CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-303

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-303

Shire Laboratories Inc
Attention: Tammy Martin
Vice President, Regulatory Affairs
1901 Research Blvd., Suite 500
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for SLI-381 (mixed salts of a single-entity amphetamine) modified-release capsules.

We also refer to your March 2, 2001, request to discuss an expedited review designation for SLI-381 intended to treat ADHD and narcolepsy. In this submission you state that an expedited review is necessary because of the mounting evidence of increased misuse and diversion of stimulant medications within elementary and secondary schools, and that the replacement of short-acting stimulant medications with long acting stimulant medications would significantly reduce the need for in-school dispensation of stimulant medications.

We remind you that there are sustained release amphetamine based products, Desoxyn Gradumet and Dexedrine Spansules, approved for use in ADHD. Therefore, we do not agree that, based upon increased misuse and diversion of stimulant medications, an expedited review is warranted.

You may wish to review the "Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application Review," located at http://www.fda.gov/cder/guidance/index.htm.

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

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

/s/

Russell Katz
3/15/01 08:49:29 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-303

INFORMATION REQUEST LETTER

Shire Laboratories Inc.
Attention: Debbie Aleknavage
Manager, Regulatory Affairs
1901 Research Blvd
Rockville, MD 20850
USA

Dear Ms. Aleknavage:

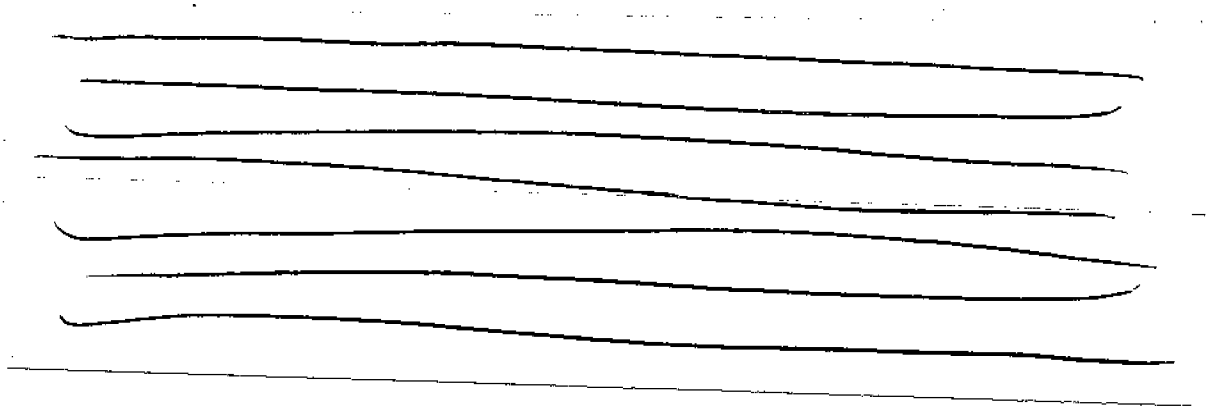
Please refer to your October 04, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SLI 381 (amphetamine salts) 10 mg, 20 mg, 30 mg.

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

This letter is a follow up of your conversation with Christy S. John, Ph.D. on June 13, 2001 concerning methods validation for SLI 381 capsules NDA 21303 and sample request for methods validation.

Christy John, Ph.D. had informed you that FDA laboratories from St. Louis are in the process of sending you DEA-222 forms for the shipment of 0.5 g of each of four amphetamine drug substance and 50 capsules of each 10 mg, 20 mg and 30 mg strengths for methods validation testing.

In particular we want you to address the following questions in detail:



the submission of this application, they must be submitted for our reviews.

2) Please explain why the results of two chemists (Vol. 1.7, Page 4-900) for average percent label claim did not meet the absolute difference criteria [redacted] for d-amphetamine recovery for the lot 98077 [redacted]

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Robert H. Seevers
6/19/01 10:43:57 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-303

Shire Laboratories, Inc.
Attention: Tami Martin
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SLI 381 (amphetaine sulfate, amphetamine aspartate, dextroamphetamine sulfate, dextroamphetamine saccharate) Capsules 10 mg, 20 mg, 30 mg

Review Priority Classification: Standard (S)

Date of Application: October 3, 2000

Date of Receipt: October 3, 2000

Our Reference Number: NDA 21-303

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 2, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 3, 2001 and the secondary user fee goal date will be October 3, 2001.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days

from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Jack Purvis
11/13/00 04:39:32 PM

Shire Laboratories Inc.
1550 East Gude Drive Rockville MD 20850 USA
Tel 301 838 2500 Fax 301 838 2501

Shire

October 3, 2000

Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852
Attention: Dr. Russell Katz, Division of Neuropharmacological Drug Products

Product Name: **ADDERALL XR™ CII (extended release capsule--Mixed Salts of a Single-Entity Amphetamine Product)**
NDA #: **21-303**
Type of Submission: Original New Drug Application

Dear Dr. Katz:

In accordance with 21 CFR 314.50, Shire Laboratories Inc. is submitting this original New Drug Application for a modified release mixed salt amphetamine product known by the code name SLI 381, the subject of IND ——— Shire's expectation is that this product will receive a standard review. Although technically not a 505(b)(2) submission because Shire owns the reference product (ADDERALL®), there are frequent references to the existing NDA for ADDERALL, NDA #11-522. Shire believes this New Drug Application complies with regulatory requirements and is reflective of comments and suggestions received by the sponsor during the research and development process.

Technical Section comments
Shire Laboratories Inc. has followed recommendations made by FDA at End-of-Phase II and Pre-NDA meetings, and other regulatory contacts for this product. We believe we have conducted a chemistry, toxicology, biopharmaceutical and clinical program that will meet the requirements the Food and Drug Administration indicated for review.

For **chemistry**, Shire has had separate End-of-Phase II and Pre-NDA meetings with the chemistry reviewers, and has followed the suggestions presented at those meetings. At the Pre-NDA meeting, one of the topics was in vivo/in vitro correlation for ADDERALL XR. A validated method for in vivo/in vitro correlation is provided in this application.

For **toxicology**, Shire responded to the Food and Drug Administration's correspondence of June 25, 1999, by 1) providing information from the National Toxicology Program research on amphetamines, as well as, other literature search information (submission #014 to IND ——— dated October 29, 1999), 2) conducting two new mutagenicity tests, and 3) by initiating Segment I and II reproductive toxicology studies. By agreement with your group at the pre-NDA meeting, the Segment I and II reproductive toxicology study results will be presented at the time of the four-month safety update.

Shire

For **biopharmaceutics**, Shire conducted a number of biopharmaceutical studies that characterized this modified release product's profile. A food, fasting, and sprinkle study evaluated the effects of food and supports the suitability of administration with or without food, or as a sprinkle administration.

For **clinical**, Shire conducted two controlled clinical studies, one in a laboratory classroom setting, and another in a natural home and school setting. Based on a meeting with FDA held on July 20, 1999, these clinical studies were deemed necessary for approval of this modified release product. As such, and in accordance with 21 CFR 314.50(j), Shire claims market exclusivity. This market exclusivity is provided for in section 21 CFR 314.108(4)(iv) which states that if the application contains reports of new clinical investigations that were essential to the approval of the application, three years of market exclusivity will be provided. Shire was told at the meeting, above, that a clinical development program was necessary for this modified release product. Therefore, Shire believes it is entitled to this market exclusivity protection.

Shire is currently conducting a long-term safety study. At this time, we have presented adverse event listings to a cut off date of August 1, 2000, in this submission. At the time of the four-month safety update, Shire will provide an interim report on this study.

Additional copies/computer diskettes/volumization
The following electronic copies may be found directly behind this cover letter: 1) Computer diskettes that contain SAS data sets as requested in the agency's correspondence dated August 18, 2000, and 2) a CD of section 4.0 Chemistry, Manufacturing and Controls section.

One extra copy of the Methods Validation Package (instead of three) is provided as directed.

The Integrated Summary of Efficacy and the Integrated Summary of Safety are bound in separate volumes for your convenience.

Three desk copies of volumes 1.1 through 1.3 are provided as requested. An additional copy of the Drug Abuse Potential section is provided as requested. The desk copies and the Drug Abuse Potential section have been provided directly to the project manager at the Neuropharmacological Drug Products Division.

Section 8 and Section 10 - Duplication

As requested, Section 10 is a duplicate copy of Section 8. However, Section 8 is paginated 8-1 to the end of the section, and Section 10 is paginated 10-1 to the end of the section. Tabs for Section 10 are identical to Section 8 except for the 10 prefix. However, section headers in Section 10 retain the 8 prefix numeration.

Certifications
Shire certifies that a field copy of the methods validation section of this application has been sent to the Baltimore field office. Certifications concerning debarment, patent status, and financial disclosure are included in the body of the submission as well as in Volume 1.1. User fees for this product have been paid, and their receipt has been confirmed.

Confidentiality
Shire's expectation is that usual measures for protecting the confidential nature of this document will be followed by FDA.

Product and Company Names Appearing in Submission
At the time of this submission, the preferred trade name of "ADDERALL XR™" is under consideration by the APDRA committee in the Drug Risk Assessment Division. You will find the terms "SLI 381" and "ADDERALL XR" used interchangeably in the text. Shire understands that the preferred trade name of "ADDERALL XR" has not been officially accepted and is subject to comment from the APDRA committee and the Neuropharmacological Drug Products Division.

The names "Shire Laboratories Inc.", "Shire Pharmaceutical Development", "Shire Richwood" and "Shire US" may be utilized throughout the document. Reorganization and name changes have been occurring as a consequence of a merger with Roberts Pharmaceuticals, which occurred in late 1999. As clarification, the regulatory agent for these entities in the United States is the Regulatory Group housed in Rockville, Maryland. All contact concerning this application should be directed to this group at the number below. In the near future, this group will be moving to new office space and consequently, **the contact number will change**. Shire will advise you as soon as possible of the change in contact number.

Thank you for the time already spent by your division in the course of this product's development. We look forward to your review.

If you have any questions regarding this submission, please contact Debbie Aleknavage or me at (301) 838-2500.

Sincerely,

Tami Martin

Tami Martin, R.N., Esq.
Vice President
Regulatory Affairs

Enclosures

Shire Pharmaceutical Development Inc.
1901 Research Boulevard Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

Shire

September 25, 2001

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2 Building
1451 Rockville Pike
Rockville, MD 20852

Product Name: **ADDERALL XR™ CII (extended release capsule--Mixed Salts of a Single-Entity Amphetamine Product)**
NDA #: **21-303**
Submission #: **023**
Type of Submission: **General Correspondence: Revised Draft Final Package Insert**

Dear Dr. Katz:

Reference is made to our New Drug Application filed with the Food and Drug Administration (FDA) on October 3, 2000 for SLI 381 (An extended-release capsule of mixed salts of a single-entity amphetamine product).

Further reference is made to the Agency's fax received September 18, 2001, containing a copy of the final draft package insert for ADDERALL XR™.

Please find enclosed an original and a duplicate of Shire's revised final draft labeling for ADDERALL XR™ Capsules. The revised draft labeling is red-lined to indicate the changes made for reviewer ease. Shire would like to schedule a telecon with the Agency at the first available time to discuss this final draft package insert.

If you have questions or concerns regarding this submission, please call Debbie Aleknavage at (240)-453-6446 or me at (240) 453-6450.

Sincerely,

Tami Martin

Tami Martin, R.N., Esq.
Vice President
Regulatory Affairs

Enclosures