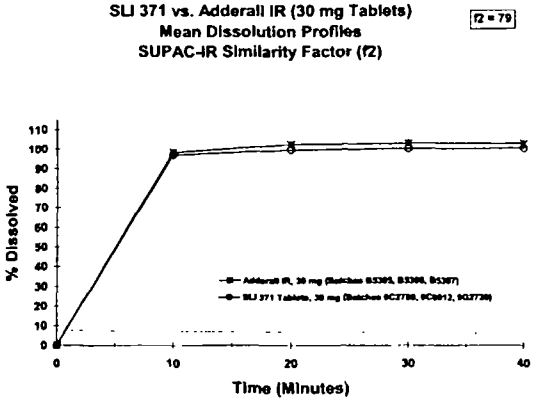


Fig 9



(3) Can a bioavailability waiver be granted for these multiple postapproval changes in Adderall for the 5, 7.5, 12.5, 15 and 20mg five strengths of tablets?

The biowaivers for 5, 7.5, 12.5, 15 and 20mg strengths can be granted based on the following results:

- The two in-vivo BE studies performed on the highest strengths (10 or 30mg) of each common blend met the recommended criteria for BE (0.8-1.25).
- The compositional proportionality for the 2 common blends for the 5.0, 7.5 and 10mg strengths , and the 12.5, 15, 20 and 30mg tablets respectively.
- Dose-proportional pharmacokinetics: the PK parameters (Cmax, AUC0-inf) of d- and l-amphetamine increased approximately from 10 mg to 30mg indicating dose-proportional pharmacokinetics (Table 13).
- Both approved and test products have similar dissolution profiles in the application medium (water) evaluated for all strengths except the 5 mg strength. However, the dissolution profiles obtained in 0.1N HCl for the 5mg strength were similar and indicated that % of the tablet dissolved in 15 minutes suggesting rapid dissolution. Hence a biowaiver can be granted for the 5mg strength also.

Table 13

Table 2-6 Comparison of the new 10 mg and 30 mg ADDERALL tablet formulations after oral administration of single doses to healthy volunteers (Studies 371.101 and 371.102)

Parameter[1]	10 mg (Study 371.102)	30 mg (Study 371.101)	Ratio[2]
d-Amphetamine			
C_{max} (ng/mL)	15.7 ± 3.01	53.1 ± 10.7	3.38
AUC_{∞} (h•ng/mL)	276 ± 61.8	911 ± 238	3.27
l-Amphetamine			
C_{max} (ng/mL)	5.02 ± 0.89	17.0 ± 3.72	3.37
AUC_{∞} (h•ng/mL)	108 ± 26.5	339 ± 92.7	3.13

[1]Arithmetic mean ± standard deviation.
[2]Calculated from the geometric means

Appendices

Individual study synopsis (excerpted from the sponsor) with reviewer's comments

Note: Comments are applicable for both studies since the only differences between the two studies were dose and tablet strength (10mg vs 30mg)

Name of Study Drug: Mixed Salts Amphetamine	IND #:	Protocol No.: 371.101[1)]	Phase: I	Country: USA

Title:
A pharmacokinetic study to assess the single dose relative bioavailability of two formulations of Adderall 30 mg tablets in fasting volunteers.

Principal Investigator/Affiliation:	No. of Study Centers: 1	Study Period: First enrollment date: May 31, 2000 Last completion date: June 12, 2000

Objectives:

To assess the relative bioavailability of a new immediate-release amphetamine 30 mg tablet formulation with reference to the marketed Adderall® 30 mg tablet formulation following a single 30 mg oral dose.

Methodology:
This study utilized a single dose, randomized, open-label, two-way crossover design. Eighteen (18) healthy male and female subjects were enrolled. For the first study period, subjects were randomly assigned to receive a single 30 mg oral dose of either Adderall® (the reference product) or a new immediate-release amphetamine formulation (the test product) after an overnight fast. The alternate product was administered during the subsequent study period. Dosing for each study period was separated by a minimum 7-day washout interval.

For each study period, 18 blood samples were collected through the 60-hour postdose interval for d-amphetamine and l-amphetamine analysis. These blood samples were collected hour 0 (predose) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 60 hours postdose. Blood samples were centrifuged within 60 minutes and the separated plasma was stored at or below minus 20°C. determined plasma d-amphetamine and l-amphetamine levels (by method) and calculated pharmacokinetic parameters. The Sponsor analyzed the pharmacokinetic parameters for bioequivalence.

Each subject provided a medical history, underwent a physical examination, 12-lead EKG, and clinical laboratory tests within 21 days prior to study enrollment. Subjects were confined to the clinic from the evening before dosing until the 24-hour postdose blood samples. Subjects returned to the clinic for the 36-, 48-, and 60-hour postdose samples. Blood pressure, pulse, and EKG were measured at predose and at 2 and 4 hours postdose. Urine drug screening test and serum pregnancy test were done during the screening period, and prior to entering each study phase.

Author:	Signature:	Date: 20 Dec 2000
Statistician(s):	Signature:	Date: 21 Dec 2000
Safety:		
Efficacy:	Signature:	Date: 12-20-2000
Approved by: Sponsor's Medical Officer	Signature:	Date: 12/28/00

Name of Study Drug:	IND #:	Protocol No.:	Phase:	Country:
Mixed Salts Amphetamine		371.101	I	USA

Number of Subjects (planned and analyzed):
The protocol called for 18 subjects to ensure sufficient statistical power to assess the bioequivalence of the single 30 mg dose of a new immediate-release (IR) amphetamine formulation to a single 30 mg dose of the Adderall marketed product. Eighteen (18) subjects participated in the study and all completed the study. All data collected from the study participants were evaluated for bioequivalence, bioavailability, and safety.

Diagnosis and Main Criteria for Inclusion:
Healthy volunteers of either sex, 19 to 55 years old, with body weight within ± 10% the ideal weight for their gender, height, and estimated frame size.

Test Product, Dose, Mode of Administration, and Batch Number:
New immediate-release formulation of amphetamine 30 mg tablets (lot number 0C2780) for oral administration was provided by the Sponsor.

Duration of Treatment:
This was a single-dose, two-period crossover study with a minimum 7-day washout interval between each dose administration. Dosing time was approximately 7:00 am of each dosing day.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Marketed Adderall® 30 mg tablets (lot number B5306) for oral administration was provided by the Sponsor.

Criteria for Evaluation:
Efficacy (Pharmacokinetics):
Extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between the two formulations using analysis of variance (ANOVA). Analysis of bioequivalence was carried out using the ANOVA model with log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions of bioequivalence.
Safety:
All safety parameters collected were assessed either descriptively and/or comparatively. These parameters included adverse events (AE), clinical laboratory tests (chemistry, hematology, and urinalysis), medical history, physical examinations, 12-lead electrocardiogram (ECG), and vital signs.

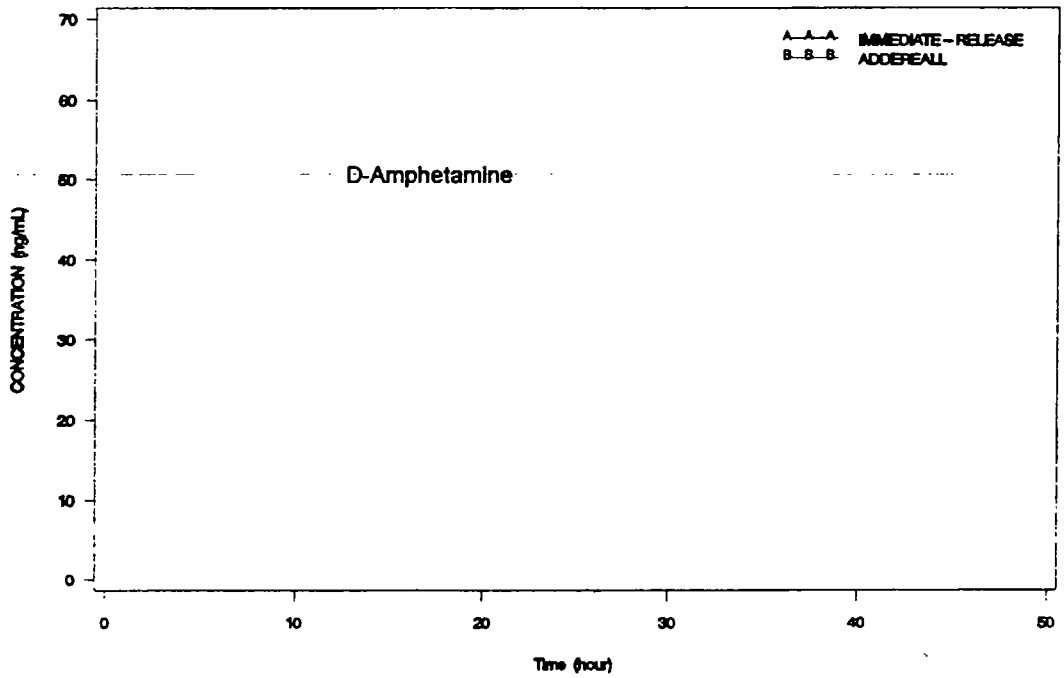
Statistical Methods:
Efficacy (Pharmacokinetics):
The extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between the two formulations using analysis of variance (ANOVA) with a general linear approach. The ANOVA model included sequence, subject within sequence, period, and formulation. The statistical significance level was set at 0.05 for comparative evaluation. Analysis of bioequivalence was carried out using the same ANOVA model with log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests approach. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions of bioequivalence.

Safety:
Observed adverse events and vital signs were analyzed either descriptively or comparatively using paired t-test for each of the two formulations.

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine		371.101	I	USA

SUMMARY RESULTS
EFFICACY:

Plasma D- and L-Amphetamine Concentration-Time Plot



D-Amphetamine

Formulation	Parameters (means) AUC (0-inf) (ng hr/mL)	AUC (0-t) (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
New Adderall IR, 1x30mg (test)	911.14	890.66	53.14	2.50
Marketed Adderall®, 1x30mg (reference)	884.08	864.57	52.24	2.58
	Bioequivalence			
Ratio of test-to-reference	1.03	1.03	1.02	
90% CI	0.99-1.08*	0.99-1.08*	0.99-1.05*	

L-Amphetamine

Formulation	Parameters (means) AUC (0-inf) (ng hr/mL)	AUC (0-t) (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
New Adderall IR, 1x30mg (test)	339.12	322.71	17.02	3.03
Marketed Adderall®, 1x30mg (reference)	334.00	318.43	16.89	2.94
	Bioequivalence			
Ratio of test-to-reference	1.02	1.02	1.01	
90% CI	0.97-1.08*	0.97-1.07*	0.98-1.03*	

* Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine		371.101	I	USA

SUMMARY RESULTS (continued)

SAFETY:

All 18 subjects received a single 30 mg dose of new immediate-release amphetamine and a single 30 mg dose of marketed Adderall®. There were no deaths, no serious adverse events, and no withdrawals from this study.

Sixteen of 18 subjects reported one or more adverse events during the study. The majority of treatment-emergent adverse events (83/102, 81%) were judged as possibly or probably related to study medication. All adverse events were mild or moderate in severity. The number of adverse events reported was similar under the two formulations (new immediate-release Adderall: 51% of total adverse events vs. marketed Adderall®: 49%).

The incidence of subjects reporting adverse events was the same for the two formulations (16/18 subjects, 89%). The most frequently reported adverse events (>2%) included euphoria, dry mouth, hyperkinesia, chills, dizziness, headache, asthenia, insomnia, and peripheral vascular disorder. All of them were not unexpected.

Compared to pre-dosing, significant ($p<0.01$) increases in mean pulse and blood pressure were observed at 2 and 4 hours post dose for both the test and reference formulations. The mean vital signs increases observed with the new immediate-release formulation were similar to those observed with the marketed formulation.

No clinically significant abnormalities in EKG parameters were observed, as assessed by investigator.

CONCLUSIONS:

The objective of this study was to evaluate the bio-availability of the new Adderall immediate-release tablet formulation of 30 mg strength in comparison to the marketed Adderall® tablet formulation of the same strength in fasting, healthy adult subjects.

Efficacy

This study demonstrated that the new Adderall immediate release tablet formulation of 30 mg strength was bio-equivalent as measured by all relevant PK parameters to the marketed Adderall® tablet formulation of the same strength in fasting adult subjects for both d- and l-amphetamine. No statistically significant differences were noted between the two formulations for AUC, Cmax, or Tmax parameters with either d- or l-amphetamine. No significant treatment effect for $t_{½}$ was observed with both isomers.

Safety

Both formulations were well and similarly tolerated. A total of 102 adverse events were observed with 16 of 18 subjects reporting one or more adverse events during the study. The number of adverse events was similar under the two formulations.

For both formulations, statistically significant increases were noted in mean vital signs at 2 and/or 4 hours post dose. The relative increases were similar for the two formulations. No clinically significant abnormalities were noted in pre- or post-treatment EKG parameters for any of the subjects under either formulation.

In conclusion, results of this study indicated that the new 30-mg immediate-release Adderall tablet was bio-equivalent to the marketed 30-mg Adderall® tablet given in a fasting state to healthy adult subjects. The safety profiles of the two formulations were similar and both formulations were well tolerated.

Name of Study Drug:	IND #:	Protocol No.:	Phase:	Country:
Mixed Salts Amphetamine		371.102	I	USA

Title:
A pharmacokinetic study to assess the single dose relative bioavailability of two formulations of Adderall 10 mg tablets in fasting volunteers.

Principal Investigator/Affiliation:	No. of Study Centers:	Study Period:
	1	First enrollment date: November 01, 2000 Last completion date: November 14, 2000

Objectives:

To assess the relative bioavailability of a new immediate-release amphetamine 10 mg tablet formulation with reference to the marketed Adderall® 10 mg tablet formulation following a single 10 mg oral dose.

Methodology:
This study utilized a single dose, randomized, open-label, two-way crossover design. Eighteen (18) healthy male and female subjects were enrolled. For the first study period, subjects were randomly assigned to receive a single 10 mg oral dose of either Adderall® (the reference product) or a new immediate-release amphetamine formulation (the test product) after an overnight fast. The alternate product was administered during the subsequent study period. Dosing for each study period was separated by a minimum 7-day washout interval.

For each study period, 18 blood samples were collected through the 60-hour postdose interval for d-amphetamine and l-amphetamine analysis. These blood samples were collected at hour 0 (predose) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 60 hours postdose. Blood samples were centrifuged within 60 minutes and the separated plasma was stored at or below minus 20°C. determined plasma d-amphetamine and l-amphetamine levels (by method) and calculated pharmacokinetic parameters. The Sponsor analyzed the pharmacokinetic parameters for bioequivalence.

Each subject provided a medical history, underwent a physical examination, 12-lead EKG, and clinical laboratory tests within 21 days prior to study enrollment. Subjects were confined to the clinic from the evening before dosing until the 24-hour postdose blood samples were completed. Subjects returned to the clinic for the 36-, 48-, and 60-hour postdose samples. Blood pressure, pulse, and EKG were measured at predose and at 2 and 4 hours postdose. Urine drug screening tests and serum pregnancy tests were done during the screening period, and prior to entering each study phase.

Author:	Signature:	Date: 4/17/01
Statistician(s): Safety:	Signature:	Date: 4-17-2001
Efficacy:	Signature:	Date: 4-20-2001
Approved by: Senior Director of Medical Affairs Sponsor's Medical Officer	Signature:	Date: 04/26/01

Name of Study Drug:	IND #:	Protocol No.:	Phase:	Country:
Mixed Salts Amphetamine		371.102	I	USA

Number of Subjects (planned and analyzed):
The protocol called for 18 subjects to ensure sufficient statistical power to assess the bioequivalence of the single 10 mg dose of a new immediate-release (IR) amphetamine formulation to a single 10 mg dose of the Adderall marketed product. Eighteen (18) subjects participated in the study, seventeen (17) subjects completed the study. All data collected from the study participants were evaluated for bioequivalence, bioavailability, and safety.

Diagnosis and Main Criteria for Inclusion:
Healthy volunteers of either sex, 19 to 55 years old, with body weight within ± 10% the ideal weight for their gender, height, and estimated frame size.

Test Product, Dose, Mode of Administration, and Batch Number:
New immediate-release formulation of amphetamine 10 mg tablets (lot number 012775A) for oral administration was provided by the Sponsor.

Duration of Treatment:
This was a single-dose, two-period crossover study with a minimum 7-day washout interval between each dose administration. Dosing time was approximately 8:00 am of each dosing day.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Marketed Adderall® 10 mg tablets (lot number 0H5I57) for oral administration was provided by the Sponsor.

Criteria for Evaluation:
Efficacy (Pharmacokinetics):
Extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between the two formulations using analysis of variance (ANOVA). Analysis of bioequivalence was carried out using the ANOVA model with log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions of bioequivalence.
Safety:
All safety parameters collected were assessed either descriptively and/or comparatively. These parameters included adverse events (AE), clinical laboratory tests (chemistry, hematology, and urinalysis), medical history, physical examinations, 12-lead electrocardiogram (ECG), and vital signs.

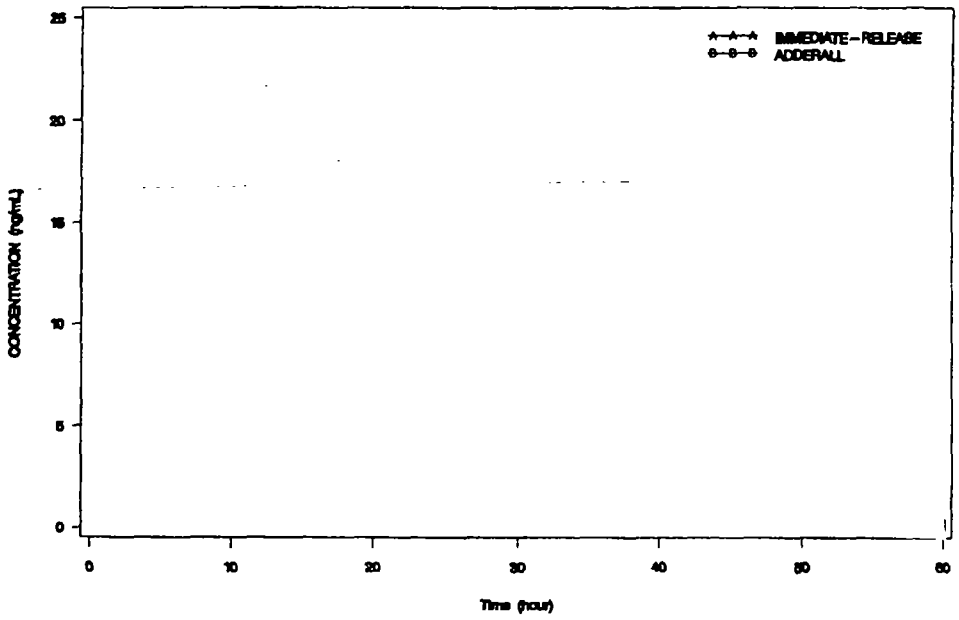
Statistical Methods:
Efficacy (Pharmacokinetics):
The extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between the two formulations using analysis of variance (ANOVA) with a general linear approach. The ANOVA model included sequence, subject within sequence, period, and formulation. The statistical significance level was set at 0.05 for comparative evaluation. Analysis of bioequivalence was carried out using the same ANOVA model with log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests approach. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions of bioequivalence.

Safety:
Observed adverse events and vital signs were analyzed either descriptively or comparatively using paired t-test for each of the two formulations.

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine		371.102	I	USA

SUMMARY RESULTS
EFFICACY:

Plasma D- and L-Amphetamine Concentration-Time Plot



D-Amphetamine

	Parameters (means)			
Formulation	AUC (0-inf) (ng hr/mL)	AUC (0-t) (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
Immediate Release, 1x10mg (test)	275.57^	262.60^	15.67	2.72
Marketed Adderall®, 1x10mg (reference)	290.03	277.23	15.78	2.62
	Bioequivalence			
Ratio of test-to-reference	0.96	0.95	0.98	
90% CI	0.93-1.00*	0.92-0.99*	0.96-1.01*	

L-Amphetamine

	Parameters (means)			
Formulation	AUC (0-inf) (ng hr/mL)	AUC (0-t) (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
Immediate Release, 1x10mg (test)	107.19	92.10	5.02	2.89
Marketed Adderall®, 1x10mg (reference)	112.25	97.41	5.00	2.80
	Bioequivalence			
Ratio of test-to-reference	0.97	0.96	1.00	
90% CI	0.93-1.01*	0.92-1.00*	0.97-1.02*	

^ $p<0.05$ compared to reference formulation by ANOVA
* Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine		371.102	I	USA

SUMMARY RESULTS (continued)

SAFETY:

All 18 subjects received a single 10 mg dose of new immediate-release amphetamine. Seventeen subjects received a single 10 mg dose of marketed Adderall®. One subject was withdrawn from the study for personal reasons prior to the second dosing day. There were no deaths and no serious adverse events.

Six of 18 subjects reported a total of 18 adverse events during the study. The majority of treatment-emergent adverse events (17/18, 94%) were judged as possibly or probably related to study medication. Nearly all adverse events (17/18, 94%) were mild or moderate in severity. One subject reported severe restlessness after receiving the immediate release (test) formulation. All adverse events resolved before study completion.

The incidence of subjects reporting adverse events was similar under the new immediate release formulation (5/18, 28%) and the marketed Adderall® formulation (4/17, 24%). The most frequently reported adverse events (>10%) included headache and dizziness, which were not unexpected.

Compared to pre-dosing, significant ($p<0.01$) increases in mean pulse and blood pressure were observed at 2 and/or 4 hours post dose for both the test and reference formulations. The mean vital signs increases observed with the new immediate-release formulation were similar to those observed with the marketed formulation.

No clinically significant abnormalities in EKG parameters were observed, as assessed by investigator.

CONCLUSIONS:

The objective of this study was to evaluate the bio-availability of the new immediate-release amphetamine tablet formulation of 10 mg strength in comparison to the marketed Adderall® tablet formulation of the same strength in fasting, healthy adult subjects.

Efficacy

This study demonstrated that the new immediate release amphetamine tablet formulation of 10 mg strength was bio-equivalent as measured by all relevant PK parameters to the marketed Adderall® tablet formulation of the same strength in fasting adult subjects for both d- and l-amphetamine. No statistically significant differences were noted between the two formulations for Tmax with either d- or l-amphetamine.

Safety

Both formulations were well and similarly tolerated. A total of 18 adverse events were observed with 6 of 18 subjects reporting one or more adverse events during the study. For both formulations, statistically significant increases were noted in mean vital signs at 2 and/or 4 hours post dose. The relative increases were similar for the two formulations. No clinically significant abnormalities were noted in pre- or post-treatment EKG parameters for any of the subjects under either formulation.

In conclusion, results of this study indicated that the new 10-mg immediate-release amphetamine tablet was bio-equivalent to the marketed 10-mg Adderall® tablet given in a fasting state to healthy adult subjects. The safety profiles of the two formulations were similar and both formulations were well tolerated.

Comments:

Note: Comments are applicable for both studies (study #371.101 and 371.102) since the only differences between the two studies were dose and tablet strength (10mg vs 30mg).

Study design: We consider the design acceptable.

PK measures

- It should be noted that no efficacy variable was evaluated in this BE study conducted in healthy volunteers. Only pharmacokinetics and safety were assessed.
- % CV for Cmax for d- or l- amphetamine was approximately 20%, which was comparable for test and marketed products (tables 6 and 7 of QBR).
- Terminal t1/2 of d- and l-amphetamine were comparable for marketed and test products of Adderall 10 and 30 mg tablet (see table 14 below).

Table 14. Terminal t1/2 (Mean ±SD) of d- and l-amphetamine:

	d-amphetamine		l-amphetamine	
	10mg tablet (study# 371.102)	30mg tablet (study# 371.101)	10mg tablet (study# 371.102)	30mg tablet (study# 371.101)
test product	10.9±1.67 h	9.77±1.93h	13.5±2.46 h	11.5±2.48 h
marketed product	11.0±1.96 h	9.97±1.80 h	13.8±2.37 h	11.9±2.26 h

- Terminal t1/2 of l-amphetamine (11.5-13.8 hours) was prolonged when compared to the t1/2 of d-isomer (9.77-11hours).
- The PK parameters (Cmax, AUC0-inf) of d- and l-amphetamine increased approximately from 10 mg to 30mg indicating dosage form proportionality (Table 13 of QBR).

BE:

We consider the test products of Adderall (10mg and 30mg) bioequivalent to the marketed products of Adderall. The 90% CI of test-to-reference ratio fell within the recommended 0.80-1.25 goal-post for average BE assessment for Cmax and AUC0. The elimination half-lives and tmax were comparable for test and marketed products for both isomers.

Demographic and other baseline characteristics:

- The sponsor did not assess race or gender effects on PK parameters.
- Study #371.101 (30mg): Thirty-nine percent (7/18) of subjects enrolled were male and 61% (11/18) were female. Race distribution was primarily Caucasian (83%, 15/18), with one Black subject (6%) and two subjects of race other than Caucasian or Black (11%).
- Study #371.101 (100mg): Fifty-six percent (10/18) of subjects enrolled were male and 44% (8/18) were female. All subjects were Caucasian (18/18).

Bioanalytical method and assay validation:

- We consider the bioanalytical assay used in these 2 BE studies acceptable since it is a validated method and has been used for the existing Adderall tablet product.
- Overall the analytical method for d- or l-amphetamine in EDTA treated human plasma was found to be specific, reproducible, sensitive and adequate to characterize the PK of d- and l-amphetamine.

- Method:

- This reviewer has summarized Assay validation in following 3 tables:

Pre-study assay validation summary for d- and l-amphetamine in EDTA human plasma for both studies (371.101 and 371.102 unless otherwise indicated)		
Parameters	Quality control samples (d-/l-amphetamine)	standard curve samples (d-/l-amphetamine)
concentration (ng/ml)		
Intra-day precision (%CV)		
Intra-day accuracy (% accuracy)		
Inter-day precision (%CV)		
Inter-day accuracy(% accuracy)		
correlation (range of R2 values)		
Linear range (ng/ml)		
Sensitivity/LLOQ		
Extraction Recovery of analyte		
Extraction recovery of internal standard		
Stability in Plasma		
1) reinjection/ refrigeration extract at 2-8°C (hrs)		
2) Bench-top stability of extract at room temperature (hrs)		
3) freeze-thaw stability (cycles)		
4) storage stability (temp, months)		
Specificity		

* due to multiple processing steps including derivatization

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commercial

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Within-study assay performance for d- and l-amphetamine in EDTA human plasma				
	Study #371.101(30mg)		Study# 371.102 (10mg)	
Parameters	Quality control samples (d-/l-amphetamine)	standard curve samples (d-/l-amphetamine)	Quality control samples (d-/l-amphetamine)	standard curve samples (d-/l-amphetamine)
concentration (ng/ml)				
Intra-day precision (%CV)				
Intra-day accuracy (% accuracy)				
Inter-day precision (%CV)				
Inter-day accuracy (% accuracy)				
correlation (range of R2 values)				
Linear range (ng/ml)				
Sensitivity/LLOQ				

Comment to be sent to the sponsor:

- We request that you address the issue regarding procedure for bioanalysis of plasma samples for which concentrations were outside of the linear range defined by the bioanalytical method. We note that nearly 100 out of the 648 concentration values for the d-amphetamine in human plasma samples in study#371.101 were outside of the linear range ng/ml) as defined by the bioanalytical method.