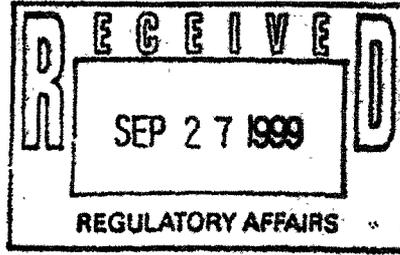




DEPARTMENT OF HEALTH & HUMAN SERVICES

IND [REDACTED]



Food and Drug Administration
Rockville MD 20857

SEP 24 1999

Shire Laboratories, Inc.

[REDACTED]
1550 East Gude Dr.
Rockville, MD 20850

Dear [REDACTED]

Please refer to the meeting between representatives of your firm and FDA on July 20, 1999, to discuss your proposed clinical development plan for a modified-release form of Adderall.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting.

If you have any questions, contact Anna Marie Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

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

Enclosure

MEETING MINUTES

Date: July 20, 1999

IND: [REDACTED]

Location: Woodmont II, Conference Room E

Firm: Shire Laboratories

Drug: SLI 381 (modified release Adderall®)

Indication: attention deficit disorder

Meeting Type: Clinical Development Meeting

Participants:

FDA:

Russell Katz, M.D.

Thomas Laughren, M.D.

Andrew Mosholder, M.D.

Leonard Kapcala, M.D.

Kun Jin, Ph.D.

Richard Chen, Ph.D.

Ray Baweja, Ph.D.

Anna Marie Homonnay, R.Ph.

Acting Division Director

Teamleader, PDP

Medical Reviewer

Medical Reviewer

Teamleader, Biostatistics

Biostatistician

Teamleader, Clinical Pharmacology

Regulatory Project Manager

Shire:

[REDACTED]

[REDACTED]

BACKGROUND:

This meeting was requested by Shire in order to obtain the Division's input on their proposed clinical development plan for a modified-release capsule formulation of Adderall[®] which may also be sprinkled on food. Shire has filed an IND for SLI 381 on March 25, 1999, for a formulation consisting of two types of pellets, an immediate release component and a delayed-release component, in order to produce a bimodal release pattern mimicking twice daily dosing with Adderall IR given four to six hours apart. They have proposed two different development plans: a biopharmaceutical approach and a clinical development approach.

DISCUSSION:

- Shire presented 24 hour comparative PK data to provide support for the biopharmaceutical approach. FDA stated that seeking approval through the bioequivalence route may be difficult since the comparative PK profile indicated a slightly different kinetic pattern between the IR and ER Adderall® formulations for the two plasma peaks. Since for this drug, the rate of input may be related to clinical efficacy, the plasma concentration time curves would have to be superimposable for both peaks, and the standard PK parameters will need to be assessed for both peaks.

- Two possible development plans were outlined from an OCPB perspective:

Option 1: Ideally, all BE studies should be conducted in children. In this case, the following studies would be required: a multiple dose BE assessment with the lowest strength and 'waiving up' of the higher strengths through dissolution, a single dose food effect/sprinkle study at the lowest strength, and a single dose dosage strength equivalency study comparing 1X30 mg versus 3X10 mg. All studies should monitor for both the dextro- and levo-isomers.

Option 2: However, from a practical standpoint, the BE program may consist of two studies in adults and one in children. The following studies would be required under this option: a multiple dose BE assessment at multiple dosing with the highest strength in adults, and 'waiving down' of the lower strengths through dissolution, a single dose food/sprinkle study at the highest strength, and a single dose dosage strength equivalency study comparing 1X30 mg versus 3X10 mg in children. All studies should monitor for both the dextro- and levo-isomers.

- Dissolution profile testing should be conducted with the biobatches from the performed biostudies such that a common meaningful dissolution procedure and specification can be set for all strengths of these capsules. The sponsor was also advised to 'lock' the ratio of their immediate release:delayed release beads in the capsule.

- For Study 301, a multicenter, outpatient, randomized, double-blind, placebo-controlled trial, FDA noted that the validity of the Conners 10-Item Scale as a primary efficacy measure for the time course of activity over the course of the day may need to be further justified; the sponsor was asked to check for any precedents. The sponsor explained that twice daily ratings from teachers on this scale will be used as the primary efficacy measure. FDA added that while the outpatient setting is ideal for determining drug efficacy, it may not be the best setting for determining time course of the drug effect. The laboratory classroom setting may be more appropriate. The Division is willing to consider the possibility of allowing a descriptive statement about the time course of drug activity in the labeling, if this can be accurately assessed.
- FDA pointed out that the proposed labeling for the clinical approach contains a comparative claim that is based on a classroom laboratory study where there was no IR arm included. It was also noted that the validity of the SKAMP instrument in detecting a persistence of drug effect over the course of a day needs to be justified.
- The sponsor stated that the efficacy endpoint is defined as the average of the 10-item Conners Global Index Scale (teacher's version) score calculated separately for the morning and afternoon assessments obtained during the last treatment week. FDA responded that if two endpoints are employed, the sponsor must specify an appropriate algorithm for a positive study. The sponsor should clarify whether they plan to use the morning or afternoon average score, the average of both, or both scores as endpoints. Further, the appropriate baseline score (either the morning or afternoon score) should be pre-specified by the sponsor as the covariate in the statistical model.
- FDA also advised that the sponsor should describe how they will deal with missing data in different situations. In addition, the center effect should be tested in the statistical model. The sponsor should also describe in detail their plans regarding randomization and protection codes.

Signature, minutes preparer:

Anna M. Homonnay-Weikel
 Anna M. Homonnay-Weikel, R.Ph.
 Regulatory Project Manager

Concurrence Chair:

Thomas P. Laughren 9-17-04
 Thomas Laughren, M.D.
 Medical Teamleader PDP