CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-303

ADMINISTRATIVE DOCUMENTS

13.1 Patent Exclusivity Information

SLI 381 drug product is the subject of one pending patent application. The patent, titled "Oral Pulsed Dose Drug Delivery System" was initially submitted to the Patent and Trademark Office on October 21, 1998 by Shire Laboratories, Inc. (US Service Number 09/176542).

Under the Patent Cooperation Treaty (PCT), Shire applied for international patent consideration in Australia, Mexico, Japan, the European Union, and Canada. On October 20, 1999, Shire received notice that the PCT-assigned number is US99/24554.

At the time of this New Drug Application submission, the patent is pending in all countries.

14.0 PATENT CERTIFICATION

SLI 381 is being submitted as a 505(b)(1) application. The active ingredient in SLI 381 is the same as in Shire's marketed product, ADDERALL®. ADDERALL® is no longer protected by patent. Furthermore, Shire is the sponsor of the ADDERALL® drug product New Drug Application 11-522. Therefore, no patent certification information is required for this submission.

EXCLUSIVITY SUMMARY FOR NDA # 21-303

Trade Name: **Adderall XR** Generic Name: mixed salts of a single entity amphetamine product

Applicant Name: Shire Laboratories HFD # 120

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 7-90
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /X/ NO /_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 11-522 Adderall

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /X/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1) 381.201 2) 381.301

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 381.201 YES /___/ NO /X/

Investigation #2 381.301 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 381.201 YES /___/ NO /X/

Investigation #2 381.301 YES /___/ NO /X/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

381.201 _____

381.301 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /X/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /X/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

/S/
Signature
Title: Reg Mangmt. Officer

July 31, 2001
Date

/S/
Signature of Office/
Division Director

10/11/01
Date

cc: Original NDA Division File HFD-85/HA/OVAC

13.2 Market Exclusivity

Shire is seeking market exclusivity under 21 CFR 314.50(j) and 21 CFR 314.108(b)(4). Shire conducted several bioequivalence trials and two clinical studies, as discussed with the Neuropharmacological Drugs Division, in order to submit this NDA for SLI 381. Based on 21 CFR 314.108(b)(4) we believe that Shire is entitled to a three year period of market exclusivity for SLI 381 for the treatment of ADHD and narcolepsy.

16.0 DEBARMENT CERTIFICATION

On behalf of Shire Laboratories Inc. (Shire), I hereby certify that Shire did not and will not use in any capacity the services of any individual, partnership, corporation, or association debarred under Subsection (a) or (b) of §306 of the Federal Food, Drug, and Cosmetic Act in connection with this NDA application for SLI 381.

Tami T. Martin

Sept 8 2000

Tami T. Martin, RN, Esq
Vice President, Regulatory Affairs

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Tami T. Martin, R.N., Esq.	Vice President Regulatory Affairs
FIRM/ORGANIZATION	
Shire Laboratories Inc.	
SIGNATURE	DATE
Tami T. Martin	September 29, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

COMPLETE NOV 16 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCES STAFF

Date: November 15, 2000

To: Teresa Wheelous
HFD-120 (Div. of Neuropharmacological Drug Products)

From: Katherine Bonson, Ph.D., Pharmacologist KBonson
Controlled Substances Staff

Through: Deborah Lejderman, M.D., Director
Controlled Substances Staff

Subject: Consult on Abuse Potential of Adderall XR
(mixed amphetamine and dextroamphetamine salts)
treatment for ADHD
NDA 21-303
Shire Laboratories, Inc.,

Sponsor Statements in the IND regarding Adderall XR:

The Sponsor states that Adderall XR (a long-acting, modified-release, single entity product for once-daily administration that combines the neutral sulfate salts of dextroamphetamine and amphetamine) is a Schedule II controlled substance and is therefore considered to be associated with significant abuse potential. The Sponsor suggests that once-daily dosing with a slow release formulation will be advantageous in the targetted ADHD population (6-12 year old children) by eliminating the need for drug administration during the day at school. Similar benefits were seen for narcolepsy patients. The Sponsor suggests that single dosing will reduce diversion of the drug.

No preclinical or clinical abuse liability studies were submitted by the Sponsor for review.

The Sponsor does not request a specific scheduling for Adderall XR, based on their recognition that contents of the drug product are Schedule II substances.

Controlled Substances Staff Assessment:

The CSS concurs with the Sponsor that Adderall XR should be controlled under the CSA in Schedule II.

M E M O R A N D U M

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

DATE: July 30, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Adderall XR (modified release formulation of a mixture of d- and l-amphetamine) for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

TO: File NDA 21-303
[**Note:** This overview should be filed with the 10-3-00 original submission.]

1.0 BACKGROUND

This mixture of d- and l-amphetamine salts is a stimulant that has been available for many years in the US as a treatment for ADHD in an immediate release form (in recent years this formulation has taken the name Adderall; previously it was marketed as Obetrol [NDA 11-522]). The immediate release formulation often needs to be given twice a day. The necessity of giving this drug at lunchtime in a typical school setting is considered a major disadvantage to the immediate release form. Thus, a major advantage of Adderall XR would presumably be its effectiveness with only AM dosing.

Other immediate release stimulant products approved for ADHD include other amphetamines (d-amphetamine and methamphetamine), methylphenidate, and pemoline. D-amphetamine is also available in a sustained release formulation, as is methylphenidate. Thus, there are other stimulant products available for q AM dosing.

IND [redacted] for the Adderall XR was originally submitted 3-25-99. The IND for the immediate release formulation is IND [redacted]

We informed the sponsor in a 5-4-99 letter that, assuming bioequivalence between the IR and XR formulations could not be shown, one adequate and well-controlled clinical trial would suffice to show

efficacy of the XR formulation. We described what we considered an acceptable trial, i.e., a parallel group outpatient study of several weeks duration focusing on an assessment of typical ADHD symptoms. We recommended a meeting with DNDP to discuss a development plan in more detail.

We met initially with the sponsor on 7-20-99 for what was essentially an end-of-phase 2 meeting. Shire tried to make a case for bioequivalence, but we indicated that the data provided was not sufficient to make the case for bioequivalence. As an alternative, they proposed study 301, which we considered acceptable. We did advise that they select an overall averaged rating on the teacher's version of the 10-item Conners Global Index Scale as the primary outcome, with conditional testing of morning and afternoon scores if the overall rating was positive. We advised that the proposed laboratory classroom study (201) may be sufficient to support labeling statements regarding time course of effect during the day, providing that the primary outcome and the sequence for testing were properly specified and all other aspects of the very complicated study design were appropriately explained and addressed.

We met a second time with the sponsor on 8-16-00 for a preNDA meeting. Much of discussion focused on the failure of Shire to submit detailed analyses plans for studies 201 and 301. They insisted that they had such plans in place, but acknowledged not having submitted them. They, however, promised to submit these plans promptly. We cautioned that what they could claim in labeling would be closely linked to the analysis plans as well as the outcomes for these trials.

The original NDA 21-303 for Adderall XR was submitted 10-3-00. There was a 2-13-01 safety update. The clinical data were reviewed by Andrew Mosholder, M.D. of the clinical group. Yuan-li Shen, Ph.D. of the biometrics group also reviewed the efficacy data.

We decided not to take Adderall XR to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

The chemistry review was conducted by Dr. Christy John, Ph.D. As of this time, it is my impression that there remains a significant GMP deficiency at the manufacturing site that will likely result in a recommendation for a nonapproval action by the CMC group. However, an inspection is planned for the end of July, and it is anticipated that the deficiencies will have been corrected. The only other problematic CMC issue is the proposed name, i.e., Adderall XR, since this implies a sustained release performance, when in fact this is not a typical sustained release product. The name issue is still under review, and this fact will be communicated to Shire.

3.0 PHARMACOLOGY

The original pharmacology/toxicology review was conducted by Edward Fisher, Ph.D. As of this time, I am not aware of any pharmacology/toxicology issues that would preclude the approvability of Adderall XR.

4.0 BIOPHARMACEUTICS

The biopharmaceutics review was conducted by Hong Zhao, Ph.D. As of this time, I am not aware of any biopharmaceutics issues that would preclude the approvability of Adderall XR. This product is a modified release formulation consisting of IR and ER pellets in a 1:1 ratio. Adderall XR is intended to mimic the effect of taking 2 doses of the IR form 4 hours apart, and, in fact, it behaved in this manner in a comparative trial.

5.0 CLINICAL DATA

5.1 Efficacy Data

The focus of the efficacy review was on two studies, (1) 201, a laboratory classroom study, and (2) 301, a 3-week outpatient study.

5.1.1 Summary of Studies Pertinent to Efficacy of Adderall XR

5.1.1.1 Study 201

This was a randomized, double-blind, 5-arm crossover study conducted in a laboratory classroom setting, at 4 different sites. Each treatment arm was 1 week, and the arms included 3 fixed doses of Adderall XR (10, 20, and 30 mg qd), Adderall IR 10 mg, and placebo (all given in the morning). The population studied was children aged 6-12 with ADHD (DSM-IV). Randomization was by Latin square. Assessments were done in the laboratory classroom each Saturday, and included the following: SKAMP, PERMP, and PK at 0, 1.5, 3.0, 4.5, 6.0, 7.5, 10.5, and 12.0 hours post dose. The primary outcomes were the attention and deportment subscales of the SKAMP, focusing on the 3 Adderall XR dose groups vs placebo.

A total of n=51 patients were randomized, and n=44 were able to complete the 5 periods. The mean age was 9 years, and these were mostly males (86%) and the most frequent ethnic groups were as follows: white (49%); hispanic (24%); black (16%).

The sponsor's analysis of SKAMP attention and deportment subscales was highly significant in favor of all Adderall doses vs placebo. However, Dr. Shen had many concerns about the study design and analysis

plan. There were discrepancies between the protocol, statistical analysis plan, and study report, and no clear objective or primary hypotheses were specified. Consequently, she has recommended against presenting any results pertinent to time course in labeling, the findings from this trial of greatest interest to the sponsor. My understanding of these deficiencies is summarized as follows:

-Two primary concerns regarding the study design have not been adequately addressed by the sponsor:
  -Insufficient specification of exactly how randomization was accomplished, i.e., simply referring to the use of a Latin square is inadequate, since many sequences would be possible.
  -The sponsor does not address the concern about carryover effect.

-The following aspects of the analysis plan remain unclear:
  -The time course analysis had been designated as secondary in the original protocol and was only changed to a primary analysis two months after study completion. Furthermore, time course was never adequately defined.
  -Neither the original protocol nor the subsequent analysis plan stated clearly what outcome would be required to consider the study positive overall.
  -The many sources of multiplicity, e.g., multiple endpoints and subscales, multiple doses, and multiple testing times, are not adequately addressed in the analysis plan.
  -The model assumptions and specifications need better explanation and justification
  -The impact of missing data has not been adequately addressed.

Comment: I agree that there are many questions that remain to be answered about the results from study 201 before we should consider adding information from this trial to labeling. Fortunately, the results of this trial are not critical to an approvable action, since study 301 is, by itself, sufficient to support the efficacy of Adderall XR.

5.1.1.2 Study 301

This was a randomized, double-blind, parallel group, 3-week, multicenter (47 US sites) study comparing Adderall XR at 3 fixed doses (10, 20, and 30 mg qd) and placebo in n=584 children aged 6-12 with ADHD (DSM-IV). Randomization to the 3 drug groups and placebo was as follows: 2-2-2-3. The sample included only patients who were of the combined type or the predominantly hyperactive-impulsive type; patients with the predominantly inattentive type were excluded. Dosing was before breakfast. Adderall XR was initiated at 10 mg for the first week; dosage was then increased by 10 mg/day each week until the assigned target dose was reached in each group. The primary outcome was mean change from baseline of the averaged score (morning and afternoon for 3 days of each week) of the teacher's version of the Conners 10-item Global Index Scale (CGIST) at week 3. The 6-20-00 analysis plan indicated that, conditional upon a positive result on the primary analysis, they would look at morning and afternoon CGIST scores separately. Secondary outcomes included: CGI-S and CGI-I, by parents, on either Saturday or Sunday, at 10:00 am, 1:00 pm, and 4:00 pm; and, a parent's global assessment (CGISP). For the primary outcome, ANCOVA of the LOCF data was the protocol specified analysis.

The plan was to randomize approximately n=450 patients. The actual number randomized was n=584:

	10 mg	20 mg	30 mg	Placebo
Randomized:	129	121	124	210
Completed:	119 (92%)	105 (87%)	112 (90%)	173 (82%)

The mean age was about 9, and the sample was mostly male (77%) and Caucasian (76%).

The primary outcome was signficant vs placebo for all 3 dose groups (P<0.001), and separate analyses of morning and afternoon scores were also highly significant for all 3 dose groups (p<0.001). There was a slight, but probably not statistically significant, numerical advantage for the higher doses vs the 10 mg dose. Analyses of the parent CGI-S scores were also highly significant, both overall, and at each of the 3 time points. Subgroup analyses revealed a greater effect in boys vs girls. An analysis based on the first n=450 patients was also highly significant in favor of Adderall XR.

Comment: Drs. Mosholder and Shen consider this a positive study, and I agree. Dr. Shen questions whether or not the sponsor clearly specified its intent to do conditional hypothesis testing on the morning and afternoon CGIST scores. In my view, this was clear enough in their analysis plan and in our discussions with the sponsor to justify the inclusion of these results in labeling. The sponsor also seeks to include information on the following in labeling: (1) parent ratings; (2) onset of effect by the first week. The parent ratings were not properly specified for conditional hypothesis testing, and thus, should not be mentioned in labeling. On the other hand, time of onset, which was week 1, with continued effect throughout the 3 weeks, was an entirely predicted finding, even without specification. Thus, I am inclined to allow these results to be described in labeling.

5.12 Conclusions Regarding Efficacy Data

In summary, I consider study 301 positive support for the claim of short-term effectiveness of Adderall XR. In the approval letter, we will need to ask Shire to commit to conducting, postapproval, a study in children less than 6, under the Pediatric Rule.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for Adderall XR were reviewed by Dr.Andrew Mosholder. This original review was based on an integrated database submitted with the original NDA and additional data submitted in the 2-13-01 safety update. There were 5 PK studies, and 3 clinical studies; the latter were in predominantly Caucasian male children with ADHD (ages ranging from 6-12). The total Adderall XR-exposed sample included n=90 subjects in PK studies and n=553 ADHD patients in clinical studies. The clinical sample included n=336 patients exposed for $\geq$ 3 months and n=195 exposed for $\geq$ 6 months.

5.2.2 Adverse Event Profile for Concerta

5.2.2.1 Common Adverse Event Profile

The adverse event profile for Adderall XR was similar to that known for other stimulant products, including notably insomnia, anorexia, and abdominal pain.

5.2.2.2 Conclusions Regarding Safety Data

Overall, there were no adverse event findings observed in the clinical trials with Adderall XR that would preclude an approvable action. The adverse event profile observed is similar to that seen with other stimulant formulations and it can be adequately characterized in labeling.

5.3 Clinical Sections of Labeling

We have substantially rewritten the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

There was no published literature to review that was specifically pertinent to the Adderall XR product.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Adderall XR is not approved anywhere at this time. We will ask for an update on the regulatory status of Adderall XR in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take Adderall XR methylphenidate to the PDAC.

9.0 DSI INSPECTIONS

Two sites from study 301 were inspected, including one for which DSI recommended not accepting the data. This was the [redacted] site for study 301. Their complaint was that there was no documentation of the teacher ratings for 7 patients. The key outcome in this study was teacher ratings, and these were recorded by personnel at each site, apparently sometimes by phone, often with tapes recordings, and sometimes by fax. DSI was concerned that there was no way to independently document teacher ratings when the

information was conveyed by phone and tape recordings were not available. However, the protocol did not specify how the information was to be obtained, thus, either of these methods should be considered acceptable, with or without tape recordings. In fact, it is not uncommon for investigators to obtain outcome data by phone, without any independent documentation. Both Drs. Mosholder and Shen considered all the data from this site acceptable, and I agree.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft from the recent labeling update.

10.2 Approvable Letter

The approvable letter includes draft labeling and requests for a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Shire has submitted sufficient data to support the conclusion that Adderall XR is effective and acceptably safe in the treatment of ADHD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 21-303
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/TWheelous

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/s/

Thomas Laughren
7/30/01 07:13:39 AM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: October 6, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Adderall XR (modified release formulation of a mixture of d- and l-amphetamine) for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

TO: File NDA 21-303
[**Note:** This memo should be filed with the 8-14-01 response to our 8-3-01 approvable letter.

Background

In our 8-3-01 approvable letter, we proposed draft labeling, and we asked for (1) a safety update, (2) a regulatory status update, (3) the adoption of our proposed dissolution specifications, (4) a commitment to provide (post approval) information regarding the bioavailability of amphetamine from both Adderall IR tablets and Adderall XR capsules relative to an optimally available dosage form, such as a solution, and the metabolic fate of amphetamine for labeling purposes, and (5) a satisfactory resolution of various CMC deficiencies.

The sponsor responded to these issues with submissions dated 8-7-01, 8-9-01, 8-13-01, and 8-14-01.

Safety Update

The cutoff date for the safety update was 4-30-01. This safety update included safety data from only one ongoing open label study, 302. The safety results provided included information for only 42 new patients, and additional safety data for the remainder. Dr. Mosholder reviewed these data, and concluded that there were no new safety findings that would impact on the approvability or labeling of this product. I agree. However, he did note that the data provided for this open study included only change from the last visit of

study 301, i.e., these were on-drug visits, rather than the original drug-free baseline. Thus, he has asked that Shire provide the changes from drug-free baseline for the various laboratory and vital signs parameters. I am less inclined to think such data would be of value, given the fact there there is no control group for comparison. In any case, any such request need not be included in the approval letter.

Regulatory Status Update

To my knowledge, this product has not been approved in any country, but an application is apparently pending in Canada.

Dissolution Specifications

The sponsor accepted our proposed dissolution specifications.

Bioavailability/Metabolism Commitment

The sponsor has committed to obtaining the requested information post approval.

CMC Deficiencies

To my knowledge, all remaining CMC issues have been resolved.

Pediatric Waiver

Currently approved immediate release Adderall is approved down to age 3, however, the labeling we are approving for Adderall XR states that this new formulation is approved only for children 6 and older. I recommend that we include in the approval letter the standard language asking that they submit a development plan for studying this drug in children with ADHD who are less than 6, or justify a waiver.

Labeling

We exchanged various versions of labeling with Shire, based on their response to our approvable letter, and ultimately met with them on 10-2-01 to discuss final labeling. Based on that meeting, and several additional exchanges over the next few days, we reached agreement on final labeling. There were 3 issues for which there was some difficulty reaching final agreement.

-Study 201: As indicated in the approvable letter, we disagreed with Shire on whether or not the results of this study, particularly in reference to characterizing the time course of effect, could be described in labeling. However, we did finally reach agreement with Shire, including among both clinical and statistical members of our review staff, on language that characterized study 201 as a separate study that provided evidence of the efficacy of Adderall XR, but without reference to time course of effect.

-Characterization of BP and PR data for study 201: Minimal to no effect on BP and PR was observed in this study, and this finding is inconsistent with what is believed to be a fairly predictable effect of amphetamines on BP and PR. Describing these minimal findings in labeling was also inconsistent with the fairly precautionary language in labeling regarding patients with pre-existing hypertension. Thus, we asked Shire to postpone adding these findings until they could submit a more comprehensive review of these findings in the context of other available data regarding amphetamines and BP/PR. They agreed with this suggestion.

-Decreased systemic exposure to amphetamine in children compared to adults: There was disagreement between Shire and OCPB staff regarding the correct number to use in labeling (20% vs 30%), however, we ultimately obtained Shire's agreement that this issue could be resolved post approval, and our proposed 30% value could stand for now. They agreed with this approach.

Thus, as of 10-5-01, we reached agreement with Shire on the version of final labeling that is attached to the approval letter.

Conclusions and Recommendations

I believe that Shire has submitted sufficient data to support the conclusion that Adderall XR is effective and acceptably safe in the treatment of ADHD. I recommend that we issue the attached approval letter with our mutaully agreed upon labeling.

cc:
Orig NDA 21-303
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