CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 11522, S010

Trade Name: ADDERALL TABLETS 10 MG and 20 MG

Generic Name: Dextroamphetamine saccharate, Dextroamphetamine sulfate, Amphetamine aspartate, Amphetamine sulfate

Sponsor: RICHWOOD PHARMACEUTICAL COMPANY, INC.

Approval Date: 02/13/96

INDICATION(s): TREATMENT OF NARCOLEPSY

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APPLICATION: 11522, S010

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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 Tanner's Gate Drive, Suite 200
Florence, KY 41042

FEB 13 1996

Dear Mr. Nuerge:

Please refer to your supplemental new drug application of September 21, 1995 (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 overdosage section should be updated, as follows:
(additions are in redline font, deletions are in strikeout 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 overdosage, administration of intravenous phentolamine (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 products'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 2/12/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 11522, S010

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 11-522 (Obetrol/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 Obetrol. (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 Desoxyn or Adderall in ADHD. Nonetheless, Desoxyn is approved for this indication. As Desoxyn 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, buproprion), 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 10/19/94

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

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

11-23-94
I agree with the above review & comments by Mosholder.
Thomas P. Laughren, MD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 11522, S010

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Doc. Rm

MEMORANDUM

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

DATE: November 1, 1994

FROM: Steven D. Hardeman, R.Ph. SH 11/1/94
Consumer Safety Officer
Division of Neuropharmacological Drug Products, HFD-120

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

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

TO: 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)

4.

5.

6.

7. In his telecon of February 26, 1982, to John Geiger (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. (attachment 3)

8. 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.

   c. 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.

   d. 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.

   e. 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.

9. 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)

10. 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 Daurio 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 Pharmacal) 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\NDA\OBETROL\OBETROL.MEM

MEMORANDUM FOR RECORD

Attachment 1

D-120 NDA 11-522

additive will not have a significant environmental impact. Copies of the environmental impact analysis report are available in the Office of the Assistant Commissioner for Public Affairs, Rm. 15B-42 or the Office of the Hearing Clerk, Food and Drug Administration, Rm. 6-86, 5600 Fishers Lane, Rockville, MD 20852.

Dated September 12, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-20299 Filed 9-24-73;8:45 am]

[DESI 5378; Docket No. FDC-D-662; NDA 11-522]

CERTAIN 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 130.46) concerning amphetamines for human use. The statement contained the findings of the Food and Drug Administration based upon 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 5378) on drugs containing amphetamines and their salts, 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 produced and prescribed 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 NDA approval. Holders of approved NDAs 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 published in the FEDERAL REGISTER (38 FR 4249) 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 is ordinarily regarded as a single drug entity. A similar conclusion as to a mixture of dextroamphetamine and methamphetamine, and/or amphetamine and methamphetamine, was not made. In § 3.66 (21 CFR 3.66) 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, are 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 4279), 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 evaluation of data submitted 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 also 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 combination products decrease the incidence or severity of side effects associated with the abuse potential of the single entity anorectic drug. Notice was therefore given to holders of the named new drug applications and all other interested persons, including those marketing similar, identical or related drugs (§ 130.40 (21 CFR 130.40)) that the Commissioner proposed to withdraw approval of these new drug applications based on a lack of substantial evidence of effectiveness 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 full-factual analysis of the clinical and other investigational data they were 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 notice stated that if substantial evidence of effectiveness and evidence of safety was received for any of the named drugs, or for similar, identical and related drugs, the notice would be rescinded as to such drugs.

In response to the notice in the FEDERAL REGISTER of February 12, 1973, requests for a hearing were received from four persons for five drugs. The persons and the drugs were named in the FEDERAL REGISTER notice of March 30, 1973 (38 FR 8290). The subject final order concerns only two of those persons requesting hearings.

Rexar Pharmacal Co., 396 Rockaway Ave., Valley Stream, NY 11582, requested a hearing for the drugs Obetrol-10 and Obetrol-20 Tablets (NDA 11-522). These drugs are the subject of an NDA which was made conditionally effective on July 24, 1959, and fully effective on February 23, 1960. The Obetrol drugs had been reviewed by the NAS-NRC and found to be possibly effective as an adjunct in the management of some forms of obesity in which an appetite depressant is indicated. The NAS-NRC finding was incorporated into the August 8, 1970 FEDERAL REGISTER notice discussed above (35 FR 12678).

Delco Chemical Co., 7 McQuesten Parkway North, Mount Vernon, NY 10550, requested a hearing for the drugs Delcobese Sustained Release Tablets and Capsules and Delcobese Tablets and Capsules. Pursuant to the August 8, 1970 FEDERAL REGISTER order, the Commissioner received from Barrows Pharmacal Inc., 300 Prospect St., Inwood, NY 11696, four new drug applications on the following dates for the following drugs: March 15, 1971, NDA 17-161, Delcobese Tablets, 5 mg., 10 mg., 15 mg., and 20 mg.; March 15, 1971, NDA 17-161, Delcobese Capsules, 5 mg., 10 mg., 15 mg., and 20 mg.; March 26, 1971, NDA 17-160, Delcobese Sustained Release Capsules, 5 mg., 10 mg., 15 mg., and 20 mg.; and June 24, 1971, NDA 17-150, Delcobese Sustained Release Double-Layer Tablets, 5 mg., 10 mg., 15 mg., and 20 mg. All four of the drugs consist of a combination of amphetamines and methamphetamines. No data was submitted in support of the efficacy of these combination drugs; the sponsor merely paraphrased the conclusions stated in the August 8, 1970 FEDERAL REGISTER notice in support of the safety and efficacy of the drugs for use as anorectics 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, 1972. On January 18, 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

failed to demonstrate that each component of the drug makes a contribution to the claimed effect and that the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug (21 CFR 3.86). In response to this letter, Delco Chemical Co., Inc., 7 McQuesten Parkway North, Mount Vernon, NY 10550, notified the Food and Drug Administration that it was reformulating the products subject to the submitted new drug applications into "single entity amphetamine preparations." No further communication has taken place.

The other drugs named in the FEDERAL REGISTER notice of March 30, 1973, will be the subject of orders ruling on the requests for hearings to be published in the FEDERAL REGISTER at a future date.

I. *The Drugs* a. Obetrol 10 and Obetrol 20 Tablets, respectively contain 2.5 mg. each or 5 mg. each of methamphetamine saccharate, methamphetamine hydrochloride, amphetamine sulfate, and dextroamphetamine sulfate per tablet.

b. The four Delcobese drugs are combinations of dextroamphetamine sulfate, methamphetamine hydrochloride, methamphetamine adipate and amphetamine sulfate.

II. *Recommended Uses* a. Obetrol 10 and Obetrol 20 Tablets are recommended in exogenous obesity as a short-term (a few weeks) adjunct to a regimen of weight reduction based on caloric restriction.

b. The Delcobese drugs are recommended in exogenous obesity, as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, and in the treatment of narcolepsy and minimal brain dysfunction in children.

III. *The Data to Support Claims of Effectiveness A. Obetrol 10 and Obetrol 20 Tablets 1. Published Studies.* Rexar has submitted five literature reprints which it contends support the efficacy of Obetrol Tablets. For the following reasons, these studies are not substantial evidence of the effectiveness of Obetrol Tablets since they are not adequate and well-controlled clinical investigations.

a. *Modern Management of Obesity—The "Social Diet"*, Milton Plotz, M.D., *J.A.M.A.*, July 28, 1950, Vol. 170, pp. 1513-1515. This report is substantially a discourse on the causes of obesity and the various methods of treating the condition. It merely reports that the author feels that some investigators, including himself, have established a genuine therapeutic action with certain drugs in promoting weight reduction. There is no actual clinical data presented, no discussion of the investigations as to size of the studies, no controls or statistical methods, and no reference to the composition of the drugs that were employed in the investigations, as required by § 130.12(a)(5) (21 CFR 130.12). The author mentions that Obetrol was used in "this" study, but the reference to which study is unclear. The criteria for establishing that a study is adequate and well-controlled, set forth at § 130.12(a)(5), have not been met.

The study is, on its face, insufficient to support any claim of effectiveness for the Obetrol Products. The Commissioner finds that this article is not substantial evidence of the efficacy of Obetrol Tablets.

b. *The Treatment of Obesity in Patients With Cardiovascular Disease*, Franklin Simon, M.D. and Arthur Bernstein, M.D., *Angiology*, Vol. 12 No. 1, January, 1961, 32-37. This is a report of the obesity problem in the United States and a study conducted with Obetrol.

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 "overweight by any standard used." Both Obetrol 10 and Obetrol 20 were administered, with dosage and time of administration altered to conform to individual requirements.

No attempt was made to use any controls in the study. The investigators reported that a placebo substitute was attempted with twenty-five patients after four weeks of treatment, but this type of placebo employment is not a placebo control contemplated by § 130.12(a)(5)(ii)(a)(4)(iii), 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 regulation.

The patient population was made up of patients some of whom had some sort 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 effectiveness of an anorectic, and no assurance of comparability of the test group with a control group, since a control group was not employed (§ 130.12(a)(5)(ii)(a)(2)(i) and (iii)). 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 related to the effectiveness of Obetrol is of questionable value.

Section 130.12(a)(5)(ii)(a)(5) 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 analytical and statistical methods employed in order to determine the validity of the results and the investigator's conclusions.

The results of the study were stated in general terms of the total number of pounds lost, with an average being assigned to each patient. No actual patient results were stated. The investigators state that the range of weight loss varied from "almost nothing" to 25 pounds. The authors admit that their results are "made up of combining the good with the bad, the effective with the ineffective weight reducer." Thus, it is impossible to draw any meaningful conclusions as to the efficacy of Obetrol from the study because full reports of patient data obtained from the study are not presented as required by § 130.12(a)(5)(ii)(a)(5).

In addition, since Obetrol is a combination drug within the meaning of § 3.86, the investigators must show that both the amphetamine and methamphetamine components of the drug contribute to the drug's purposed effect. No such showing was made in this study.

The Commissioner finds that this study is not substantial evidence of the effectiveness of Obetrol Tablets.

c. *Treatment of Obese Diabetics and Arteriosclerotics*, Arthur Bernstein, M.D. and Franklin Simon, M.D., Reprint from *Clinical Medicine*, May, 1961, pp. 1-6. This is another report of the study discussed in b, above. It contains no more patient information or data than does the other report, and no statistical analysis. For the reasons stated above, the Commissioner finds this study is not substantial evidence of the effectiveness of Obetrol Tablets.

d. *Use of an Amphetamine-Combination Drug in an Anti-Obesity Clinic*, Merrill Berman, M.D. and Ian Anderson, M.D., *Mid. St. Med. J.*, Jan., 1965, pp. 22-31. This is a report of study conducted with Obetrol-10 Tablets. The patient population numbered 43; the only medical problem of the group was obesity. The drug was tested in 25 patients and compared with 18 patients to whom no 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 clinic program."

The patients were selected at random, and randomly placed on either the drug or no treatment. Both test and control patients were weighed each week, 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 20.2 pounds over a ten week period, while the control group lost an average of 9.61 pounds over the ten week period. The actual weight loss for each patient is tabulated. 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 presented. (§ 130.12(a)(5)). Data is not presented as to the number of entrants in the study and the

number of dropouts. This data is necessary both in order to demonstrate that equal numbers of patients were placed in each group and to follow up on these patients to ascertain why they dropped out. Finally, the analytical technique for evaluating the results is not described making it impossible to establish the significance of the differences of treatment of the two groups (§ 130.12(a)(5)(ii)(a)(4)).

In addition to the above deficiencies, the study is not adequate and well-controlled to establish the efficacy of Obetrol for the following reasons. As pointed out by the investigators in this and the other studies submitted by Rexar, one of the major factors contributing to obesity, and crucial in its treatment, is the psychological condition of the patient. In order to conduct an adequately controlled test with an obesity drug, it is imperative that placebo controls as set forth in § 130.12(a)(5)(ii)(a)(4)(iii) be employed so that all patients think that they are receiving some medication in order to adequately compare the test and control groups. No treatment controls are insufficient in this type of study since a placebo has a definite and significant effect in obesity studies (§ 130.12(a)(5)(ii)(a)(4)(i)). As with all placebo studies, true double blinding is required. Thus, a third party must package both the active drugs and the placebos in containers which are indistinguishable and which can only be identified by code numbers known only to the third party. The placebos and drugs must be physically indistinguishable to both the physician and the patient. Only in this manner will the study result in neither the physician nor the patient being aware, at the time of treatment, which patient is receiving the drug or the placebo. This is required so that physician and patient expectations do not bias the study. Double blinding was not done in this study.

Finally, the study was not conducted in such a manner that the investigators demonstrated that both the amphetamine and the methamphetamine constituents of Obetrol contributed to its anorectic effect. Such a showing is required to establish the efficacy of a fixed combination drug such as Obetrol. In order to show the contribution of each ingredient it is necessary to have four test groups—one on the combination drug, one each on each of the active ingredients, and one on a placebo. This was not done (§ 3.86).

The Commissioner finds that this study is not substantial evidence of the efficacy of Obetrol Tablets.

c. *Comparison of Weight Losses With Their Reducing Regimens-Diet Therapy, Phenmetrazine, and . . . Obetrol*, Merrill Berman, M.D. and Ian Anderson, M.D., *J. Am. Geriatric Soc'y*, Vol. 14 No. 6, pp. 623-630.

In this study, 88 overweight female outpatients in the Anti-Calory Clinic were randomly divided into three groups, unequal in size: 18 to whom no medication was administered; 41 to whom phenmetrazine hydrochloride was administered; and 29 to whom Obetrol was administered. There is no explanation given for the variation in the number of subjects in each group. The no treatment group had an obesity duration of 10 years or longer in all cases; the other two groups had a long obesity duration. There is no reason given why the 10 years for the no-treatment group is 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 2.0 pounds in two weeks, 4.2 pounds in four weeks, 6.4 pounds in six weeks, 8.6 pounds in eight weeks and 10.3 pounds in 10 weeks for the controls. For the phenmetrazine group, the average weight loss was 3.6 pounds in two weeks, 6.8 pounds in four weeks, 9.7 pounds in six weeks, 11.9 pounds in eight weeks and 13.8 pounds in 10 weeks. Finally, the Obetrol group averaged a weight loss of 5.0 pounds in two weeks, 9.5 pounds in four weeks, 13.8 pounds in six weeks, 18.3 pounds in eight weeks and 22.6 pounds in 10 weeks.

The results are not meaningful since there are no data relevant to the amount and frequency of medication. The degree of overweight of the patients is not given so that an objective comparison of the test subjects' weight loss is not possible. There is no method of randomizing 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 differences of treatment of the various groups cannot be established (§ 130.12(a)(5)(ii)(a)(4), and (a)(5)(ii)(a)(4)(i), (iii), and (iii)).

As with the study discussed in paragraph d. above, the necessary placebo 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)(5)(ii)(a)(4)(iii)). Furthermore, the follow-up study, in which only Obetrol was used, and then, only as needed, has no significance for purposes of demonstrating the efficacy of Obetrol. The study is not adequately double blinded for the reasons set forth in d above. Finally, there are no data to show that both the amphetamine and methamphetamine constituents of Obetrol contributed to the efficacy of the drug (§ 3.86).

The Commissioner finds that this study is not substantial evidence of the efficacy of Obetrol Tablets.

2. *Unpublished Studies.* a. *The Lebereo studies.* Rexar also submitted two studies conducted by Lebereo Laboratories in 1962. The studies are apparently acute toxicity studies. The first was conducted with Dexedrine. The purpose of this uncontrolled study is not stated. The target population ostensibly consisted of "normal, healthy albino rats", although the criteria for determining the condition of the rats is not stated (§ 130.12(a)(5)(ii)(a)(2)(i)). The animals were fed 10 milligrams of Dexedrine per cc of a suspension substance for an unspecified length of time, possibly only once, although this is not clear. The investigator concluded that "when the above results were calculated according to the method of Behrens, the LD_{50} was established to be 112 milligrams per kilogram of rat. This is equivalent to 6,720 milligrams in a 60 kilogram human being."

The second study was conducted with 500 tablets of "Oby-Rex #1", composition not stated. The purpose of this uncontrolled study is not stated. In this study, the target population ostensibly consisted of "normal, healthy albino rats", although the criteria for determining the condition of the rats is not stated (§ 130.12(a)(5)(ii)(a)(2)(i)). The test animals were fed 40 milligrams of Oby-Rex #1 per cc of a suspension substance for an unspecified length of time, possibly only once, although this is not clear. The investigator concluded that "when the above results were calculated according to Behrens, it was found that the LD_{50} of the test material is 282 milligrams per kilogram of rat. This is analogous in the human to 16,890 milligrams".

Rexar states that these two studies were comparative, but fails to state what was being compared, and the results of any such a comparison are nowhere stated. Furthermore, the results are not confirmed by clinical data since they are only acute data. The results of such animal studies cannot be extrapolated to man. Therefore, these studies do not prove the safety of Obetrol Tablets in human beings.

The two studies do not establish either the effectiveness or safety of Obetrol. Indeed, whether or not the "Oby-Rex #1" is of the same composition as Obetrol is not stated. The Commissioner finds that these studies do not constitute evidence of safety or substantial evidence of the efficacy of Obetrol Tablets for its intended use.

b. *The Nedelman study.* In a letter dated September 21, 1971, Rexar was advised by the Food and Drug Administration that a proposed clinical protocol for a double-blind efficacy study of Obetrol was deficient in several respects; several requirements for the study to be adequate and well-controlled were provided to Rexar. One of these requirements was that Rexar "should provide for acquiring data on the contributions of the individual constituents to the total claimed effect for the drug." Rexar submitted with its request for a hearing, a copy of a protocol of a study to be conducted with Obetrol for Rexar by Medical and Technical Research Associates, Medford, MA, dated January 20, 1972. There is no mention in the protocol of acquiring data on the contribution of the individual constituents to the total claimed effect for the drug. The protocol only provided for two test groups: one to whom Obetrol would be administered, and one to whom placebo medication would be administered. Rexar submitted the results of this study, which was conducted by Phillip B. Nedelman, M.D. In the foreword to the study,

Rexar stated that pursuant to the September 21, 1971 Food and Drug Administration letter, it was incorporating new requirements for the study, and set them out. These revised requirements did not include a provision for acquiring data on the contribution of the individual constituents to the total claimed effect of the drug. Thus, at the threshold, the study is not adequate since Rexar failed to comply with the requirements for the study to be considered adequate and well-controlled.

In addition, the study itself is deficient in several respects. There are no data provided on patient selection, condition, randomization, comparability of test and control groups, or steps taken to minimize bias (§ 130.12(a)(5)(ii)(a) (2) and (4)). There are no data presented to show that an adequate placebo control was employed since the data presented do not state whether a certain number of patients received only the drug and a certain number received only the placebo. The investigator states that the groups were designated X and Y, but states both X and Y groups received Obetrol. Furthermore, the investigator states that both groups received a known placebo during the last one week of the study. Therefore, a comparison of the test and control groups is not possible (§ 130.12(a)(5)(ii)(a)(4)(iii)).

The Commissioner finds that the Nedelman [illegible] not substantial evidence [illegible] of Obetrol Tablets.

B. *Delco.* As stated above, no data from clinical investigations were submitted in the approval new drug applications for the Delcobese drugs. In Delco's request for a hearing, no investigations, including adequate and well-controlled clinical investigations were submitted. All that Delco has presented is 47 physicians' reports from a survey conducted by Delco from 1964 to 1968. Most of the physicians used the drug for treating obesity, although some did not state for what purpose they used the drug. Only one physician stated he used the drug to treat narcolepsy, and none stated they used the drug to treat minimal brain dysfunction in children. There are also no data presented on whether capsules or tablets were administered or whether the medication was of the sustained release type. The material, five to ten years old, was not submitted with the NDAs.

The physician reports are testimonials at best. There are no actual patient data in any report. None of these "investigations" were controlled. Furthermore, there are no data that demonstrate that the constituent ingredients in the Delcobese drugs contribute to the total claimed effect for the drugs. The Commissioner finds that these testimonials are not substantial evidence of the efficacy of the Delcobese drugs.

IV. *General Objections.* Both Rexar and Delco object to the Commissioner's finding in the February 12, 1973 FEDERAL REGISTER final order (38 FR 4269), that while a mixture of dextroamphetamine and amphetamine is ordinarily regarded as a single drug entity, a mixture of amphetamine and methamphetamine, or a mixture of dextroamphetamine and methamphetamine is not regarded as a single drug entity. The Commissioner's finding is sound from a pharmacological and chemical standpoint, and no evidence was submitted to refute it.

Dextroamphetamine is one of the two optical isomers which constitute the racemic mixture known as amphetamine; its chemical formula is identical with that of amphetamine. Methamphetamine, however, is a distinct chemical entity with a formula different from amphetamine or dextroamphetamine. Methamphetamine is one of many different sympathomimetic amines, such as ephedrine or phenylpropanolamine. While methamphetamine and amphetamine are at times lumped together due to their similar pharmacological action, namely central nervous system stimulation, the differences in pharmacological actions and chemistry make a mixture of amphetamine and methamphetamine a combination drug subject to § 3.86 (Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1970, pp. 501-506, 293-296).

The fixed combination prescription drug policy, set forth at § 3.86, provides that where two or more drugs are combined into a single dosage form, each drug must make a contribution to the claimed effect. In addition, the dosage of each drug in the combination must be safe and effective for a significant patient population requiring concurrent therapy as defined in the drug's labeling. Exceptions to this general rule are where a component is added to enhance the safety or effectiveness of the principal active component or to minimize the potential for abuse of the principal active component.

Since the Obetrol and Delcobese drugs are fixed combination drugs because they consist of two separate drug entities, amphetamines and dextroamphetamines as one drug entity and methamphetamines as a second drug entity, these drugs are subject to the fixed combination prescription drug policy. Neither of the two special cases applies here, since no data were submitted to show that one drug entity enhanced the safety or effectiveness of the other; the drugs consist of equal parts of the two drug entities. Second, the abuse potential of both amphetamine and dextroamphetamine, and methamphetamine is well known throughout both the medical and lay communities. Therefore, addition of one drug entity to the other does not minimize the potential for abuse for one or the other. The fixed combination policy thus applies to Obetrol and Delcobese.

Rexar and Delco, to establish the safety and efficacy of Obetrol and Delcobese, would have had to submit studies in which four test groups were used: one to whom the combination drug was administered; one to whom the amphetamine and dextroamphetamine drug entity was administered; one to whom the methamphetamine drug entity was administered; and one to whom a placebo was administered. As pointed out above, none of the submitted studies were carried out in this manner. Thus, the effectiveness of these fixed-combination prescription drugs has not been proven by either Rexar or Delco.

V. *Legal Objections.* No legal objections to the withdrawal of approval of NDA 11-822 were raised by either Rexar or Delco. Delco admitted in its request for a hearing that the Delcobese drugs are similar to the Obetrol drugs. The Delcobese drugs are thus subject to the conclusions of the Commissioner reached with respect to the Obetrol drugs and their NDA (§ 130.40).

VI. *Findings.* The Commissioner, based on the review of the medical documentation offered to support the claims of safety and efficacy for Obetrol Tablets as a short term adjunct to a regimen of weight reduction based on caloric restriction in exogenous obesity, and Delcobese tablets and capsules and Delcobese sustained release tablets and capsules as a short term adjunct to a regimen of weight reduction based on caloric restriction in exogenous obesity and in the treatment of narcolepsy and minimal brain dysfunction in children, finds that Rexar Pharmacal Corp. and Delco Chemical Co. have failed to present substantial evidence of effectiveness for these products. No data was submitted on these fixed-combination drugs for prescription use that establishes that each of the drug components make a contribution to the claimed effect of the drug (§ 3.86).

Neither Rexar or Delco presented any data to establish that there is no potential for abuse of the Obetrol and Delcobese drugs. In addition, there is nothing in the record to show that there are not safer and effective drugs available for use for the conditions for which Obetrol and Delcobese are intended. The only safety data submitted were the apparent acute toxicity studies conducted with a drug "Oby-Rex #1", the results of which were not confirmed with clinical data. Therefore, no evidence has been submitted which challenges the Commissioner's finding as to the lack of proof of safety or which, in fact, proves the safety of Obetrol and Delcobese, and a hearing is not necessary on this issue. Nevertheless, the safety issue, for the purposes of this order, becomes moot since no substantial evidence of the effectiveness of Obetrol or Delcobese has been submitted. Therefore, the drugs would be withdrawn from the market even if they could be proven safe.

The Commissioner further finds that the approval of the New Drug Application heretofore approved for Obetrol-10 and Obetrol-20 Tablets (NDA 11-822) should be withdrawn on the basis of a lack of substantial evidence of effectiveness and lack of proof of safety. This finding applies with full force to the Delcobese drugs (§ 130.40).

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 701, 52 Stat. 1052-1053, 1055-1056, as amended; (21 U.S.C. 355,

...), and under authority delegated to the Commissioner (21 CFR 2.120), notice is given that the approval of the New Drug Application for Obetrol-10 and Obetrol-20 Tablets (NDA 11-522) is withdrawn, effective October 5, 1973. This order applies with full force and effect to the Delcobese drugs (§ 130.40).

(Sec. 505, 701, 52 Stat. 1052-1053, 1055-1056, as amended; (21 U.S.C. 355, 371).)

Dated September 17, 1973.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.73-20205 Filed 9-24-73;8:45 am]

[DESI 9418]

[Docket No. FDC-D-602; NDA No. 9-418 etc.]

CERTAIN DRUGS CONTAINING PENTAERYTHRITOL TETRANITRATE IN COMBINATION WITH RAUWOLFIA ALKALOIDS

Notice of Withdrawal of Approval of New Drug Applications

A notice was published in the FEDERAL REGISTER of March 6, 1973 (38 FR 6090), extending to the holders 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.

NDA No.	Drug	NDA holder
9-418...	Pentaerythrol Tablets, containing pentaerythritol tetranitrate and alseroxylon.	Riker Laboratories, Inc., Subsidiary 3M Co., 1901 Northeast St., Northridge, Calif. 91328
10-081...	Nitrolan Tablets, containing pentaerythritol tetranitrate and alseroxylon.	Dorsey Laboratories, Division of Sanders-Wamsley, Inc., Northeast U.S. 6 & Interstate 80, Lincoln, Nebr. 68501.
10-218...	Pentaserpine Tablets and Pentaserpine "Sa" Tablets, containing pentaerythritol tetranitrate and reserpine.	USV Pharmaceutical Corp., 1 Reversdale Rd., Tuckahoe, N.Y. 10707 (N) (formerly held by Nysco Laboratories, Inc.).
11-139...	Reserpt Tablets, containing pentaerythritol tetranitrate and reserpine.	Westerfield Laboratories, Inc., 711 Straitstone Rd., Cincinnati, Ohio 45237.

Both Riker Laboratories and USV Pharmaceutical Corp. (formerly Nysco Laboratories, Inc.) had previously discontinued their products and elected not to request a hearing. Neither Dorsey Laboratories, Inc. nor Westerfield 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 included in the notice of March 6, 1973. Their Pharmaceuticals, Inc., holder of NDA 10-998 for Cartrax 10 and Cartrax 20 Tablets (pentaerythritol tetranitrate and hydroxyzine hydrochloride), American Home Products Corp., holder of NDA 11-423 for Equanitrate 10 and Equanitrate 20 Tablets (pentaerythritol tetranitrate and meprobamate), and Carter-Wallace, Inc., holder of NDA 11-502 for Miltrate Tablets (pentaerythritol tetranitrate and meprobamate), elected to avail themselves of the opportunity for a hearing on their drugs. Their requests for a hearing are under review and will be the subject of a future publication in the FEDERAL REGISTER.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug applications reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, October 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, MD 20852.

The Commissioner of Food and Drugs pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1053, as amended; 21 U.S.C. 355), and the Administrative Procedure Act (5 U.S.C. 554), and under authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with regard to the drugs, evaluated together with the evidence available to him when the applications were approved, there is a lack of substantial evidence that the drugs will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing finding, approval of new drug applications Nos. 9-418, 10-081, 10-218, and 11-139 and all amendments and supplements thereto is withdrawn.

Shipment in interstate commerce of the above-listed drug products or of any identical, related, or similar product, not the subject of an approved new drug application, is henceforth unlawful.

Effective date.—This order shall become effective on October 5, 1973.

Dated September 19, 1973.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.73-20296 Filed 9-24-73;8:45 am]

[FAP 3D7856]

SANDOZ COLORS & CHEMICALS

Notice of Filing of Petition for Food Additive

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409 (b)(5), 72 Stat. 1786 (21 U.S.C. 348(b)(5))), notice is given that a petition (FAP 3D7856) has been filed by Sandoz Colors & Chemicals, East Hanover, NJ 07936, proposing that § 121.2426 Components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 121.2526) be amended in paragraph (a)(5) to provide for the safe use of polyamide-epichlorohydrin water-soluble thermosetting resins prepared by reacting adipic acid with diethylenetriamine to form a basic polyamide and further reacting the polyamide with an epichlorohydrin and dimethylamine mixture for use in the manufacture of paper and paperboard intended for use in contact with food.

Dated September 11, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-20300 Filed 9-24-73;8:45 am]

[DESI 11073]

[Docket No. FDC-D-841; NDA 11-073]

VAMPOLE LABORATORIES

Notice of Withdrawal of Approval of New Drug Application

On January 12, 1973, there was published in the FEDERAL REGISTER (38 FR 1404) a notice of opportunity for hearing (DESI 11073) in which the Commissioner of Food and Drugs proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new drug application 11-073 for Vastran Forte Capsules containing niacin (375 mg.) with ascorbic acid, riboflavin, thiamine mononitrate, cyanocobalamin, pyridoxine hydrochloride, and calcium pantothenate; Wampole Laboratories, 35 Commerce Road, Stamford, CT 06904. The basis of the proposed withdrawal of approval was the lack of substantial evidence that this fixed combination drug, offered for hypercholesteremia, will have the effects that it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application reviewed and are subject to this notice. See 21 CFR 130.40 (37 FR 23185, Oct. 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, MD 20852.

Pursuant to the notice, Wampole Laboratories has reformulated Vastran Forte Capsules into a new product named Wampocap Capsules containing 500 mg. niacin. In the FEDERAL REGISTER of April 18, 1972 (37 FR 7818) and an amendment on March 19, 1973 (38 FR 7270) (DESI 9760), niacin as a single active ingredient was evaluated as effective for hypercholesterolemia and hyperbetalipoproteinemia. The amendment of March 19, 1973 stated the following indications:

As adjunctive therapy in addition to diet and other measures in the treatment of hypercholesterolemia and hyperbetalipoproteinemia.

Attachment 2

3 Pages Purged

Unapproved Supplement

Attachment 3

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 2/26/82
FROM: DAVE BARASH		OFFICE
TO: NOA 11-522 (OBETROL)		DIVISION DNDP
SUBJECT: Inspection Request (attached)		

SUMMARY

I called John Geiger, who then referred me to Ray Fazzari 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 this 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 Ruby Apodaca, for regulatory action.

He said I would be informed of any action or correspondence which takes place.

SIGNATURE

DOCUMENT NUMBER

Attachment 4

3 Pages Purged

Unapproved Supplement

Attachment 5

W.L. fil

5NYK-95

MEMORANDUM

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

DATE: OCT 18 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 Pharmacal Division
Valley Stream, New York 11581

5-NYK-95

TO: Director
New York District, HFR-NE100

WARNING LETTER APPROVED

We concur that a Warning Letter should be issued to Mr. Roger Griggs, 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 28, 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.

CSO Contact: Leon Drapkin, HFD-313
(301)594-2073

Bradford W. Williams

Attachment

Warn ltr. file
5-NYK-95

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NEW YORK DISTRICT
850 THIRD AVENUE
BROOKLYN, NY 11232
TEL. (718) 965-5300

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Roger D. Griggs
President
Richwood Pharmaceutical Co., Inc.
Rexar Pharmacal Division
396 Rockaway Avenue
Valley Stream, New York 11581

October 24, 1994

Ref: 5-NYK-95

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 Saccharate, 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(g)(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 505 of the Act. They may not be introduced or delivered for introduction into interstate commerce under section 505(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(i) 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 201.115 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) 11-522 for Rexar Pharmacal Co.'s Obetrol 10 mg. and 20 mg. Tablets 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". 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 drugs remain in trade channels at this time, they should be immediately recalled. We request that your reply include an estimate of the amounts of these products that are in inventory under your control and which remains 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. These include seizure and/or injunction.

Your reply should be sent to Compliance Branch, Food and Drug Administration, 850 Third Avenue, Brooklyn, New York 11232, Attention: Laurence D. Daurio, Compliance Officer.

Sincerely,

Edward T. Warner
District Director

Attached:
Federal Register, September 28, 1973,
Certain Combination Anorectic Drugs

FAX COVER SHEET

U.S. FOOD and DRUG ADMINISTRATION
NEW YORK DISTRICT
850 THIRD AVENUE, BROOKLYN, NY 11232

COMPLIANCE BRANCH

DATE: 10/31/94

PAGES (including cover): 4

FROM: Larry Daurio, Compliance Officer, HFR-NE140

Tel. No.: 718-965-5300x570R

Fax No.: 718-965-5117

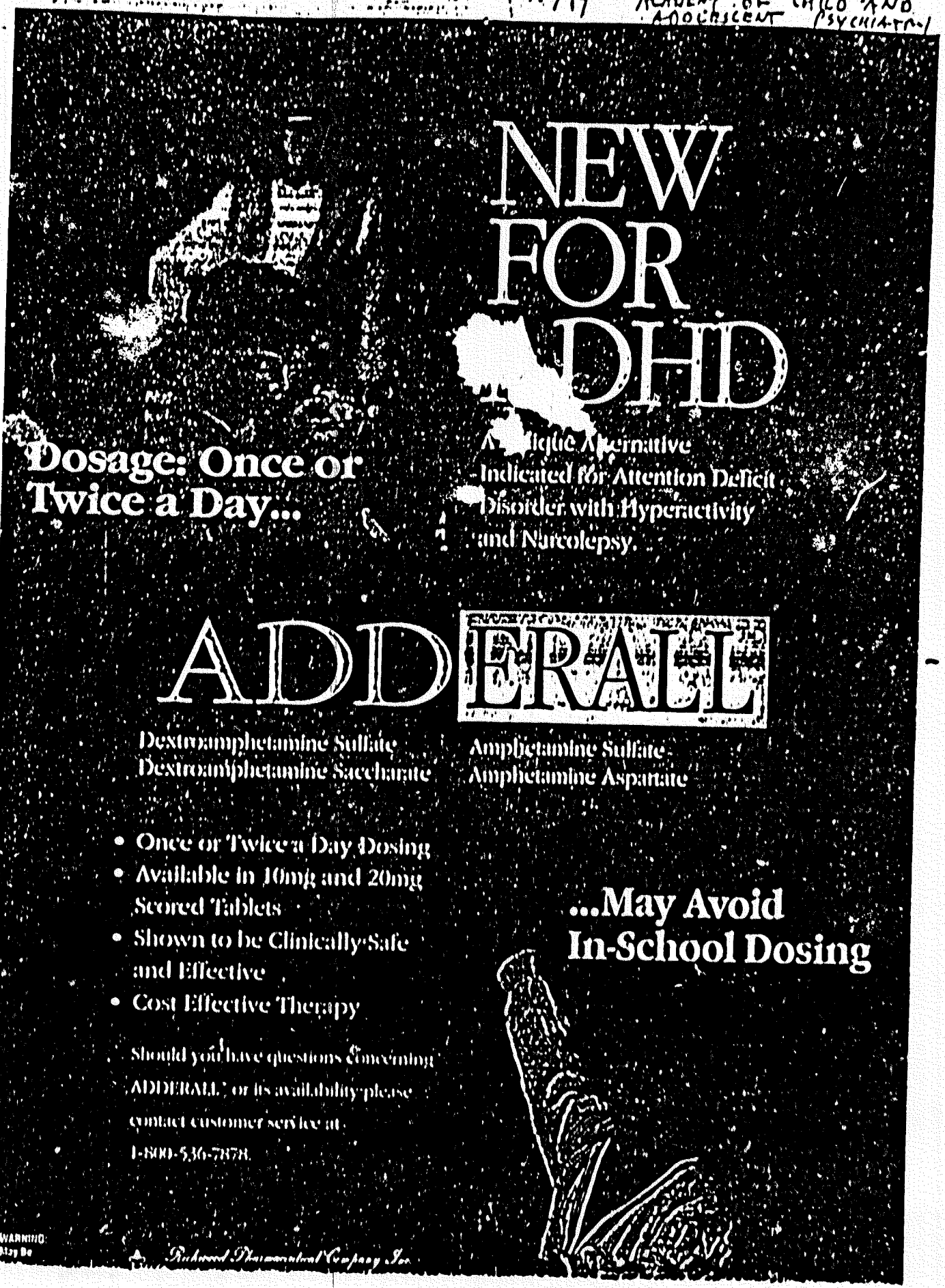
TO: STEVE HARDEMAN
HFD-120

TEL. NO.: 301-594-2850

FAX NO.: 301-594-2859

MESSAGE: as requested
Warning Letter, re: Richwood's Obelisk

10/94 JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY



CII

ADDERALL TABLETS

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. THEY SHOULD THUS BE TRIED ONLY IN WEIGHT REDUCTION PROGRAMS FOR PATIENTS IN WHOM ALTERNATIVE THERAPY HAS BEEN INEFFECTIVE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME IN OBESITY 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 OR DISPENSED SPARINGLY.

DESCRIPTION: A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate.

EACH TABLET CONTAINS:

	10 mg	20 mg
Dextroamphetamine Saccharate	[illegible]	[illegible]
Amphetamine Aspartate	[illegible]	[illegible]
Dextroamphetamine Sulfate	[illegible]	[illegible]
Amphetamine Sulfate	[illegible]	[illegible]

Inactive Ingredients: Sucrose, Lactose, Cornstarch, Acacia and Magnesium Stearate
Colors: ADDERALL 10 mg contains FD&C Blue #1
Colors: ADDERALL 20 mg contains FD&C Yellow #6 as a color additive

ACTIONS: Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressure and weak bronchodilator and respiratory stimulant action. Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics". It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects, may be involved, for example.

[illegible]

INDICATIONS: [illegible]

CONTRAINDICATIONS: [illegible]

WARNINGS: [illegible]

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

[illegible]

Drug/Laboratory Test Interactions:

[illegible]

ADVERSE REACTIONS:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure.

[illegible]

Allergic: Urticaria

Endocrine: Impotence, changes in libido

DRUG ABUSE AND DEPENDENCE: [illegible]

OVERDOSAGE: [illegible]

SYMPTOMS: [illegible]

TREATMENT: [illegible]

DOSAGE AND ADMINISTRATION: [illegible]

HOW SUPPLIED:

ADDERALL 10 mg [illegible]
ADDERALL 20 mg [illegible]

In bottles of 100 tablets.

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP
Store at controlled room temperature 15° - 30°C (59° - 86°F)

CAUTION: Federal law prohibits dispensing without prescription

Manufactured for

Richwood Pharmaceutical Company, Inc.

Attachment 6
Preliminary Draft

4 Pages
Purged

Attachment 7

DIV

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 20, 1994

DCTIION

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

SUBJECT: Response to Consult Request

TO: HFY-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 Response:

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,

RLK for PL 10/26/94

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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 Pharmacal 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

Post-it™ Fax Note 7671 | Date 6/20/94 | # of pages ▶ 1
To Roger Griggs | From Thad Demos
Co-Dept. | Co
Phone # | Phone #
Fax # | Fax #

FAXED

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).

DIV FILE

MINUTES OF MEETING
Commercial Sponsor - Richwood Pharmaceuticals
NDA 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, SCSO	CDER/DNDP
Steve Hardeman, CSO	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. Stribling, 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 Daurio, 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
DNDP

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

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

MEETING MINUTES

NATIONAL ACADEMY OF SCIENCES—NATIO... ...H COUNCIL
Division of Medical Sciences

DRUG EFFICACY STUDY

274

Form A
(To be submitted in duplicate by applicant)

DA Number 11522 2. Date Originally Approved February 23, 1960 3. Rx ☒ OTC ☐

Brand Name Obetrol-10 and Obetrol-20 tablets

5. Applicant's Name Obetrol Pharmaceuticals, Division of Rexar Pharmacal Corp.

and Address 382 Schenck Avenue, Brooklyn, New York 11207

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Obetrol-10	
Methamphetamine Saccharate	2.5 mg.
Methamphetamine Hydrochloride	2.5 mg.
Amphetamine Sulfate	2.5 mg.
Dextro Amphetamine Sulfate	2.5 mg.
Obetrol-20	
Methamphetamine Saccharate	5 mg.
Methamphetamine Hydrochloride	5 mg.
Amphetamine Sulfate	5 mg.
Dextro Amphetamine Sulfate	5 mg.

7. Dosage Form (tablets, etc.) Tablets (2 dyes)

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

Labels and package inserts attached.

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

See back of form.

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

No unpublished supplemental material submitted.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

No unpublished supplemental material submitted.

Blue copy is original
White copy is duplicate

The back of this form may be used if additional space is needed.

10. Berman, M.I., and Anderson, I.R., Comparison of weight losses with three reducing regimens--diet therapy, phenmetrazine, and an amphetamine combination (Obetrol), J. Amer. Geriat. Soc. 14:623-30, June 1966.

Berman, M.I., and Anderson, I.R., Use of an amphetamine-combination drug in an anti-obesity clinic, Maryland Med. J. 14:29-31, January 1965.

Simon, F., and Bernstein, A., The treatment of obesity in patients with cardiovascular disease, Angiology 12:32-37, January 1961.

Plotz, M., Modern management of obesity--the "social diet," J.A.M.A. 170:1513-1515, July 25, 1959.

Supplemental References

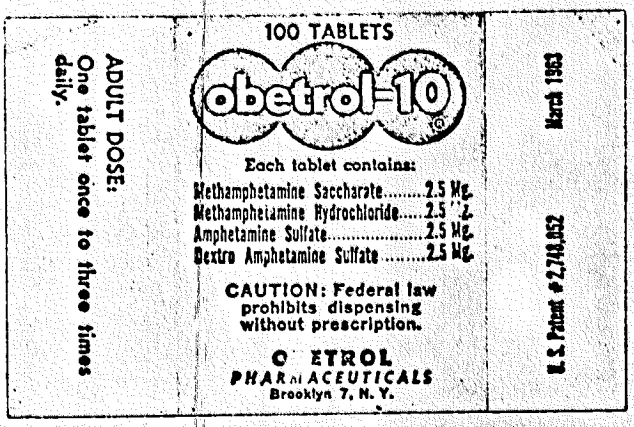
The following references are informative with reference to the efficacy of the amphetamine ingredients of Obetrol tablets as appetite depressants and weight-reducing aids:

Goodman, L.S., and Gilman, A., Pharmacological Basis of Therapeutics, New York, Macmillan Co., 3rd ed., 1965, pp. 501-2.

A.M.A. Council on Drugs, New Drugs, Chicago, American Medical Association, 1965, p. 91.

Simon, R.I., Obesity as a depressive equivalent, J.A.M.A. 183:208-10, Jan. 19, 1963.

Fazekas, J.F., Ehrmantraut, W.R., and Kleh, J., Study of effectiveness of certain anorexigenic agents, Am. J. M. Sc. 236:692-9, December 1958.



OBETROL-10 TABLETS AND OBETROL-20 TABLETS

DESCRIPTION:

Obetrol-10		Obetrol-20	
Each tablet contains:		Each tablet contains:	
Methamphetamine Saccharate	2.5 mg.	Methamphetamine Saccharate	5 mg.
Methamphetamine Hydrochloride	2.5 mg.	Methamphetamine Hydrochloride	5 mg.
Amphetamine Sulfate	2.5 mg.	Amphetamine Sulfate	5 mg.
Dextro Amphetamine Sulfate	2.5 mg.	Dextro Amphetamine Sulfate	5 mg.

INDICATIONS: This combination of amphetamines may be useful as an adjunct in the management of certain forms of obesity where an appetite depressant is indicated.

CONTRAINDICATIONS: Hypertension, advanced arteriosclerosis, coronary artery disease, cardiac arrhythmias, peripheral vascular disease, states of undue restlessness, anxiety, excitement, agitated depression, hyperthyroidism, idiosyncrasy to amphetamine, concomitant administration of a monoamine oxidase inhibitor.

PRECAUTIONS: Use with caution in individuals with anorexia, insomnia, vasomotor instability, asthenia, psychopathic personality, a history of homicidal or suicidal tendencies, and individuals who are known to be hyperreactive to sympathomimetic agents, or emotionally unstable individuals who are known to be susceptible to drug abuse. Certain monoamine oxidase inhibitors may potentiate the action of Obetrol.

SIDE EFFECTS: The most common side effects attended with the use of amphetamines include nervousness, excitability, euphoria, insomnia, dryness of mouth, nausea, vertigo, constipation, and headache.

DOSAGE AND ADMINISTRATION: Initial adult dose is one-half to one 'Obetrol-10' tablet daily, preferably one-half one hour before meals. This may be gradually increased to one 'Obetrol-10' or 'Obetrol-20' tablet one to three times daily as indicated.

AVAILABILITY: The preparation is furnished in two strengths, with a total of 10 mg. or 20 mg. of the four ingredients previously described, designated as 'Obetrol-10' and 'Obetrol-20' respectively, in bottles of 100, 500, and 1,000 scored tablets.

Obetrol Pharmaceuticals
DIVISION OF REXAR PHARMACAL CORP.
Brooklyn, New York 11207

Revised November 6, 1964

OBETROL TABLETS 10 & 20
NDA 11522
LOG 274

Panel on Psychiatric Drugs

INDICATIONS

I. Obetrol, a combination of amphetamines, may be useful as an adjunct in the management of some forms of obesity in which an appetite depressant is indicated.

EVALUATION: Possibly effective.

COMMENTS: The Panel feels that it can evaluate this compound of sympathomimetic stimulants as no better than "Possibly effective," because it contains methamphetamine.

This drug is apparently similar pharmacologically to dextroamphetamine. On the basis of the presumed pharmacologic similarity, it may have a similar effect, although documentation of efficacy of this drug for this indication is meager. There is, however, inadequate direct supporting evidence for its use for this indication. The preferential abuse of methamphetamine, compared with dextroamphetamine, raises some suspicion that it is different pharmacologically from the parent compound, dextroamphetamine. Additional studies on this compound for this indication are necessary.

A majority of the Panel evaluated the sympathomimetic stimulants as "Effective, but . . ." as anorectic agents, with the following comment. Sympathomimetic stimulants as a class have been shown to have a generally short-term anorectic action. Anorectic agents suppress appetite. They are not a treatment of obesity in themselves and should be used primarily as an adjunct to a total program of weight reduction for obese patients that includes patient education, motivation calorie restriction, and exercise. The anorectic effect of anorectic agents often plateaus or diminishes after 4-6 weeks (1-4).. The dosage of drug must be individually titrated and given at least 1 hr before meals.

Clinical opinion as to the contribution of the sympathomimetic stimulants in a weight-reduction program varies widely. Most studies of these preparations are for short periods. The Panel suggests that controlled studies of the long-term effects of the sympathomimetic stimulants in weight-reduction programs be conducted. These preparations have a significant potential for drug abuse.

A minority of two of the Panel members agreed with the above comment of the majority of the Panel, but evaluated the sympathomimetic stimulants as "Probably effective" as anorexiants. Their reasoning for the "Probably effective" evaluation was that: (a) most studies of these preparations have been for short periods, (b) there is no available evidence that the use of these anorexiant preparations alters the natural history of obesity, (c) there is some evidence that anorectic effects may be strongly influenced by the suggestibility of the patient, and (d) there are reservations about the adequacy of the controls in some of the clinical studies. The minority suggested that controlled studies on the long-term anorectic efficacy of the sympathomimetic stimulants be conducted.

OBETROL TABLETS 10 & 20
NDA 11522
LOG 274

DOCUMENTATION:

1. Fazekas, J. F. Anorexigenic agents. New Eng. J. Med. 264:501-503, 1961.
2. Harris, S. C., A. C. Ivy, and L. M. Searle. The mechanism of amphetamine-induced loss of weight; a consideration of the theory of hunger and appetite. J.A.M.A. 134:1468-1475, 1947.
3. Kinard, S., L. C. Mills, J. Terrell, and J. H. Moyer. Use of d-amphetamine to curb the increased appetite and over-eating induced by reserpine therapy. J. Amer. Geriat. Soc. 4:1073-1077, 1956.
4. Thorn, G. W., and P. K. Bondy. Obesity, p. 398. In T. R. Harrison, R. D. Adams, I. L. Bennett, Jr., W. H. Resnik, G. W. Thorn, and M. M. Wintrobe, Eds. Principles of Internal Medicine. (5th ed.) New York: McGraw-Hill Book Co., 1966.

GENERAL COMMENTS

The 20-mg preparation is recommended for dosage at one tablet three times a day. The Panel feels that a daily intake of 60 mg of amphetamine-like material is not consonant with good medical practice.

The 10-mg preparation, if taken at three tablets/day as recommended, would lead to a daily intake of 30 mg of amphetamine-like materials, a dose usually considered too large for most patients.

Amphetamine psychoses have occurred at doses as low as 60 mg/day.

Approved by _____
Chairman