CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 11522, S010

APPROVAL LETTER
NDA 11-522 / S-010

Richwood Pharmaceutical Company, Inc.
Attention: William A. Nuerge
Chief Operating Officer
7900 Tannen's Gate Drive, Suite 200
Florence, KY 41042

Dear Mr. Nuerge:

Please refer to your supplemental new drug application of September 21, 1993 (S-010), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall (dextroamphetamine saccharate, dextroamphetamine sulfate, amphetamine aspartate, and amphetamine sulfate) 10 mg and 20 mg tablets.

Supplemental application S-010 consists of the resubmission and provides critical analyses for the quantitation of d- and l-amphetamine, and updated manufacturing, controls and test procedures. The supplemental application also provides draft labeling revised in response to the Federal Register notice of August 8, 1970 (DESI 5378), classifying this drug effective for use in the treatment of narcolepsy, attention deficit disorder with hyperactivity, and exogenous obesity.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended with the labeling changes listed below. Accordingly, the application, with these labeling revisions, is approved effective as of the date of this letter. This action also approves this application on the basis of effectiveness of the drug as well as safety and supersedes the Federal Register notice of September 25, 1973, thus re-establishing the approval of NDA 11-522.

The labeling revisions, as agreed to by Rob Falconer of your firm during his telephone conversation with Steven D. Hardeman, R.Ph., of this agency on January 26, 1996, are as follows:

1. The statement currently placed in Warnings, "Clinical experience suggests ... growth should be monitored during treatment," should not be repeated under Precaution--Pediatric Use.

2. The statement under Precautions that FD&C Yellow #6 causing allergic reactions is unnecessary and should be deleted, as this statement applies to FD&C Yellow #5 rather than #6.
3. Under Adverse Reactions—Cardiovascular, the statement, "There have been isolated reports of cardiomyopathy associated with chronic amphetamine use," should be added.

4. The treatment of overdose section should be updated, as follows:
   (additions are in redline font, deletions are in strikout font)

OVERDOSAGE:

TREATMENT—Consult with a Certified Poison Control Center for up to date guidance and advice: Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdose, administration of intravenous phenolamine (Regitine®. CIBA) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

We also have the following request and acknowledgment regarding chemistry and manufacturing controls:

1. We request that you place all 6 validation batches on long-term stability at ambient (i.e., either 30°/ambRH or 25°/60%RH) conditions. Please provide your stability protocol and commitment (i.e., storage conditions, sampling times, and tests to be performed).

2. As requested, a 24-month expiration dating period at ambient conditions is acceptable.

These revisions are terms of the supplement approval. Marketing the product before making, exactly as agreed to, the revisions in the product’s labeling may render the product misbranded and an unapproved new drug.
Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed or 6 months from the date of this letter. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 11-522 / S-010. Approval of this labeling by FDA is not required before it is used. Should additional information relating to the safety and effectiveness of the drug become available, further revision of that labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact Steven D Hardeman, R.Ph., Regulatory Management Officer, at (301)594-2777.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research
REVIEW AND EVALUATION OF CLINICAL DATA

NDA 11-522 (Obterol/Adderall)
Sponsor: Richwood Pharmaceutical
Drug: Dextroamphetamine saccharate/amphetamine aspartate/dextroamphetamine sulfate/amphetamine sulfate
Material Reviewed: Prepublication draft of a Medical Letter article regarding Adderall and other drugs for attention deficit/hyperactivity disorder
Date Received: October 17, 1994

I. Material Reviewed

The Office of Health Affairs has asked our Division to comment upon this Medical Letter draft article, "Adderall and other drugs for attention deficit hyperactivity disorder." Adderall is a combination amphetamine product (see above) which was formerly called Obterol. (I understand that this product may be subject to a compliance action; apparently it is being marketed without an approved NDA. This information, however, is still confidential.)

The draft article begins with a reference to the "vigorous" promotion of Adderall, and concludes by stating that no literature studies are available to support the safety and efficacy of the medication, or the claim that its effect lasts throughout the school day after one dose. The body of the article reviews the pharmacotherapy for attention deficit hyperactivity disorder (ADHD), and presents a balanced although brief summary of important clinical considerations. The information on dosing, pharmacokinetics and adverse effects for the most part agrees with what is commonly cited in the literature or described in the labeling for the psychostimulants. Some items which might deserve mention as adverse effects are toxic psychosis and cardiovascular effects; also, there is no reference to the fact that psychostimulants are associated with many drug-drug interactions (e.g., with monoamine oxidase inhibitors, pressors, etc. as noted in their respective labels). The article does not mention lowering of the seizure threshold as an adverse effect; however, this is a somewhat controversial topic and the literature on this purported effect of the stimulants is mixed.

Regarding efficacy, the article states that no controlled studies have been published to support the efficacy of Dexmoxyn or Adderall in ADHD. Nonetheless, Dexmoxyn is approved for this indication. As Dexmoxyn was approved in 1943, however, the particular clinical trial data which led to approval may not be readily accessible. A few compounds which have been used "off label" in ADHD are also mentioned (clonidine, desipramine, bupropion), but the article is not inordinately promotional regarding these drugs.

II. Conclusions and Recommendations

On balance, the draft article is an objective and rational summary of pharmacotherapy for ADHD.

Suggested comments for letter to Dr. Mark Abramowitz, editor of The Medical Letter

We have reviewed your draft article on "Adderall and other drugs for attention deficit hyperactivity disorder" and we believe that it presents a balanced and fair summary of pharmacotherapy for this disorder. We have no corrections to suggest, but some minor
additions might be in order. Space permitting, toxic psychosis and cardiovascular effects probably deserve mention in the paragraph on adverse effects: likewise, reference could be made to the fact that many drug-drug interactions, some potentially serious, occur with the psychostimulants (e.g., with monoamine oxidase inhibitors, pressors, anticonvulsants etc: see their respective package inserts). Additionally, with respect to the use of non-stimulant drugs, it could be noted that clinical experience with such drugs is limited compared to the extensive experience with psychostimulants, and that non-stimulants are not considered first line drugs; no non-stimulant drugs have been approved by FDA for this indication.

We greatly appreciate the opportunity to comment upon this manuscript, and if we may help by providing commentary on other drafts in the future, please do not hesitate to ask.

Andrew Mosholder, M.D.
Medical Officer, HFD-120

10/19/94

orig NDA 11-522 Div File
cc: PLeber/TLaughren/SHardeman/AMosholder

11-20-94

I agree with the above

Please comment

[Signature]

[Signature]
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 11522, S010

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS
November 1, 1994

Steven D. Hardeman, R.Ph.
Consumer Safety Officer
Division of Neuropharmacological Drug Products, HFD-120

Thomas Laughren, M.D.
Psychiatric Group Leader
Division of Neuropharmacological Drug Products, HFD-120

NDA 11-522 Obetrol® / ADDERALL™ (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate, amphetamine aspartate) 10 mg and 20 mg Tablets

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products, HFD-120

During my conversation of May 13, 1993, with Peggy Spade (NY District - FDA) and Brad Williams (Office of Compliance), the approval status of NDA 11-522 (Obetrol®) came into question. I attempted to conduct a detailed administrative review of the NDA, however, no record of the original file could be located. The Division Document Room Personnel insist that the NDA is withdrawn and the file has been retired by the Central Document Room. Subsequent efforts to retrieve the application were unsuccessful. I located a personal file and the following issues emerged:

1. In the Federal Register notice of February 12, 1973, the Commissioner announced an opportunity for hearing on his proposal to withdraw approval of new drug applications for combination amphetamines.

2. 

3. The Commissioner, based on the review of the medical documentation offered to support the claims of safety and efficacy for Obetrol tablets, found that Rexar Pharmacal Corp. failed to present substantial evidence of effectiveness. Approval of NDA 11-522 was withdrawn by the Commissioner's order effective on October 5, 1973. Notice of the ruling was published in the Federal Register of September 25, 1973, "Final Order on Certain Combination Anorectic Drugs". (attachment 1)
In his telecon of February 26, 1982, to John Gelger (compliance), Dave Barash, CSO, explained that the product was being marketed without an approved NDA, and asked what action would be taken. An inspection took place on January 28, 1982, and no validation data was available.

The sponsor (Thad Demos - Richwood Pharmaceuticals) contacted me via phone in early 1994 to request the status of the review of their reformulation supplement. I informed him of the following:

a. It appears that the NDA was withdrawn by the commissioner in a Federal Register Notice in September 1973.

b. Aside from references in COMIS and a personal file, the Division has no records on the NDA. I informed him that COMIS is merely a document tracking database.

c. I advised that he should request a complete (unpurged) copy of all documents including supplements, amendments and annual reports under the Freedom of Information Act. I reminded him that he must also provide proof of ownership of Rexar's NDA. He informed me that Richwood had purchased Rexar.

d. I informed him that Rexar (Richwood) is in a precarious situation in that they are unable to provide documentation of their NDA's approval status and appear to be marketing without an approved NDA.

In the letter of October 21, 1994, the sponsor requested copies of material contained in my personal file. In my letter of October 26, 1994, I forwarded a copy of the September 25, 1973, Federal Register notice and a copy of the Division’s letter of September 9, 1980. (attachment 4)

Following the sponsor's initial inquiry, I contacted Doug Ellsworth and Lee Drapkin (compliance) to ask the status of compliance actions for this product. In his phone call of September 23, 1994, Larry Daunno of FDA NY District Compliance informed me that a "Warning Letter" for the Obetrol products was to be issued to the sponsor on October 24, 1994. (attachment 5)
11. In the September 1994 edition of the Journal of the American Academy of Child and Adolescent Psychiatry, Richwood Pharmaceuticals (new owners of Rexar Pharmaceutical) is promoting Obetrol (renamed ADDERALL) as a unique once a day alternative in the treatment of ADHD. (attachment 6)

12. In a consult request from HFY-1/Office of Health Affairs, the Division was asked to comment on the Medical Letter draft article "Adderall and Other Drugs for Attention Deficit Hyperactivity Disorder". (attachment 7)

13. A copy of the ADDERALL advertising and a copy of the "Warning Letter" was forwarded to Sherry Danese (DDMAC) on October 31, 1994.

cc:
HFD-120
HFD-120/Leber
   /Laughren
   /Purvis
   /Hardeman

November 1, 1994

C:\DOCS\NDAOBETROL\OBETROL.MEM

MEMORANDUM FOR RECORD
CURENT COMBINATION ANORECTIC DRUGS

Final Order on Objections and Request for

A Hearing Regarding Withdrawal of Approval of New Drug Applications

In the Federal Register of August 8, 1970 (35 FR 12652) the Commissioner of Food and Drugs published a statement of policy (21 CFR 120.45) concerning anorectics for human use. The statement contained the findings of the Food and Drug Administration based on data and reports received from the National Academy of Sciences-National Research Council (NAS-NRC) Drug Efficacy Study Group. Also published in the Federal Register of August 8, 1970 (35 FR 12678) was a notice (DESI 5/378) on drugs containing amphetamine and their use, stating that the drugs were regarded as possibly effective for their claimed anorectic effect and lacked substantial evidence of effectiveness for their other labeled indications. The statement of policy also contained the findings of the Commissioner that because of the extensive use of the drugs in the treatment of obesity, and their stimulant effect on the nervous system, they have a potential for misuse and actual abuse, and production data indicated that amphetamines are being produced and used in quantities greatly in excess of demonstrated medical needs. As a condition for continued marketing of amphetamines, the statement of policy required relabeling as specified and the submission of a new drug application (NDA) within one year for all such drugs not then the subject of a new drug application (NDA) or approved. NDA were required to submit additional evidence of safety and substantial evidence of efficacy in the form of adequate and well-controlled clinical investigations.

On February 12, 1973, the Commissioner, in the Federal Register (38 FR 4298) in a final order stating that there was a lack of substantial evidence of effectiveness for, and a recognized potential for the abuse of, fixed combination drugs for anorectic use which contained, among other ingredients, amphetamine, methamphetamine, or dextroamphetamine. In addition, the Commissioner found that alternative therapeutic measures which are safe and effective are available for use. The Commissioner also stated in the final order that a mixture of dextroamphetamine and amphetamine may be marketed as a single drug entity. A similar conclusion was to a mixture of dextroamphetamine and methamphetamine, and/or dextroamphetamine and methamphetamine was not made. In § 224 (21 CFR 120.69) the Food and Drug Administration set forth a policy on fixed-combination drugs for prescription use requiring that each drug in a fixed-combination drug contribute to the claimed effect of the drug; section IV, infra. Therefore, drugs containing combinations of amphetamine and methamphetamine and/or dextroamphetamine and methamphetamine, or fixed combination drugs. The final order also stated that a proposal to withdraw approval of such combination drugs for anorectic use was published elsewhere in the same issue of the Federal Register.

In a notice in the Federal Register of February 12, 1973 (38 FR 4278), the Commissioner announced an opportunity for hearing on his proposal to withdraw approval of new drug applications for the combination amphetamine or other anorectic drugs. This notice was based on aggregate evidence collected pursuant to the Federal Register notice of August 8, 1970 (35 FR 12678). This data was found, after review, not to provide substantial evidence that the drugs named in the Federal Register notice of February 12, 1973, were effective as fixed combination for their claimed anorectic uses. Based on this lack of substantial evidence of effectiveness of the drugs as fixed combinations, the recognized potential for abuse of these combination drugs, and the availability of alternative therapeutic measures which are safe and effective, the named drugs were found to be lacking in proof of safety. The Commissioner further found that the data submitted in response to the Federal Register notice of August 8, 1970, did not support a contention that the complaints decreased the incidence or severity of side effects associated with the abuse potential of the single entity anorectic drug. Notice was also given to hold these of the named new drug applications and all other interested persons, including those marketing such single-entity anorectic drugs (38 FR 120.60 (21 CFR 120.60)) that the Commissioner proposed to withdraw approval of these new drug applications based on substantial evidence of ineffectiveness and a lack of proof of safety. All holders of the NDA's and persons marketing similar, identical or related drugs, and other interested persons were invited to request a hearing on the proposed withdrawals and to submit with such request a well organized and well-developed record of the clinical and other investigational data they are prepared to prove in support of their opposition to the withdrawal of the named NDA's and any such similar, identical or related drugs. The notices stated that if substantial evidence of ineffectiveness and evidence of safety was received for only one of the named drugs, or for similar, identical and related drugs, the notice would be modified accordingly.

In response to the notice in the Federal Register of February 12, 1973, requests for a hearing were received from two companies and the drugs were named in the Federal Register notice of March 20, 1973 (38 FR 8920). The subject final order concerns only two of those persons requesting hearings.

Texas Pharmaceutical Co., 305 Rockaway Ave., Valley Stream, N.Y. 11581, requested a hearing for the drugs Obetrol-10 and Obetrol-15 Tablets (NDA 11-563), which are the subject of an NDA which was made conditionally effective on July 24, 1959, and fully effective on February 26, 1960. The Obetrol drugs have been reviewed by the NAS-NRC and were found to be possibly effective as an adjunct in the management of some forms of obesity in which an appetite depressant was indicated. The Obetrol drug was incorporated into the August 8, 1970 Federal Register notice discussed above (38 FR 12678).

Chester Chemical Co., 7 McLouest Parkway North, Mount Vernon, N.Y. 10550, requested a hearing for the drugs Delcobe Blisteed Release Tablets and Delcobe Tablets and Delcobe Capsules and Tablets. Pursuant to the August 8, 1970 Federal Register order, the Commissioner received from Barrows Pharmaceutical Inc., 9 Prospect St., Inwood, N.Y. 11921, four new drug applications on the following dates for the following drugs:

- March 10, 1971, NDA 17-162, Delcobe Tablets, 5 mg.; March 10, 1971, NDA 17-161, Delcobe Tablets, 5 mg.; March 10, 1971, NDA 17-160, Delcobe Blisteed Release Tablets, 5 mg.; March 10, 1971, NDA 17-159, Delcobe Blisteed Release Double-Layer Tablets, 5 mg., 10 mg., 15 mg., and 20 mg.; and June 24, 1971, NDA 17-158, Delcobe Capsules, 5 mg., 10 mg., 15 mg., and 20 mg. All four of the drugs consist of a combination of amphetamines and methamphetamine. No data was submitted in support of the efficacy of these combination drugs other than anorectic activity and in treating narcolepsy and minimal brain dysfunction in children.

Due to the large number of new drug applications received pursuant to the August 8, 1970 Federal Register order, a review and evaluation of the new drug applications submitted by Barrows was delayed. Barrows was notified of this delay by a letter from the Food and Drug Administration on February 23, 1973. On January 19, 1973, a letter was sent to Barrows from J. Richard Crout, M.D., Acting Director, Office of Scientific Evaluation, Bureau of Drugs, stating the conclusion of the Food and Drug Administration that the four new drug applications submitted by Barrows could not be approved because the submissions...
NOTICES

The study is on its face, insufficient to support a conclusion for the approval of the use of the Obetrol Product. The Commissioner finds that this article is not substantial evidence of the efficacy of Obetrol Tablets.


The study reported consisted of 100 patients who were seen by the investigators for "varying" periods of time. The authors stated the test was conducted for two months, an "appropriate" period of time. Why the two months was "appropriate" is not stated. The standard for determining "overweight" was given as the "40% above standard" used. Both Obetrol 10 and Obetrol 20 were administered, with dosage and time of administration altered to conform to individual patient's needs.

No attempt was made to use any controls in the study. The investigators reported that a placebo substitute was used, with both patients after four weeks of treatment but this type of placebo employment is not a placebo control contemplated by §120.12(a)(8) since the regulation requires that the test drug be compared with the results of a patient group to whom a placebo, in all respects physically identical to the test drug, has been administered throughout the study. The subject study did not comply with the regulations.

The patient population was made up of patients some of whom had already had some type of cardiovascular disease with or without diabetes, some with diabetes alone, and some with no other disease conditions. There is no information as to suitability of the patients to be included in a study to determine the use of the drug as an anesthetic, and no assurance of comparability of the test group with a control group, since a control group was not employed (§120.12(a)(8) and (c))).

Because of the great variations in the physical conditions of the patients and the other medications they were taking, and the variations of dosage and duration of administration reported by the authors, any specific finding by the investigators as to the effectiveness or Obetrol is of questionable value.

Section 120.12(a)(8) (b) (ii) (d) (e) (f) requires that a summary of the methods of analysis and an evaluation of the data derived from the study, including any appropriate statistical methods" be submitted. No such data is presented in this study. Therefore, it is not possible to evaluate the analysis and statistical methods employed in order to determine the validity of the results and the investigational new drug not been met.

The study is on its face, insufficient to support a conclusion for the approval of the use of the Obetrol Product. The Commissioner finds that this article is not substantial evidence of the efficacy of Obetrol Tablets.

In addition, since Obetrol is a combination drug within the meaning of §120, the investigators must show that both the amphetamine and methamphetamine components of the drug contribute to the drug's overall effect. Such showing was not made in this study.

The Commissioner finds that this study is not substantial evidence of the effectiveness of Obetrol Tablets. The latter problem of the group was obesity. The drug was tested in 25 patients and compared with 16 patients to whom mp medication was administered. The authors stated that the final outcome of this study will await its ultimate re-evaluation when the patients are reviewed one year from the time they entered the clinical study.

The patients were selected at random, and randomly placed on either the drug or no treatment. Both test and control groups were given nutritional counseling and participated in the same group discussions. The results obtained showed that the group to whom the drug had been administered lost an average of 28.2 pounds over a ten week period, while the control group lost an average of 15 pounds over the ten week period. The actual weight loss for each patient is labeled. The authors concluded that "the group on the amphetamine preparation was able to lose twice as much, on the average, as the control group."

The study is deficient in several respects. First, the degree of overweight of the patients is not specified. Second, the method of randomizing the selection of the patients is not stated, nor is a table of random numbers included. Third, the number of entries in the study and the

Establishing that a study is adequate and well-controlled, set forth at §120.12(a)(8), has not been met.

The study is, on its face, insufficient to support a conclusion for the approval of the use of the Obetrol Product. The Commissioner finds that this article is not substantial evidence of the efficacy of Obetrol Tablets.
number of dropouts. This data is necessary both in order to demonstrate that equal numbers of patients were included in the three groups and to follow up on these patients to ascertain why they dropped out. Finally, the analytical technique for evaluating the results is not demonstrated to be statistically significant. The difference in the number of subjects in each group. The no treatment group had an obesity duration of 10 years or longer while the other two groups had a long obesity duration. There is no reason given why the 10 years for the study should be significant or why the lack of specific duration of obesity for the other two groups is significant.

The results of the study showed an average loss of 0.8 pounds in two weeks, 8.2 pounds in four weeks, 8 pounds in six weeks and 10.3 pounds in 10 weeks for the controls. For the phenmetrazine group, the average weight loss was 3.8 pounds in two weeks, 6.8 pounds in four weeks, 9.7 pounds in six weeks, and 13.3 pounds in 10 weeks.

The results are not meaningful since there are no data relevant to the amount of weight loss. The degree of overweight of the subjects is not given so that an objective comparison of the test subjects' weight loss is not possible. The results are insufficient for determining the selection of the subjects stated, nor is a table of random numbers presented. The analytical technique for evaluating the results is not described so that the significance of the difference of treatment of the various groups cannot be established.

As with the study discussed in the above, the necessary placebo group is not present. The "active drug" control is insufficient because the administration of a placebo would not be contrary to the interest of the patient (130.12(a)(3)(i)) and (a)(4)(i)). According to the follow-up study, in which only Obrelol was used, then only as needed, has no significance for purposes of demonstrating efficacy. The study is not adequately double blinded for reasons stated in the above. Finally, there is data to show that both the anti-obesity and the combination drug contained significant constituents of Obrelol contributed to its anorectic effect. Such a showing is required by section 300.2 of the regulations as noted above.

Finally, the study was not conducted in such a manner that the Commissioner demonstrated that both the anti-obesity and the combination drug contained significant constituents of Obrelol contributed to its anorectic effect. Such a showing is required by section 300.2 of the regulations as noted above.
IN C.

on C.
Reg.

New E.

[Docket No. FDC-D-810; NDA No. 4-516 et al.]

CERTAIN DRUGS CONTAINING PENTETRATETRAMINE IN COMBINATION WITH RAULPHLOIDS

Notice of Withdrawal of Approval of New Drug Applications

A notice was published in the Federal Register of March 6, 1972 (37 FTR 6099), extending the approval of the new drug applications listed below, and to any interested person who may be adversely affected, an opportunity for hearing on the proposal of the Commissioner of Food and Drugs to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act, withdrawing approval of the listed applications and all amendments and supplements thereto. The basis of the proposed action was the lack of substantial evidence that the drugs are effective for their labeled indications.

<table>
<thead>
<tr>
<th>Drug</th>
<th>NDA No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-498</td>
<td></td>
</tr>
<tr>
<td>0-520</td>
<td></td>
</tr>
<tr>
<td>0-527</td>
<td></td>
</tr>
</tbody>
</table>

Both Ritter Laboratories and DBV Pharmaceutical Corp. (formerly Nyoso Laboratories, Inc.) had previously disapproved a number of similar products and elected not to request a hearing. Neither Dorsey Laboratories, Inc., nor Westernfield Laboratories, Inc. filed a written appearance of election as provided by said notice. The failure to file such an appearance constitutes election not to avail themselves of an opportunity for hearing.

In addition to those listed above, three other new drug applications were in

V. O. WOOLERY, Director, Bureau of Foods.

[Debt 77-5299 Filed 1-26-72; 1-6 (4 am)]

[DESI 11073]

[Debt No. FDC-D-611; NDA 1-675]

WAMPOL LABORATORIES

Notice of Withdrawal of Approval of New Drug Application

On January 12, 1972, there was published in the Federal Register (38 FTR 6091) a notice of opportunity for hearing under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 366). Pursuant to the approval of the new drug application 11-619 for Vastran Forte Capsules containing niacin (275 mg.) with ascorbic acid, riboflavin, thiamine mononitrate, cyanocobalamin, pyridoxine hydrochloride, and calcium pantothenate, Wampole Laboratories, 33 Commerce Road, Stamford, CT 06904, on January 24, 1972, filed a written appearance of election as provided by said notice. Pursuant to the approval of the new drug application 11-509 for Vastran Forte Capsules containing niacin (275 mg.) with ascorbic acid, riboflavin, thiamine mononitrate, cyanocobalamin, pyridoxine hydrochloride, and calcium pantothenate, Wampole Laboratories, 33 Commerce Road, Stamford, CT 06904, on January 24, 1972, filed a written appearance of election as provided by said notice.
3 Pages Purged

Unapproved Supplement
I called John Geiger, who then referred me to Jay Ferrini regarding the outcome of the inspection request. I was told the inspection took place on January 28, 1982, and no validation data was available. Samples were collected.

I explained that the product is being marketed without an approved NDA (NDA was withdrawn effective 10/5/73) and I asked what action would be taken.

He said that he would analyze the inspection report, forward his recommendations to Roby Apodaca, and take action.

He said I would be informed of any action or correspondence which takes place.
3 Pages Purged
MEMORANDUM

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

DATE: OCT 19 1994
FROM: Director, Division of Drug Labeling Compliance, HFD-310
SUBJECT: DOC 94-726-063 Obatrol 10 mg. Tablets Obatrol 20 mg. Tablets
Firm: Richwood Pharmaceutical Co., Inc.
Rexar Pharmaceutical Division
Valley Stream, New York 11581

TO: Director, New York District, HFR-WX100

WARNING LETTER APPROVED

We concur that a Warning Letter should be issued to Mr. Regar Grigge, President of Richwood Pharmaceutical Company, Inc., for the subject products based on violations of the new drug and misbranding provisions of the FD&C Act.

We further concur with the language and information provided in your proposed Warning Letter (copy attached) and have made no changes. However, please include a copy of the September 25, 1973 Federal Register announcement regarding these kinds of products.

Please provide this office with a copy of the Warning Letter that issues and the firm's response.

OSO Contact: Leon Drapkin, HFD-313
(301) 443-2073

Attachment

Bradford W. Williams
WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Roger D. Griggs
President
Richwood Pharmaceutical Co., Inc.
Remser Pharmaceutical Division
386 Rockaway Avenue
Valley Stream, New York 11581

October 24, 1994

Dear Mr. Griggs:

This letter is in reference to Obetrol 10 mg. Tablets, and Obetrol 20 mg. Tablets manufactured and distributed by your firm.

The products are currently formulated by your firm as single-entity amphetamine products containing Dextroamphetamine Sulfate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate. The labeling for the products include the indications: 

"...Attention Deficit Disorder with Hyperactivity...", and 
"...Exogenous Obesity...". As such, these products are drugs within the meaning of section 201(q)(1) of the Federal Food, Drug, and Cosmetic Act (the Act).

The marketing of Obetrol 10 mg. Tablets and Obetrol 20 mg. Tablets is a violation of section 502 of the Act. They may not be introduced or delivered for introduction into interstate commerce under section 506(a) of the Act, since they are new drugs within the meaning of section 201(p) of the Act and no approval of applications filed pursuant to section 505(b) is effective for such drugs, and no Notice of Claimed Investigational Exemption under 505(l) is on file for the drugs.

The drugs are misbranded within the meaning of section 502(f)(1) of the Act in that their labeling fails to bear adequate directions for use for the conditions for which they are being offered and they are not exempt from this requirement under regulation 21 CFR 201.118 since they are new drugs within the meaning of section 201(p) and no approval of applications filed pursuant to section 505(b) are effective for these drugs.

Approval of New Drug Application (NDA) 12-522 for Remser Pharmaceutical Co.'s Obetrol 10 mg. and 20 mg. Tablets was withdrawn by the Commissioner's order effective on October 9, 1993. Notice of the ruling was published in the Federal Register of September 28,
1972, "Final Order on Certain Combination Anorectic Drugs". Additionally, the subsequent formulation changes were never approved.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Act and its implementing regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within 15 working days of receipt of this letter, of the action you have taken to discontinue the marketing of these drug products. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. If significant stocks of the drug remain in trade channels at this time, they should be immediately recalled. We request that your reply include an estimate of the amount of these products that are in inventory under your control and which remain in distribution channels.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Those include seizure and/or injunction.

Your reply should be sent to Compliance Branch, Food and Drug Administration, 650 Third Avenue, Brooklyn, New York 11232, Attention: Laurence D. Daurio, Compliance Officer.

Sincerely,

[Signature]

Edward T. Warner
District Director

Attached:
Federal Register, September 28, 1972,
Certain Combination Anorectic Drugs
DATE: 10/31/94
PAGES (including cover): 4
FROM: Larry Davino, Compliance Officer, HPR-NE110
Tel. No.: 718-965-9200
Fax No.: 718-965-5112
TO: STEVE HARDMAN
HFD-100
Tel. No.: 301-594-2850
Fax No.: 301-594-2859
MESSAGE: as requested,

Morning Letter re: Richard's Obertal

[Signature]

This document is intended only for the party to whom it is addressed and may contain information that is confidential and protected from disclosure under applicable law. If you are not the addressee, or person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on, or content of, this communication is not authorized. If you receive this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.
NEW FOR ADHD

Dosage: Once or Twice a Day...

ADDERALL

Dextroamphetamine Sulfate
Dextroamphetamine Aspartate

Amphetamine Sulfate
Amphetamine Aspartate

- Once or Twice a Day Dosing
- Available in 10mg and 20mg Scored Tablets
- Shown to be Clinically Safe and Effective
- Cost Effective Therapy

...May Avoid In-School Dosing

Warner-Lambert Pharmaceutical Co.
ADVERSE REACTIONS

Some adverse reactions may be related to or caused by the drug. These reactions may occur at any time during treatment and may be severe and life-threatening. Therefore, it is important to be aware of the potential adverse effects of amphetamine and to report any symptoms promptly.

- **Cardiovascular Effects:** Palpitations, arrhythmias, tachycardia, hypertension, or hypotension may occur.
- **CNS Effects:** Nervousness, irritability, anxiety, agitation, or restlessness may occur. Seizures have been reported in children and teenagers.
- **Musculoskeletal Effects:** Joint pain, muscle stiffness, or muscle cramps may occur.
- **Psychiatric Effects:** Agitation, psychosis, or paranoia may occur.
- **Gastrointestinal Effects:** Nausea, vomiting, or diarrhea may occur.

If any of these symptoms occur, discontinue the drug and seek medical attention immediately.

**PRECAUTIONS:**

- **Liver Function Tests:** Liver function tests should be monitored periodically during treatment.
- **Renal Function Tests:** Renal function tests should be monitored periodically during treatment.
- **Drug Interactions:** Drug interactions may occur with amphetamine.
- **Pregnancy:** Amphetamine should not be used during pregnancy.
- **Breastfeeding:** Amphetamine should not be used during breastfeeding.
- **Children:** Children should not use amphetamine.

**DOSE AND ADMINISTRATION:**

- **Adults:** Start with 2 mg and increase gradually as needed.
- **Children:** Start with 1 mg and increase gradually as needed.

**CONTRAINDICATIONS:**

- **Lactation:** Amphetamine is contraindicated during breastfeeding.
- **Pregnancy:** Amphetamine is contraindicated during pregnancy.
- **Allergic Reactions:** Amphetamine is contraindicated in patients with a history of allergic reactions to amphetamine.

**WARNINGS:**

- **Overdose:** Overdose may occur with amphetamine.
- **Interference with Other Drugs:** Amphetamine may interfere with the action of other drugs.

**ADVERSE EFFECTS:**

Some adverse effects may be related to or caused by the drug. These effects may occur at any time during treatment and may be severe and life-threatening. Therefore, it is important to be aware of the potential adverse effects of amphetamine and to report any symptoms promptly.

- **Cardiovascular Effects:** Palpitations, arrhythmias, tachycardia, hypertension, or hypotension may occur.
- **CNS Effects:** Nervousness, irritability, anxiety, agitation, or restlessness may occur. Seizures have been reported in children and teenagers.
- **Musculoskeletal Effects:** Joint pain, muscle stiffness, or muscle cramps may occur.
- **Psychiatric Effects:** Agitation, psychosis, or paranoia may occur.
- **Gastrointestinal Effects:** Nausea, vomiting, or diarrhea may occur.

If any of these symptoms occur, discontinue the drug and seek medical attention immediately.

**PRECAUTIONS:**

- **Liver Function Tests:** Liver function tests should be monitored periodically during treatment.
- **Renal Function Tests:** Renal function tests should be monitored periodically during treatment.
- **Drug Interactions:** Drug interactions may occur with amphetamine.
- **Pregnancy:** Amphetamine should not be used during pregnancy.
- **Breastfeeding:** Amphetamine should not be used during breastfeeding.
- **Children:** Children should not use amphetamine.

**DOSE AND ADMINISTRATION:**

- **Adults:** Start with 2 mg and increase gradually as needed.
- **Children:** Start with 1 mg and increase gradually as needed.

**CONTRAINDICATIONS:**

- **Lactation:** Amphetamine is contraindicated during breastfeeding.
- **Pregnancy:** Amphetamine is contraindicated during pregnancy.
- **Allergic Reactions:** Amphetamine is contraindicated in patients with a history of allergic reactions to amphetamine.

**WARNINGS:**

- **Overdose:** Overdose may occur with amphetamine.
- **Interference with Other Drugs:** Amphetamine may interfere with the action of other drugs.

**ADVERSE EFFECTS:**

Some adverse effects may be related to or caused by the drug. These effects may occur at any time during treatment and may be severe and life-threatening. Therefore, it is important to be aware of the potential adverse effects of amphetamine and to report any symptoms promptly.

- **Cardiovascular Effects:** Palpitations, arrhythmias, tachycardia, hypertension, or hypotension may occur.
- **CNS Effects:** Nervousness, irritability, anxiety, agitation, or restlessness may occur. Seizures have been reported in children and teenagers.
- **Musculoskeletal Effects:** Joint pain, muscle stiffness, or muscle cramps may occur.
- **Psychiatric Effects:** Agitation, psychosis, or paranoia may occur.
- **Gastrointestinal Effects:** Nausea, vomiting, or diarrhea may occur.

If any of these symptoms occur, discontinue the drug and seek medical attention immediately.
4 Pages Purged
MEMORANDUM

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

DATE: October 20, 1994

FROM: Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Response to Consult Request

TO: HPY-1/Office of Health Affairs

Background Information:

Issue Requiring Response: Medical Letter article on Adderall, et al

Underlying Documents: Medical Letter article on Adderall, et al

Date of Request: 10-17-94

Requester: Carol Kimbrough

Attached Responses:

Attached to this memo is the Division's response to your consult request. We have included our review and also a copy of our direct response to the Medical Letter.

CC:
HFD-120/Consult File
HFD-120/TLaughren/PLEber/AMosholder

DOC: MEDLTR.1A
October 20, 1994

The Medical Letter, Inc.
Attention: Mark Abramowicz, M.D.
Editor
1000 Main Street
New Rochelle, N.Y. 10801

Dear Dr. Abramowicz:

Please refer to your letter of October 7, 1994, requesting Agency comments on the draft article "Adderall and Other Drugs For Attention Deficit Hyperactivity Disorder."

We have reviewed your draft article and we believe that it presents a balanced and fair summary of pharmacotherapy for this disorder. We have no corrections to suggest, but some minor additions might be in order. Space permitting, toxic psychosis and cardiovascular effects probably deserve mention in the paragraph on adverse effects; likewise, reference could be made to the fact that many drug-drug interactions, some potentially serious, occur with the psychostimulants (e.g., with monoamine oxidase inhibitors, pressors, anticonvulsants etc: see their respective package inserts).

Additionally, with respect to the use of non-stimulant drugs, it could be noted that clinical experience with such drugs is limited compared to the extensive experience with psychostimulants, and that non-stimulants are not considered first line drugs; no non-stimulant drugs have been approved by FDA for this indication.

We greatly appreciate the opportunity to comment upon this manuscript, and if we may help by providing commentary on other drafts in the future, please do not hesitate to ask.

Sincerely yours,

[Signature]

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
DATE: November 7, 1994

FROM: Steven D. Hardeman, R.Ph.
Consumer Safety Officer
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Telecon of June 20, 1994, with Thad Demos of Richwood Pharmaceuticals in Reference to NDA 11-522 Obetrol®

TO: Record

Attachment 4 of the sponsor's submission of November 2, 1994, requesting a meeting with the Division, consists of a record of a telephone conversation. This record appears to be, in part, a compilation of several conversations. In several general dialogues, the sponsor requested that I provide information on the product, Obetrol. I was informed that the NDA had been purchased from Rexar Pharmaceutical by Richwood Pharmaceuticals. The history of the product is vague and I was unable to locate any information on the product other than a personal file maintained by previous CSOs and a reference in COMIS. As a follow-up to our October 19, 1994, telephone conversation, Mr. Demos requested that I provide any information that I had available. In my letter of October 26, 1994, I provided a copy of the deficiency letter of September 9, 1980, and a Federal Register notice, dated September 25, 1973.

My comments, documented in Mr. Demos' record of conversation of June 20, 1994, are basically accurate; however, several caveats were omitted.

Points 4 & 5: The framework of this portion of the discussion was in reference to DESI products in general, not specifically Obetrol. I explained that over several decades, unresolved DESI issues could be counted in the 100's; however, as of today, only a few issues are still unresolved and this product could be a case in point.

Point 6, 8 & 11: I asked Mr. Demos if the NY District was requesting any actions on his part and explained that based on my limited personal file, I was unaware of any requirements placed on him by this Division other than those mentioned in the letter of September 9, 1980. He explained that he also had very limited records for the product. The context of this statement was such that due to both our limited documentation, the appropriate step at this time would be to make no changes and to attempt to locate the NDA file through the FOI office. I explained that I was unable to complete an administrative history on his product, in that I had no documents to review and could not advise him at this time. I explained that the NDA file appeared to have been retired.
Point 7: I informed Mr. Demos that COMIS lists his product as "Approved 19 JAN 60". I went on to explain that COMIS is merely a computer database utilized to track documents and was one of the tools that I would utilize to reconstruct the administrative history of his product.

attachment
TO: Roger Griggs
FROM: Thad Demos
DATE: June 20, 1994

I called the Division of Neuropharmacology at FDA 301-594-2850. I spoke with Steve Hardeman via telephone.

RE: Obetrol Analytical Procedure #1000. The following are comments made by Steve Hardeman:

1. It appears there was a supplement submitted in the mid 1970's that was never approved.
2. There were numerous conversations between Rexar and the FDA regarding the procedure.
3. Rexar was permitted to market the product pending resolution.
4. He believes that this issue was never followed through by the FDA.
5. He stated there were hundreds of issues like this on other products that "fell through the cracks" in the 1970's.
6. He said to continue marketing the product using the current analytical procedure (procedure 1000).
7. Obetrol is listed in the FDA computer as an approved drug using the current formulation.
8. He said we do not have to do anything at this point.
9. He said that it may take some time for the Division of Neuropharmacology to find all of their records on this analytical issue "if at all".
10. He said "If we need a speedy resolution we should withdraw the supplement and then resubmit it to the Agency".
11. He said "we may continue to market the product with No Interruptions" using our current Analytical Method (#1000).
MINUTES OF MEETING
Commercial Sponsor - Richwood Pharmaceuticals
INDA 11-522 / IND

DRUG: Obetrol/Adderall
SPONSOR: Richwood Pharmaceuticals
INDICATION: ADHD - Narcolepsy - Exogenous Obesity
DATE/TIME: January 19, 1995 : 0900-1045 hrs
LOCATION: Woodmont II / 6th Floor Conference Room G

ATTENDEES:

FDA

Robert Temple, M.D. CDER/ODEI
Paul Leber, M.D. CDER/DNDP
Thomas Laughren, M.D. CDER/DNDP
Andrew Mosholder, M.D. CDER/DNDP
Stanley Blum, Ph.D. CDER/DNDP
John Purvis, SCOS CDER/DNDP
Steve Hardeman, COS CDER/DNDP
Stephanie Gray CDER/OC
Frank Fazzari CDER/OC
Charma Konnor CDER/OC
Bradford Williams CDER/OC
Patrick Savino CDER/EXEC SEC
Sherry Danese CDER/DDMAC
Eric Blumberg OGC

RICHWOOD PHARMACEUTICALS

Roger Griggs President, Richwood Pharmaceuticals
Robert Martz, M.D. International and Domestic Consulting Services
Robert Hunt, M.D. Center for Attention & Hyperactivity Disorders
Ronald Jones, M.D. Chairman of Pediatrics, Orem Community Hospital
Martha Bennett Bennett and Associates
Jess Stribling King & Spalding
BACKGROUND:

Approval of NDA 11-522, a combination of amphetamine and methamphetamine, was withdrawn by the Commissioner's order effective on October 5, 1973. Notice of the ruling was published in the Federal Register of September 25, 1973, "Final Order on Certain Combination Anorectic Drugs."

The Division of Neuropharmacological Drug Products notified the Office of Compliance in February 1982, that the product was unapproved, but no further action was taken. In February 1994, Richwood Pharmaceuticals purchased Rexar Pharmacal and began distributing Obetrol products as Adderall.

In May 1994, during a routine inspection of Richwood Pharmaceuticals (formerly Rexar), significant current good manufacturing (CGMP) violations, including inadequate manufacturing process and test method validation, stability data problems, and record keeping deficiencies were found. These violations were listed in a FD-483 (a list of inspectional observations) left with Richwood, and were summarized in a warning letter sent to the company in June 1994. Richwood's response to FDA's observations was deemed unsatisfactory, and Richwood was notified of the agency's evaluation by letter dated August 23, 1994. FDA's New York District Office has been working with Richwood in an effort to get the company back into compliance with CGMP. During a September 1994 meeting with the New York District Office, Richwood committed to effect, by March 1995, CGMP corrections relating to Adderall. In December 1994, FDA conducted a limited inspection of Richwood and found additional CGMP violations. Despite all of the foregoing, to date FDA has not initiated any compliance action against the company.

PURPOSE:

Following receipt of the "Warning Letter", Mr. Jess H. Stirling, Attorney for Richwood Pharmaceuticals, requested a meeting with the agency to 1) discuss the medical necessity of Adderall and 2) the sponsor's request to continue marketing the product pending completion of the application. He claimed that the product is medically necessary for a segment of ADHD patients who have insufficient response to, no response to, or significant side effects from methylphenidate, pemoline, or dextroamphetamine. The Division of Neuropharmacology, responding to a consultation request from the Office of Compliance, determined that there was no credible evidence that Adderall was different from ordinary dextroamphetamine and that the drug was not a medical necessity. The sponsor was informed of the Division's determination on December 15, 1994, by Laurence Dauro, Compliance Officer, New York District, FDA. Subsequently, the agency agreed to meet with the sponsor to discuss Adderall and the company's plans for the product.
DISCUSSION:

The agency convened the meeting with introductions and several precursory statements. The sponsor was advised that 1) Adderall is an unapproved new drug, 2) that the Adderall promotional campaign had been false and misleading, and 3) we were present to listen, but would not decide on action at this meeting.

Mr. Griggs presented a brief history of Richwood Pharmaceuticals and the purchase of Rexar Pharmacal. He stated that Rexar had represented that the NDA was approved but conceded that Richwood's due diligence process was inadequate. During the due diligence process, he discovered that Obetrol was being prescribed primarily for the treatment of Attention Deficit Disorder with Hyperactivity (ADHD) but that sales were minimal. He indicated that the product initially represented wholesale sales of only and that they had considered dropping it from the product line. Based on some physician's testimony as to special benefit in a segment of ADHD patients, he decided not to drop Obetrol, and instead, to promote it. The current market for Adderall is

Mr. Stribling acknowledged that, as a matter of law, the product is an unapproved new drug. He further stated that the product is not listed in the Orange Book (Approved Drug Products). However, since the firm was in receipt of an agency form letter referring to Obetrol as an approved new drug (Information Request "Dunner Letter"), the sponsor concluded that their product was approved. He stated that the product, as reformulated, has been marketed since 1973, and requested that the sponsor be allowed to continue marketing the product pending the submission of the appropriate chemistry and manufacturing controls supplement and the correction of several GMP deficiencies.

Following queries from the agency, the sponsor stated that there is no evidence, based on adequate and well controlled clinical trials, that would allow the inference that Adderall is different or better than any other single entity amphetamine product in the treatment of ADHD or narcolepsy. They stated that they initiated a study that addressed their question on March 1, 1994, but it was not complete. The agency informed the sponsor that clinical studies must be conducted under an IND.

The sponsor agreed that their promotions and advertising were excessive and indicated that they had not consulted the advertising regulations prior to initiating the Adderall promotional campaign. They stated that their campaign was based solely on patient and physician testimony and stated that they were no longer seeking a determination that Adderall is a medical necessity.
SUMMARY:

1. The sponsor acknowledged that their advertising campaign had been misleading, and if allowed to continue to market Obetrol, agree to corrective advertising.

2. The sponsor agreed to submit an appropriate chemistry supplement to NDA 11-522. The firm did not commit to a specific date for such a submission, but agreed to contact the agency with a proposed date.

3. The sponsor agreed to correct their GMP deficiencies and to coordinate with the New York District to specify the date for such corrections.

4. The sponsor agreed that if they were allowed to market Obetrol and then should fail to submit an appropriate chemistry supplement and correct their GMP deficiencies by the agreed upon dates; they would cease marketing the product.

5. The sponsor agreed to open an IND to conduct clinical studies.

Steven D. Hardeman, R.Ph.
Consumer Safety Officer
DNDDP

cc:
ORIG NDA 11-522
ORIG IND
HFD-120/Div File
HFD-100/Temple
HFD-120/Leber
/Laughren/Mosholder
/Blum
/Purvis
/Hardeman
HFD-244/Rose/Danese
HFD-300/Gray/Williams/Konnor
GCF-1/Blumberg

C:\DOCS\IND4\ ADDERALLI V47301\ Adderall.mml

Draft: 1/26/95, 2/2/95
Final: 2/22/95

MEETING MINUTES
NDA 11-522/S-011, S-015

Richwood Pharmaceutical Company Inc.
Attention: Robert Falconer
7900 Tanners Gate Drive
Florence, KY 41042

Dear Mr. Falconer:

Please refer to your supplemental new drug applications S-011 and S-015 for Adderal® 10mg and 20 mg Tablets.

These supplemental applications provide for the following labeling changes:

1. S-011 removes the obesity indication, includes a report of congenital anomalies under the Pregnancy/Teratogenic Effects section, and provides for some minor editorial changes.

2. S-015 removes the statement “Warning: May be habit forming” from the labeling attached to the exterior of the bottles.

We have completed our review of supplemental applications S-011 and S-015 and they are approved.

Labeling changes of this kind are permitted by section 314.70(c) of the regulations, and may be established prior to approval of the supplement. We note that these changes have been effected.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Melina Malandracco, R.Ph., Project Manager, at (301) 594-5526.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
cc:
Original NDA 11-522
HFD-120/DIV. files
HFD-120/CSO/Malandrucco 7/4/97
HFD-120/Leber/Laughren/Mosholder/Blum/Scarpetti
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)

APPROVAL (AP)

APPEARS THIS WAY ON ORIGINAL
Division of Neuropharmacological Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 11-522/S-011, S-015

Name of Drug: ADDERALL® Tablets

Sponsor: Richwood Pharmaceutical Company Inc

Materials Reviewed:
Last Approved Labeling S-010- February 29, 1996
Supplement 011- July 24, 1996 (Identified as MG 10185 Revised May 1996)
Supplement 015- December 31, 1996 (Identified as MF 2060 Revised Aug 1996)

Review and Evaluation:
SLR-011: See enclosed document which highlights changes to the last approved labeling using “stikeouts” and “additions” markings. Additionally, CSO review comments are included which identify the type of labeling change. In a line by line comparison between the last approved labeling (S-010) and the proposed labeling only those changes indicated by the sponsor were made.

SLR-015: These changes were only made to the printing of the labeling attached to the exterior of the Adderall® 10 and 20 mg bottles. The statement “Warning: May be habit forming” has been deleted.

All changes within SLR-011 and SLR-015 were submitted as “Changes Being Effected”.

Summary of Labeling Revisions (See enclosed document for specific changes):
There are 15 labeling revisions identified in the enclosed document.

Labeling changes 1,3,4,11, and 12 are deletions in various sections related to the removal of the obesity indication.
Labeling changes 5,6,9,10, and 15 are editorial changes.
Labeling changes 7 and 8 are changes to the Pregnancy Teratogenic Effects section.
Labeling change 2 is the renaming of the Actions section.
Labeling changes 13 and 14 are changes to the HOW SUPPLIED section.

Recommendation:
These indicated revisions have been approved by the medical and chemistry reviewers. I recommend approval of SLR-011 and SLR-015.

/S/
Melina Malandrucco, Project Manager

/S/ Jack Purvis, Chief Project Management Staff
4 Page(s) Redacted

DRAFT LABELING
Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

**Name of Drug:** ADDERALL-TABLETS

**NDA Number:** 11-522

**Supplement Number:** S-015

**Date of Supplement:** December 31, 1996

**Date of Receipt:** January 10, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 11, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

(Signed)

(FOR) John Purvis

Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
December 31, 1996

Paul Leber, MD
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Woodmont II, Document Room
HFD-120
1451 Rockville Pike
Rockville, MD 20852

RE: CHANGES BEING EFFECTED for Adderall® Tablets
Approved Supplemental NDA 11-522

Dear Dr. Leber:

Enclosed are twelve (12) of the final printed labeling for Adderall® (dextroamphetamine saccharate, dextroamphetamine sulfate, amphetamine aspartate, and amphetamine sulfate) 10mg and 20 mg tablets with the “Warning: May be habit forming” statement deleted. These revised labels went into effect on 12/17/96.

Sincerely,

M. Madigan (for Robert Falconer)

RICHWOOD PHARMACEUTICAL CO., INC.
Robert A. Falconer
Corporate Director,
Regulatory & Technical Affairs
Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ADDERALL—TABLETS

NDA Number: 11-522

Supplement Number: S-011

Date of Supplement: July 24, 1996

Date of Receipt: July 30, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 29, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

/S/

Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
July 24, 1996

Paul Leber, MD
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Woodmont II, Document Room
HFD-120
1451 Rockville Pike
Rockville, MD 20852

RE: CHANGES BEING EFFECTED for Adderall® Tablets

Approved Supplemental NDA 11-522

Dear Dr. Leber:

As requested in your letter dated April 9, 1996 enclosed are sixteen (16) of the final printed labeling for Adderall® (dextroamphetamine saccharate, dextroamphetamine sulfate, amphetamine aspartate, and amphetamine sulfate) 10 mg and 20 mg tablets. Also enclosed is a highlighted copy of the package insert changes. This revised package insert went into effect on 7/22/96.

Sincerely,

RICHWOOD PHARMACEUTICAL CO., INC.

Robert A. Falconer
Corporate Director, Regulatory & Technical Affairs

9/12/96 These changes remove the obesity indication, include a report of congenital anomaly under the Pregnancy Teratogenic Effects heading, and provide for some minor editorial changes. The revised labeling is acceptable.
NDA 11-522/S-017

Richwood Pharmaceutical Company Inc.
Attention: Robert Falconer
7900 Tanners Gate Drive
Florence, KY 41042

Dear Mr. Falconer:

Please refer to your supplemental new drug application S-017 for Adderall® 10mg and 20 mg Tablets.

This supplemental application provides for the following labeling changes:

1. The first sentence in the WARNINGS section reading “When tolerance...be discontinued.” has been deleted.

2. The word “antibesity” in the DRUG INTERACTIONS section has been replaced with the word “anorectic” under the Lithium Carbonate subsection.

3. The word “Amphetamine” in the CARCINOGENESIS/MUTAGENESIS section was written in lowercase instead of being capitalized.

4. In the HOW SUPPLIED section a toll-free number “1-800-536-7878” has been added for information and assistance.

We have completed our review of supplemental application S-017 and it is approved.

Labeling changes of this kind are permitted by section 314.70(c) of the regulations, and may be established prior to approval of the supplement. We note that these changes have been effected.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Melina Malandrucco, R.Ph., Project Manager, at (301) 594-5526.

Sincerely yours,

[Signature]

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
cc:
Original NDA 11-522
HFD-120/Div. files
HFD-120/CSO/Malandrucco
HFD-120/Leber/Laughren/Mosholder
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)

APPROVAL (AP)
ADDERALL® TABLETS

JUL 25 1997

BEST POSSIBLE COPY

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED IN DISPERSED FORMS.

DESCRIPTION: A single entity ampheta mine product containing the active residue salts of dextroamphetamine and amphetamine, with the excipients of amphetamine salt, croscarmellose sodium, and lactose monohydrate constituents.

EACH TABLET CONTAINS: Dextroamphetamine: 2.5 mg 5 mgamphetamine: 1.3 mg 5 mg

Total: 3.8 mg 10 mg

Active ingredients: amphetamine, lactose, croscarmellose sodium, magnesium stearate. Colors: ADDERALL 10 mg contains FD&C Blue No. 1 ADDERALL 20 mg contains FD&C Yellow No. 6 as a color additive.

CLINICAL PHARMACOLOGY: Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Pharmacologic actions include elevation of systolic and diastolic blood presures and weak bronchodilation and respiratory stimulation.

There is no specific evidence which clearly establishes the mechanism whereby amphetamines produce mental and behavioral changes in children, nor does an inductive analysis regarding how these effects relate to the condition of the central nervous system.

INDICATIONS: Attention Deficit Disorder with Hyper-
Deficit Disorder with hyperactivity (AD/HD) is classified as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for establishing success in children with behavioral symptoms characterized by the following group of developmentally inappropriate symptoms: hyperactivity, short attention span, impulsivity, distractibility, and inappropriateness. The diagnosis of the syndrome should not be made with facility since these symptoms are only of relatively recent origin. Handicapping (with) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

**In Neurology**

**CONTRAINDICATIONS**: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or electroencephalographic or electrocardiographic signs of myocardial ischemia to the sympathomimetic amines, glaucoma.

**Warnings**: Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

**WARNINGS**: Clinical experience suggests that in psychotic children, administration of amphetamines may accentuate symptoms of behavior disorder and thought disorder. Data are inadequate to determine whether chronic administration of amphetamines may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Usage in Renal Disease: Amphetamines are excreted in human urine. Depending on the degree of renal function, amphetamines should be administered according to the usual recommended dosage.

**PRECAUTIONS**: General: Caution is to be exercised in prescribing amphetamines for patients with latent hypertension.

**The least amount feasible** should be prescribed in order to minimize the possibility of overdosage.

**Informations for Patients**: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

**Drug Interactions**: Acidifying agents: Amphetamines may compete for acidifying agents (such as phenylbutazone, salicylates, etc.) for the same renal tubular site, increasing the concentration of the non-ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents cause effects on blood pressure that are additive.

**Adverse Reactions**: Amphetamines are potent adrenergic stimulants. Among others, adverse reactions include:

- **Restlessness**: Amphetamines may promote the activity of the sympathetic nervous system. For example, d-amphetamine with amphetamine or phentermine and possibly other sympathomimetics. This effect is generally thought to be due to the increased concentration of d-amphetamine in the brain, although the precise mechanism of this effect is not known.

**MAC**: MAO inhibitors, as well as other sympathomimetics, may potentiate the effects of amphetamines. This may cause adverse effects, including those mediated by the adrenergic nervous system. It is recommended that these medications be used with caution and that the patient be monitored closely for signs of toxicity.
Carboxymethyl/Amphetamine

Aguinamy, studies and long-term studies in animals to
determine the carcinogenic potential of amphetamines, have
ever been performed.

Pregnancy - Teratogenic Effects: Pregnancy Category C.

Amphetamines have been shown to have embryotoxic and
teratogenic effects when administered to rabbits and
C57BL mice at doses approxi-
mately 41 times the maximum
human dose. Embryotoxic effects were not seen in New
Zealand White rabbits given the drug in doses 7 times the
human dose or in rats at 12.5 times the maximum
human dose. While there are no adequate and well-con-
trolled studies on pregnant
women, there has been one
report of severe congenital
birth defects. Psychopheninetic
abnormalities and small
babies were associated in a
baby born to a woman who
was drug-dependent during the
first trimester of pregnancy.

Amphetamine should be used
during pregnancy only if the
cutaneous benefit justifies the
potential risk to the fetus.

Neonatal/Neurological Effects:

Infants born to mothers depen-
dent on amphetamines have an
increased risk of premature
delivery and low birth weight. Also, these infants may experi-
ence symptoms of withdrawal as demonstrated by depression,
including agitation, and signifi-
cant irritability.

Pediatric Use: Long-term effects of amphetamines in
children have not been well
established. Amphetamines are
not recommended for use in
children under 3 years of age
with Attention Deficit Disorder
with Hyperactivity described
under INDICATIONS AND USAGE.

Amphetamines have been
reported to exacerbate motor
and phonic tics and Tourette's
syndrome. Therefore, clinical
evaluation for tics and
Tourette's syndrome in children
and their families should
precede use of stimulant medica-
tions.

Drug treatment is not indicated
in all cases of Attention Deficit Disorder with Hyperactivity and
should be considered only in
light of the complete history
and examination of the child. The
decision to prescribe amphet-
amines should depend on the
benefit of increased attention,
chronicity and severity of the
child's symptoms and the
appropriateness for the age.
Prescription should last
depend only on the presence
of one or more of the behav-
ioral characteristics. When
these symptoms are associ-
ated with acute stress reac-
tions, treatment with amphet-
amines is usually not indicated.

ADVERSE REACTIONS:

Cardiovascular: Palpitation,
irritability, increased blood
pressure. Hypertension has
to be associated with chronic
use of amphetamines.

Central Nervous System:

Psychotic episodes in recom-
nended doses (less than
overstimulation, restlessness, dizziness,
headache, agitation, euphoria,
headache, paranoid ideas, delusions, mania,
headaches, exacerbation of
motor and phonic tics and
Tourette's syndrome.

Gastrointestinal: Dryness of
the mouth, unpleasant taste,
nausea, constipation, other
dysphagia and nausea.

Other: Overstimulation may
occur as an undesirable effect
when amphetamines are used
for either the anorectic or
behavioral effects.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE

AND DEPENDENCE:

Drug dependence and
abuse of amphetamines is a
Schedule II controlled sub-
stance.

Amphetamines have been
extensively abused. Tolerance,
effectiveness, psychomotory
dependence, and severe social
abuse have occurred. There
evidence of patients who have
effected the dosage to as
many times that prescribed;
Adolescent exogenous pro-
testers, high dose administra-
tions usually in extreme

cases; withdrawal symptoms
are also noted on the same
basis. Manifestations of
chronic intoxication with
amphetamines include severe
disturbances, marked insomnia,
irritability, hyperactivity, and
personality changes. The most
severe manifestations of chronic intoxication psychosis, other
cerebral manifestations from
Division of Neuropharmacological Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 11-522
Name of Drug: Adderall® 10 mg and 20 mg Tablets
Sponsor: Richwood Pharmaceutical Company, Inc
7900 Tanners Gate Drive
Florence, KY 41042

Material Reviewed
Submission Date(s): July 17, 1997 (SLR-011) - Last approved labeling
June 24, 1997 (SLR-017) - MG #10185 Revised May 1997

Background and Summary Description: Supplement 017 was submitted as a "Changes Being Effected".

Review
1. Supplement 017 includes the following changes to the package insert:
   a. The first sentence in the WARNINGS section reading "When tolerance...be discontinued." has been deleted.
   b. The word "antiobesity" in the DRUG INTERACTIONS section has been replaced with the word "anorectic" under the Lithium Carbonate subsection.
   c. The word "Amphetamine" in the CARCINOGENESIS/MUTAGENESIS section was written in lowercase instead of being capitalized.
   d. In the HOW SUPPLIED section a toll-free number "1-800-536-7878" has been added for information and assistance.

All the above changes are acceptable to the medical reviewer.

Conclusions
In a line by line comparison of the last approved supplement SLR-011 and the proposed labeling, no changes other than those specified by the sponsor were made. I recommend approval.

/S/
Project Manager

Supervisory Comment/Concurrence:

/ST
7/23/97
Supervisor, Project Management Staff
cc:
Original
HFD-120/Div. Files
HFD-120/Malandrucco
Richwood Pharmaceutical Company Inc.
7900 Tanners Gate Drive
Suite 200
Florence, KY. 41042

Attention: Robert A. Falconer

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Adderall Tablets
NDA Number: 11-522
Supplement Number: S-017
Date of Supplement: June 24, 1997
Date of Receipt: June 25, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 24, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5800 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

[Signature]

(FOR) John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FORM FDA 3217b (11/85)
June 24, 1997

Dr. Paul Leber, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Woodmont II, Document Room
HFD-120
1451 Rockville Pike
Rockville, MD 20852

RE: Special Supplement - Changes Being Effected
ADDERALL® Tablets 10 mg and 20 mg
NDA 11522
Package Insert revised 5/97

Dear Dr. Leber:

Pursuant to 21 CFR 314.70, Richwood Pharmaceutical Company Inc. is submitting the following changes to the ADDERALL® package insert:

1. Deleted the first sentence in the WARNINGS section:

When tolerance to the anorectic effect develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued.

Justification for change in the labeling:

This sentence was removed because ADDERALL is not indicated for the treatment of obesity or for an anorectic effect.

2. Changed the wording associated with Lithium Carbonate under Drug Interactions section:

The word “antiobesity” was replaced with the word “anorectic”. The statement now reads as follows: “Lithium carbonate - The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.”

7/17/97 These changes are acceptable

/S/
medical officer
Paul Leber
June 24, 1997
Page 2.

Justification for change in the labeling:

ADDERALL is not indicated for the treatment of obesity. Therefore, the proper
description of the pharmacologic effect is the use of the adjective “anorectic”
instead of suggestion of an indication which is implied by the term “antiobesity.”

3: In the Carcinogenesis/Mutagenesis section, the word “Amphetamine” should not be
capitalized; so it was changed to read “amphetamine”.

4. In the How Supplied section a toll-free company telephone number “1-800-536-7878”
has been included to assist persons who need to contact the company to obtain
information about ADDERALL®.

The revised package insert is identified as Revision 5/97 and was included with packaged

Twelve (12) copies of revised package insert are enclosed with this supplemental
submission.

If you have any questions concerning this submission, please call the undersigned at
(606) 282-2100.

Sincerely,
Richwood Pharmaceutical Company Inc.

Jon W. Banning
Jon W. Banning, Ph.D.
Manager, Regulatory & Technical Affairs

closure
NDA 11-522/S-019

Richwood Pharmaceutical Company, Inc.
Attn: Robert Falconer
7900 Tanners Gate Drive
Suite 200
Florence, KY 41042

Dear Mr. Falconer:

Please refer to your supplemental new drug application dated October 24, 1997, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetics Act for Adderall® Tablets.

The User Fee goal date for this application is April 27, 1998.

The supplemental application provides for:

The supplement was submitted as "Special Supplement - Changes Being Effectuated".

We have completed the review of this supplemental new drug application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Melina Malandrucco, Regulatory Project Management Officer, at (301) 594-2850.

Sincerely,

[Signature]

Maryla Guzewska, Ph.D.
Chemistry Team Leader, DNDC-1
Division of Neuropharmacological Drug Products
(HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
CC:
Original NDA 11-522
HFD-120/Div. Files
HFD-120/CSO/MMalandrugo
HFD-120/MGuzewski
HFD-110/RMittal
HFD-810/CHOiberg
HFD-82/DDM-DIAB
HFR-MA300/NWJ-D

APPROVAL (AP)
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA #: 11-522/S-019  REVIEW DATE: 13-MAR-98

SUBMISSION TYPE: SUPPLEMENT  SCOS-019  DOCUMENT DATE: 24-OCT-97
SUBMISSION DATE: 27-OCT-97  CDER DATE: 18-FEB-98

SUPPLEMENT PROVIDES FOR:
Special Supplement Changes being Effected

The use of revised in-process controls for tableting Adderall 30 mg Tablets.

NAME & ADDRESS OF APPLICANT
Shire Richwood Inc.
7900 Tanners Gate, Suite 200
Florence, Kentucky 41042

DRUG PRODUCT NAME

Proprietary:  ADDERALL
Nonproprietary/USAN: Amphetamine Salts

PHARMACOL. CATEGORY/INDICATION:  Attention Deficit Disorder and Narcolepsy

DOSAGE FORM: Tablets
STRENGTHS: 5 mg, 10 mg, 20 mg and 30 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

CHEMICAL NAME Drug Substance I - (+)-α-Methylphenethylamine sulfate
Drug Substance II - (±)-α-Methylphenethylamine aspartate
Drug Substance III - (+)-α-Methylphenethylamine saccharate
Drug Substance VI - (±)-α-Methylphenethylamine sulfate

CAS # 300-62-9 (Amphetamine)

MOLECULAR FORMULA C₁₇H₂₁N (Amphetamine)

MOLECULAR WEIGHT 135.21 (Amphetamine)

STRUCTURAL FORMULA (Amphetamine)

```
\begin{center}
\includegraphics[width=0.5\textwidth]{Amphetamine.png}
\end{center}
```

Amphetamine
SUPPORTING DOCUMENTS:

None.

RELATED DOCUMENTS (if applicable):

CONSULTS: None

REMARKS/COMMENTS:

In support of the applicant provided following:

- A copy of the revised current Adderall 30 mg Tablets, Master Production Batch Record dated 9/22/97.
- A representative copy of the executed batch Adderall 30 mg Tablets, which was one of the process validation batches using the revised Master Production Batch Record.
- A copy of the Field Copy Certification statement.

CONCLUSIONS & RECOMMENDATIONS:

Approval is recommended.

APPEALS HANDLED ON JOURNAL

CC:
original NDA
HFD-120/Division File
HFD-92
DISTRICT OFFICE
HFD-110/Ram Mittal
HFD-120/CSO
R/D Init by: M. Guzewska 2/14/92

/S/ Ramsharan D. Mittal Ph.D., Review Chemist

filename:C:\NDA\11522\11522.019

/S/
Shire Richwood Inc.
7900 Tanners Gate Drive
Florence, KY 41042

Attention: Robert A. Falconer

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Adderall Tablets

NDA Number: 11-522

Supplement Number: S-019

Date of Supplement: October 24, 1997

Date of Receipt: October 27, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 26, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5800 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

/S/

(For) John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Friday, October 24, 1997

Dr. Paul Leber, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Woodmont II, Document Room
HFD-120
1451 Rockville Pike
Rockville, MD 20852

RE: Adderall® Tablets, 30 mg 11-522 - Supplemental Applications
Changes Being Effect - Revised In-Process Controls

Dear Dr. Leber:

This supplemental application is to provide for the use of revised Reference is also made to our supplemental new drug application S-013, approved on 5/12/97, which provided copies of the original master batch compression record for Adderall Tablets 30 mg. The changes being effected with this supplement went into effect for regular production on 10/27/97.

Attachment A is a copy of the revised current Adderall® 30 mg Tablets Master Production Batch Record dated 9/22/97.

Attachment B is a representative copy of the executed batch B4267 Adderall® 30 mg Tablets, which was one of the process validation batches using the revised Master Production Batch Record.

Attachment C is a copy of the Field Copy Certification statement.
Letter to Dr. Leber
10/24/97
Page 2

Please contact the undersigned at (606) 282-2100 extension 2143, or Nicholas LaLima, Technical Director in New York at (516) 561-7662, if you need any further information to complete your review for this supplement.

Sincerely,

SHIRE RICHWOOD INC.

[Signature]
Robert A. Falconer
Senior Director,
Technical Affairs