CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11-522/S-030

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-522/S-030

Shire Pharmaceutical Development, Inc.
Attention: Tami Martin, R.N., Esq.
1901 Research Blvd., Suite 500
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your supplemental new drug application (NDA) dated November 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADDERALL ™ (Mixed Salts of a Single-Entity Amphetamine Product) Tablets, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg and 30 mg.

We acknowledge receipt of your amendments dated January 17, February 12, and March 14, 2002.

We also acknowledge receipt of your labeling amendment dated March 14, 2001; however, this was not reviewed for this action. Please incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This supplement provides for reformulation of the tablets and a new manufacturing site.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the deficiencies below.

1. 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. Please clarify the procedure for bioanalysis of plasma samples for which the concentration values were outside of the linear range defined by the bioanalytical method.

2. In addition to the labeling changes you have proposed in the March 14, 2002, amendment, the following pharmacokinetic 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.

3. We also note that relevant information related to ADME, PK, and intrinsic and extrinsic factors, such as, gender, age, race, renal or hepatic impairment, food and drug interactions, that could effect the PK of amphetamine is also lacking in your proposed labeling. Please update the labeling to include this information.

4. Please clarify the use of the term listed under 'HOW SUPPLIED' for the 5 mg tablet strength and whether this allows the 5 mg strength to be broken in half for a 2.5 mg dose.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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. In the absence of any such action FDA may proceed to withdraw the application. 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

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