CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-422

Generic Name:	Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10mg, 20 mg, and 30 mg
Sponsor:	Barr Laboratories, Inc.
Approval Date:	February 11, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
40-422

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-422

APPROVAL LETTER

ANDA 40-422

FEB 11 2002

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated October 31, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg. Each drug product strength represents the total of equal amounts of the four component salts.

Reference is also made to your amendments dated May 17, June 8, July 11, August 31, September 4, September 21, October 5, and November 14, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your tablets containing combined salts of Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Adderal® Tablets, 5 mg, 10 mg, 20 mg, and 30 mg, respectively, of Shire Laboratories Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,

(S) for 2/11/2002

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-422

Final Printed Labeling

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 OR DISPENSED SPAR-

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:	5 mg	10 mg	20 mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	5 mg	7.5 mg
Amphetamine Aspartate	1.25 mg	2.5 mg	5 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	2.5 mg	5 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	2.5 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg	6.3 mg	12.6 mg	18.8 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, compressible sugar, corn starch, magnesium stearate, microcrystalline cellulose and, saccharin sodium.

The 5 and 10 mg also contain FD&C blue no.1 aluminum lake.

The 20 and 30 mg also contain FD&C yellow no. 6 aluminum lake.

CLINICAL PHARMACOLOGY:

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence which clearly establishes the mechanism whereby amphetamine produces mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

INDICATIONS AND USAGE:

Attention Deficit Disorder with Hyperactivity:

Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) 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 Narcolepsy

CONTRAINDICATIONS:

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

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 amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Usage in Nursing Mothers:

Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

PRECAUTIONS:

General:

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

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Information 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: Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines.

Urinary Acidifying Agents: (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic Blockers: Adrenergic blockers are inhibited by amphetamines.

Alkalinizing Agents: Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, Tricyclic: Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO Inhibitors: MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines: Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives: Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine: Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide: Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol: Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines.

Lithium Carbonate: The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine: Amphetamines potentiate the analgesic effect of meperidine.

Methenamine Therapy: Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine: Amphetamines enhance the adrenergic effect of norepinephrine.

Phenytoin: Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene: In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum Alkaloids: Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions:

- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis:

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 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 nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

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 medications.

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 evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

ADVERSE REACTIONS:

Cardiovascular:

Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System:

Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal:

Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect.

Allergic:

Urticaria.

Endocrine:

Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE:

Dextroamphetamine sulfate is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE:

Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with

doses of less than
to 500 mg are no
In rats, the oral LI
Symptoms:
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Narcolepsy:
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FEB 17 2002

APPROVED

amphetamine Saccharate, etamine Aspartate, amphetamine Sulfate and etamine Sulfate Tablets

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sed JUNE 2001
710102 Rx only

SAMPLE

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oduct combining the neutral sulfate salts of dex- mine, with the dextro isomer of amphetamine sac- aspartate.

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is the following inactive ingredients: colloidal silicon corn starch, magnesium stearate, microcrystalline m.
FD&C blue no.1 aluminum lake.
n FD&C yellow no. 6 aluminum lake.

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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 medications.
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ADVERSE REACTIONS:
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Allergic:
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Endocrine:
Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE:
Dextroamphetamine sulfate is a Schedule II controlled substance.
Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE:
Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.
In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.
Symptoms:
Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis.
Fatigue and depression usually follow the central stimulation.
Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse.
Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.
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 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.

DOSAGE AND ADMINISTRATION:
Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

Attention Deficit Disorder with Hyperactivity:
Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.
In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.
Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

Narcolepsy:
Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response.
Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate, may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

HOW SUPPLIED:
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets is available as:

5 mg: Blue, oval, biconvex tablet with two partial bisects on one side debossed with b over **971** and four partial bisects on the other side debossed with **5**. Available in bottles of:

50	NDC 0555-0971-10
100	NDC 0555-0971-02
500	NDC 0555-0971-04

10 mg: Blue, oval, flat-faced, beveled-edge tablet with two partial bisects on one side debossed with b over **972** and two partial bisects and a full score on the other side debossed with **1/0**. Available in bottles of:

50	NDC 0555-0972-10
100	NDC 0555-0972-02
500	NDC 0555-0972-04

20 mg: Peach, oval, flat-faced, beveled-edge tablet with two partial bisects on one side debossed with b over **973** and two partial bisects and a full score on the other side debossed with **2/0**. Available in bottles of:

50	NDC 0555-0973-10
100	NDC 0555-0973-02
500	NDC 0555-0973-04

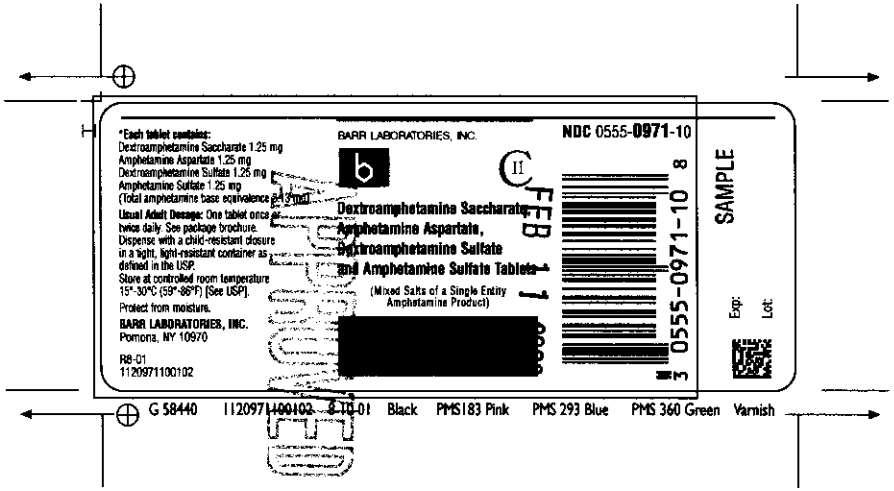
30 mg: Peach, oval, biconvex tablet with two partial bisects on one side debossed with b over **974** and two partial bisects and a full score on the other side debossed with **3/0**. Available in bottles of:

50	NDC 0555-0974-10
100	NDC 0555-0974-02
500	NDC 0555-0974-04

Dispense with a child-resistant closure in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised JUNE 2001
BR-971,972,973,974



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/10/01	**ITEM #: 1120971100102**
PRODUCT: Dextroamphetamine Saccharate Tablets, 5 mg - 50 Tablets	
DIMENSIONS: 3.625 X 1.5 inches	
PLATE NO: G58440 **PROOF NO:** 1 **MacOp Initls:** MDP	
SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*	
COLORS: ■ PMS 293 ■ PMS 360 ■ PMS 183 ■ Black □ Varnish	

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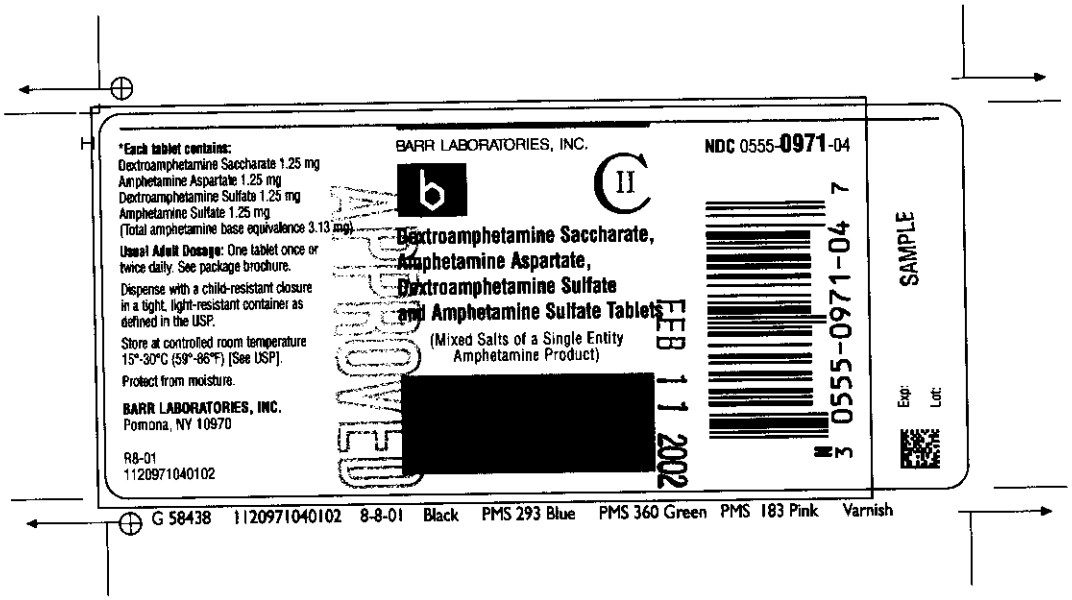
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT

AP 2/11/02

40-422



PROOF PRINT SHOWN @ 100%

CUSTOMER: **Barr Laboratories, Inc.**

DATE: 8/9/01 **ITEM #: 1120971040102**

PRODUCT: Dextroamphetamine Saccharate Tablets, 5 mg - 500 Tablets

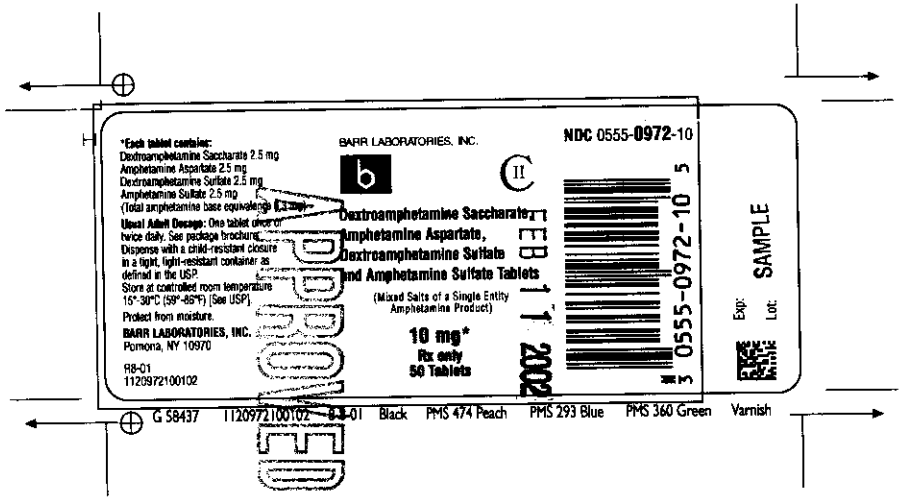
DIMENSIONS: 4.5 X 2 inches

PLATE NO: G58438 **PROOF NO:** 1 **MacOp Initls:** MDP

SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*

COLORS: ■ PMS 293 ■ PMS 360 ■ PMS 183 ■ Black □ Varnish

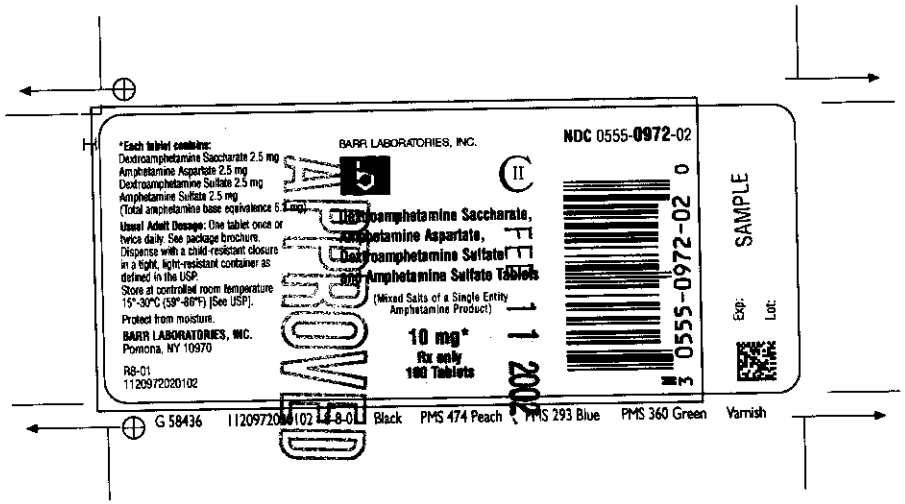
- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
- THIS LASERPROOF INDICATES COLORBREAKS ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLORS
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/9/01	**ITEM #: 1120972100102**
PRODUCT: Dextroamphetamine Saccharate Tablets,10 mg - 50 Tablets	
DIMENSIONS: 3.625 X 1.5 inches	
PLATE NO: G58437 **PROOF NO:** 1 **MacOp Initls:** MDP	
SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*	
COLORS: ■ PMS 293 ■ PMS 360 PMS 474 ■ Black □ Varnish	

- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
- THIS LASERPROOF INDICATES COLORBREAKS ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLORS
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/9/01	**ITEM #: 1120972020102**
PRODUCT: Dextroamphetamine Saccharate Tablets,10 mg - 100 Tablets	
DIMENSIONS: 3.625 X 1.5 inches	
PLATE NO: G58436 **PROOF NO:** 1 **MacOp Initls:** MDP	
SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*	
COLORS: ■ PMS 293 ■ PMS 360 PMS 474 ■ Black □ Varnish	

- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
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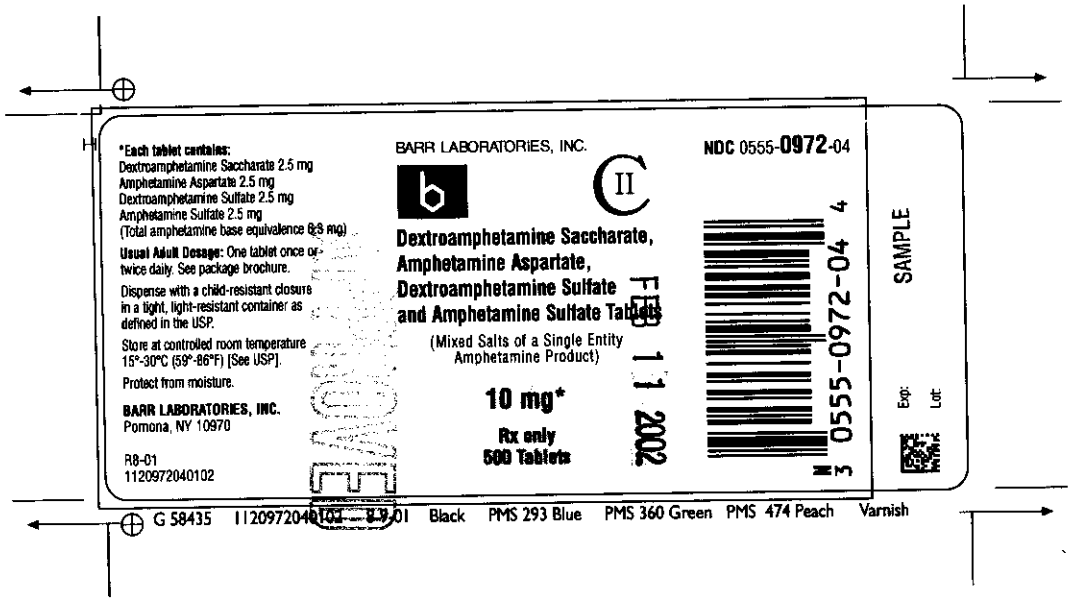
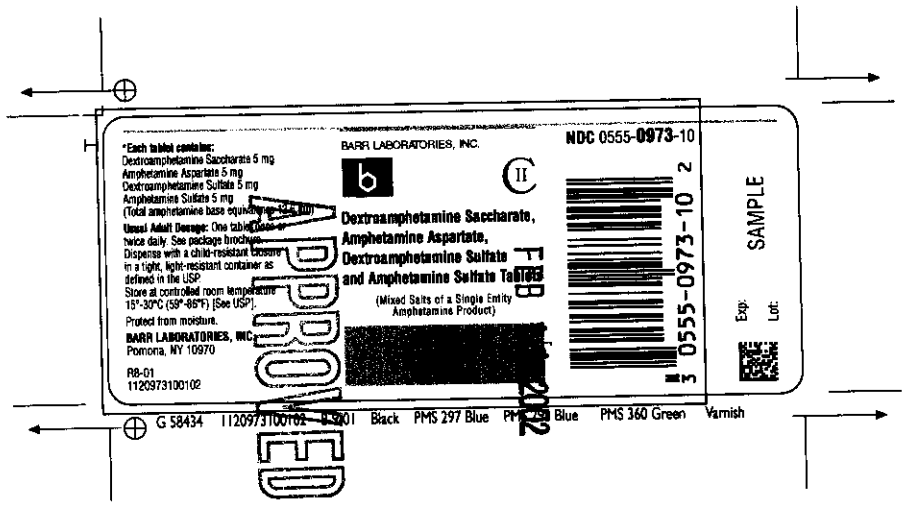


PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/8/01	**ITEM #: 1120972040102**
PRODUCT:	Dextroamphetamine Saccharate Tablets, 10 mg - 500 Tablets
DIMENSIONS:	4.5 X 2 inches
PLATE NO: G58435	**PROOF NO:** 1 **MacOp Initls:** MDP
SUPPLIER:	*New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*
COLORS:	■ PMS 293 ■ PMS 360 PMS 474 ■ Black □ Varnish

- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
- THIS LASERPROOF INDICATES COLORBREAKS ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLORS
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/9/01	**ITEM #: 1120973100102**
PRODUCT: Dextroamphetamine Saccharate Tablets, 20 mg - 50 Tablets	
DIMENSIONS: 3.625 X 1.5 inches	
PLATE NO: G58434 **PROOF NO:** 1 **MacOp Initls:** MDP	
SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*	
COLORS: ■ PMS 293 ■ PMS 360 ■ PMS 297 ■ Black □ Varnish	

- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
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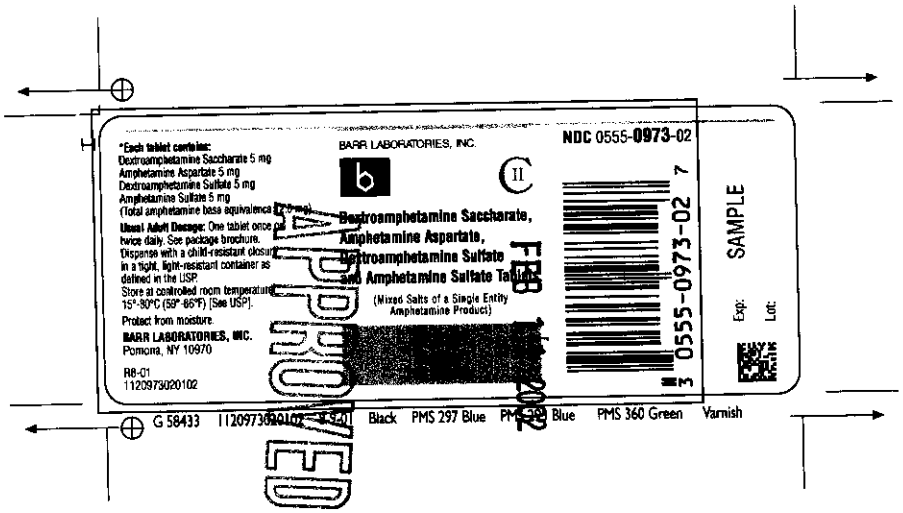
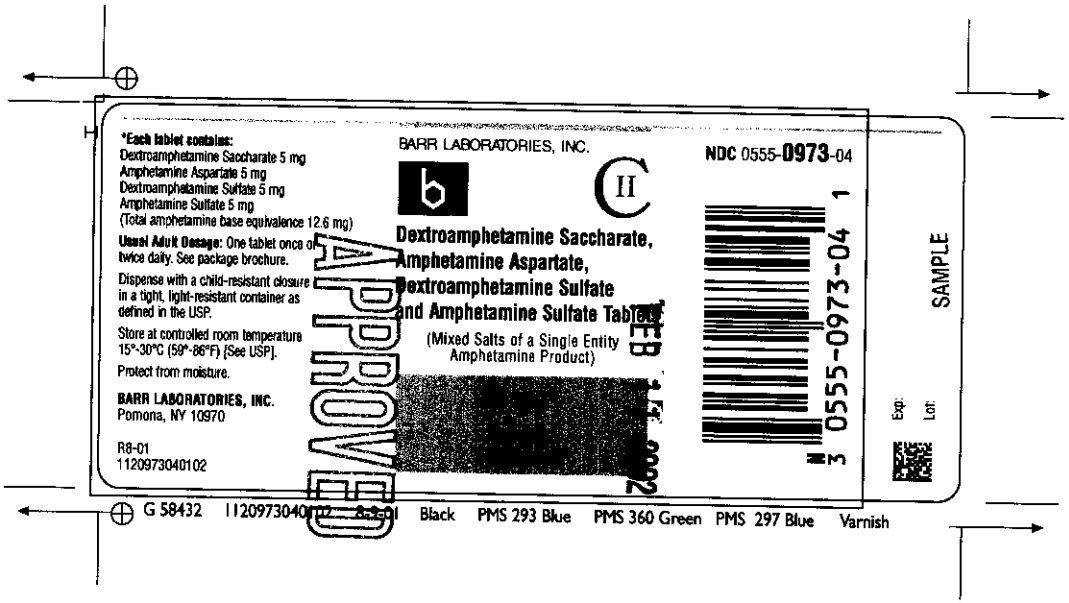
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/9/01	**ITEM #: 1120973020102**
PRODUCT: Dextroamphetamine Saccharate Tablets, 20 mg - 100 Tablets	
DIMENSIONS: 3.625 X 1.5 inches	
PLATE NO: G58433 **PROOF NO:** 1 **MacOp Initls:** MDP	
SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*	
COLORS: PMS 293 PMS 360 PMS 297 Black Varnish	

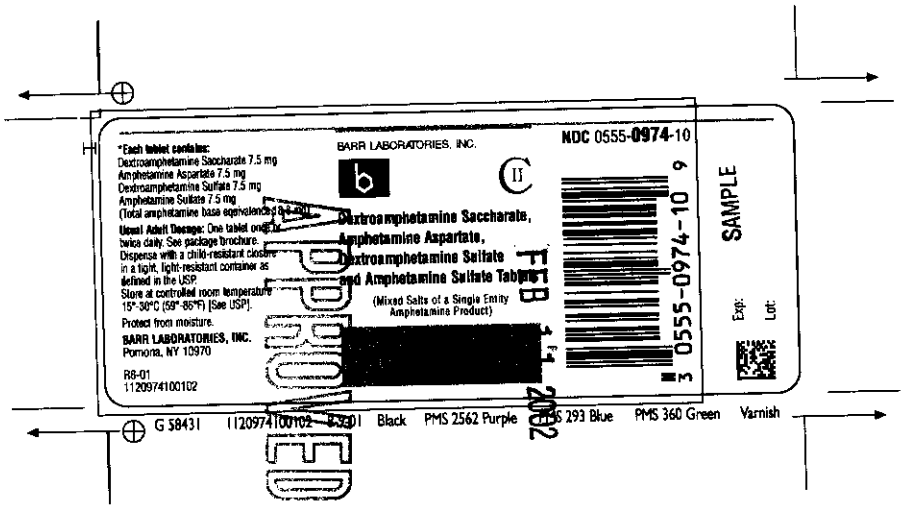
- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
- THIS LASERPROOF INDICATES COLORBREAKS ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLORS
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/9/01	**ITEM #: 1120973040102**
PRODUCT: Dextroamphetamine 20 mg 500 Tablets	
DIMENSIONS: 4.5 X 2 inches	
PLATE NO: G58432 **PROOF NO:** 1 **MacOp Initis:** MDP	
SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*	
COLORS: ■ PMS 293 ■ PMS 360 ■ PMS 297 ■ Black □ Varnish	

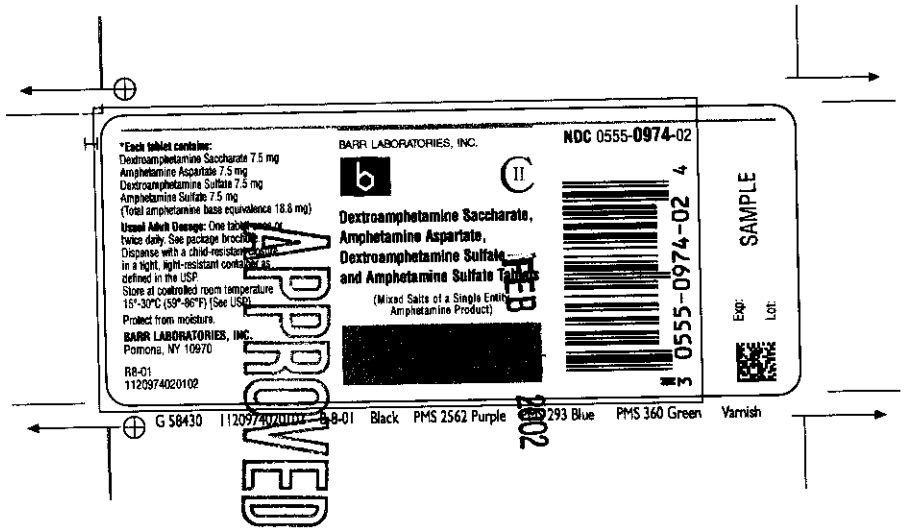
- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
- THIS LASERPROOF INDICATES COLORBREAKS ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLORS
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/8/01	**ITEM #: 1120974100102**
PRODUCT: Dextroamphetamine Saccharate Tablets,30 mg - 50 Tablets	
DIMENSIONS: 3.625 X 1.5 inches	
PLATE NO: G58431 **PROOF NO:** 1 **MacOp Initis:** MDP	
SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*	
COLORS: ■ PMS 293 ■ PMS 360 ■ PMS 2562 ■ Black □ Varnish	

- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
- THIS LASERPROOF INDICATES COLORBREAKS ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLORS
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT



PROOF PRINT SHOWN @ 100%

CUSTOMER:	**Barr Laboratories, Inc.**
DATE: 8/9/01	**ITEM #: 1120974020102**
PRODUCT:	Dextroamphetamine Saccharate Tablets, 30 mg - 100 Tablets
DIMENSIONS:	3.625 X 1.5 inches
PLATE NO: G58430	**PROOF NO:** 1 **MacOp Initls:** MDP
SUPPLIER:	*New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*
COLORS:	■ PMS 293 ■ PMS 360 ■ PMS 2562 ■ Black □ Varnish

- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
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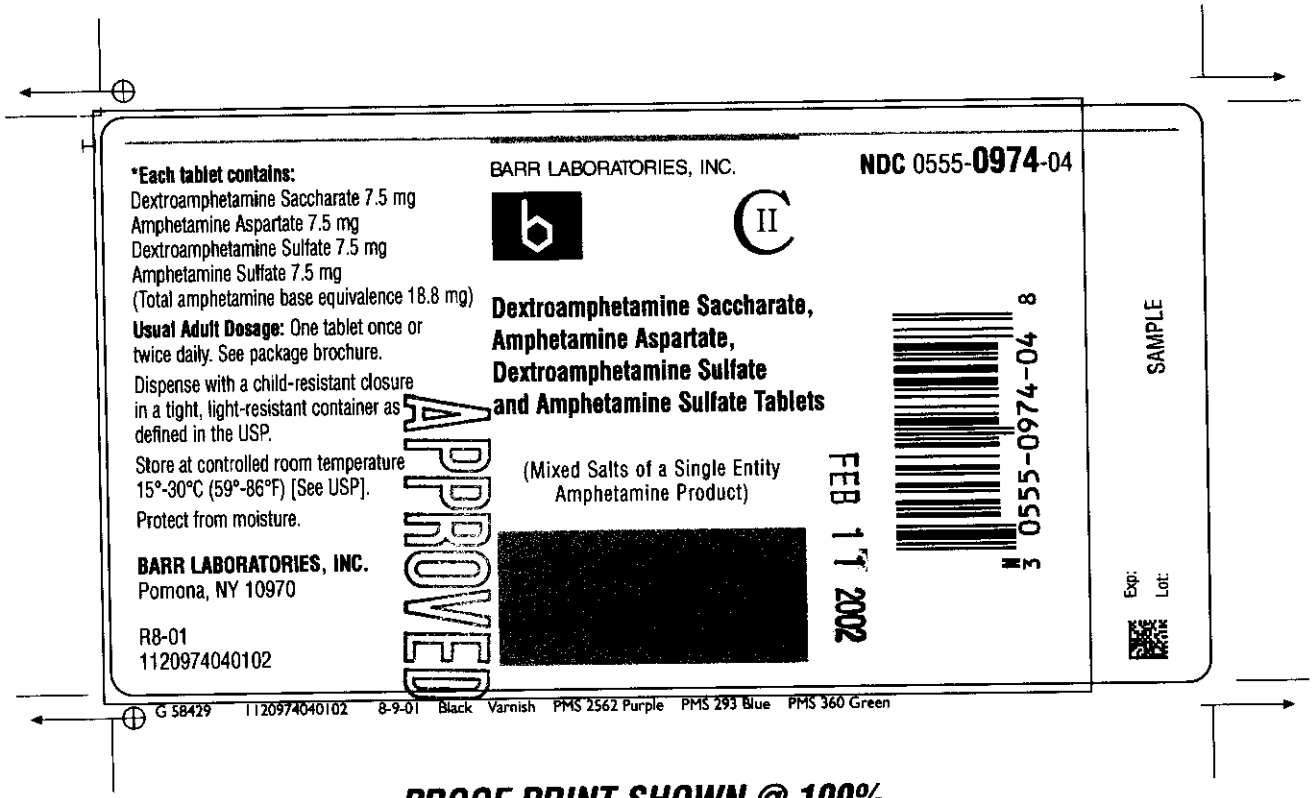


PROOF PRINT SHOWN @ 100%

CUSTOMER: **Barr Laboratories, Inc.**

DATE: 8/9/01 **ITEM #: 1120974040102**

PRODUCT: Dextroamphetamine 30 mg 500 Tablets

DIMENSIONS: 5.75 X 3.0 inches

PLATE NO: G58429 **PROOF NO:** 1 **MacOp Initls:** MDP

SUPPLIER: *New Jersey Packaging • Fairfield, NJ 07004 • 973-808-8000*

COLORS: PMS 293 PMS 360 PMS 2562 Black Varnish

- DATA MATRIX CODE AND BARCODE PRINT BLACK
- VARNISH OVERPRINTS ALL COPY SHOWN IN VARNISH AREA
- THIS LASERPROOF INDICATES COLORBREAKS ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLORS
- DIE LINES SHOWN FOR REFERENCE ONLY — DOES NOT PRINT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-422

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 40-422

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519
Phone: (914)-353-3859

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Adderall® Tablets by Shire Richwood approved in NDA #11-522. The firm filed a patent certification indicating that there are no unexpired patents for this drug (p. 3-00001). No exclusivities noted (p. 3-00002). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

~~~~~

7. NONPROPRIETARY NAME

Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate USP, and Amphetamine Sulfate USP Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm	Original Submission:	31-OCT-2000
	Telephone Amendment:	29-NOV-2000
	Amendment:	12-FEB-2001
FDA	Acceptable for Filing:	30-NOV-2000
	Labeling Deficiency:	19-JAN-2001

10. PHARMACOLOGICAL CATEGORY

CNS Stimulant

11. Rx or OTC

Rx
~~~~~

12. RELATED IND/NDA/DMF(s)

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

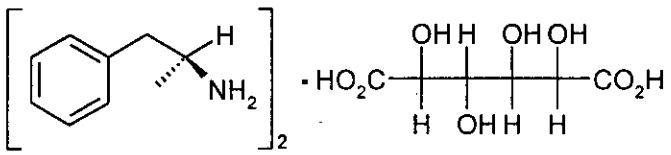
13. DOSAGE FORM

Tablets

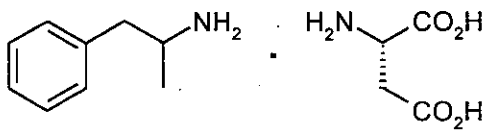
14. POTENCY

5 mg, 10 mg, 20 mg, 30 mg

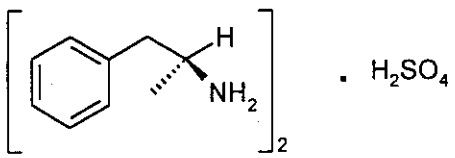
15. CHEMICAL NAME AND STRUCTURE



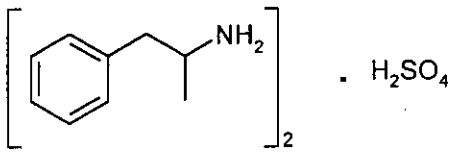
Dextroamphetamine Saccharate
$(C_9H_{13}N)_2 \cdot C_6H_8O_8$ MW=478.53



Amphetamine Aspartate
$C_9H_{13}N \cdot C_4H_7NO_4$ MW=268.31



Dextroamphetamine Sulfate USP
$(C_9H_{13}N)_2 \cdot H_2SO_4$ MW=368.49



Amphetamine Sulfate USP
$(C_9H_{13}N)_2 \cdot H_2SO_4$ MW=368.49

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MAJOR)

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 2/27/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 13

pages of trade secret and/or confidential commercial information

1. CHEMISTRY REVIEW NO. 2 2. ANDA # 40-422

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519
Phone: (914)-353-3859

4. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product: Adderall® Tablets by Shire Richwood approved in NDA #11-522. The firm filed a patent certification indicating that there are no unexpired patents for this drug (p. 3-00001). No exclusivities noted (p. 3-00002). The proposed drug product contains the same active ingredients and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

Although the firm originally proposed a Proprietary Name of [redacted] the Labeling Division and OPDRA found it unacceptable on the 6/11/01 Labeling Review. The firm has subsequently deleted the use of that proprietary name as of their 7/25/01 amendment.

7. NONPROPRIETARY NAME

Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm		
	Original Submission:	31-OCT-2000
	Telephone Amendment:	29-NOV-2000
	Amendment:	12-FEB-2001
	CMC/Labeling Amendment:	02-MAY-2001
	Bioequivalency Tcon:	08-JUN-2001
	Bioequivalency Amendment:	11-JUL-2001
	Labeling Amendment:	25-JUL-2001

FDA	Acceptable for Filing:	30-NOV-2000
	Labeling Deficiency I:	19-JAN-2001
	CMC Deficiency I:	19-MAR-2001
	Labeling Deficiency II:	19-MAR-2001
	Labeling Deficiency III:	11-JUN-2001
	Bioequivalency Deficiency:	03-JUL-2001
	Bioequivalency Acceptance:	30-JUL-2001
	Labeling Deficiency IV:	03-AUG-2001

10. PHARMACOLOGICAL CATEGORY
CNS Stimulant

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

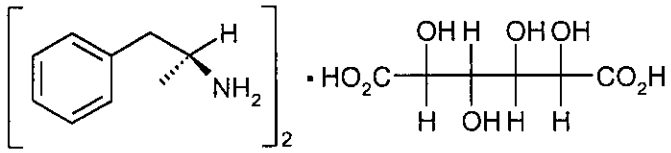
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

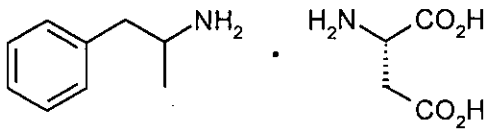
14. POTENCY
5 mg, 10 mg, 20 mg, 30 mg

APPEARS THIS WAY
ON ORIGINAL

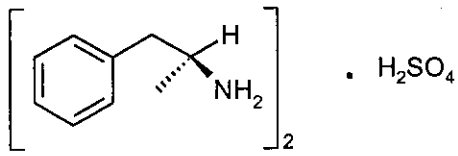
15. CHEMICAL NAME AND STRUCTURE



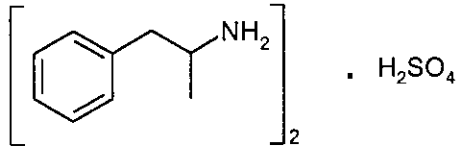
Dextroamphetamine Saccharate
$(C_9H_{13}N)_2 \cdot C_6H_8O_8$ MW=478.53



Amphetamine Aspartate
$C_9H_{13}N \cdot C_4H_7NO_4$ MW=268.31



Dextroamphetamine Sulfate USP
$(C_9H_{13}N)_2 \cdot H_2SO_4$ MW=368.49



Amphetamine Sulfate USP
$(C_9H_{13}N)_2 \cdot H_2SO_4$ MW=368.49

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Not-Approvable (MINOR)

19. REVIEWER:
M. Scott Furness

DATE COMPLETED:
8/13/01

Redacted 48

pages of trade secret and/or confidential commercial information

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 40-422

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519
Phone: (845)-353-8432

4. LEGAL BASIS FOR SUBMISSION
Reference Listed drug product: Adderall® Tablets by Shire Richwood approved in NDA #11-522. The firm filed a patent certification indicating that there are no unexpired patents for this drug (p. 3-00001). No exclusivities noted (p. 3-00002). The proposed drug product contains the same active ingredients and has the same strength, dosage form, route of administration, indication, and usage as the reference listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
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7. NONPROPRIETARY NAME
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm		
	Original Submission:	31-OCT-2000
	Telephone Amendment:	29-NOV-2000
	Amendment:	12-FEB-2001
	CMC/Labeling Amendment:	02-MAY-2001
	Bioequivalency Tcon:	08-JUN-2001
	Bioequivalency Amendment:	11-JUL-2001
	Labeling Amendment:	25-JUL-2001
	Chemistry Amendment:	31-AUG-2001

	Labeling Amendment:	04-SEP-2001
	Labeling Amendment:	21-SEP-2001
	CMC T-Con Amendment:	14-NOV-2001
FDA	Acceptable for Filing:	30-NOV-2000
	Labeling Deficiency I:	30-JAN-2001
	CMC Deficiency I:	19-MAR-2001
	Bioequivalency Deficiency I:	30-APR-2001
	Labeling Deficiency II:	19-MAR-2001
	Labeling Deficiency III:	11-JUN-2001
	Bioequivalency Deficiency II:	03-JUL-2001
	Bioequivalency Acceptance:	30-JUL-2001
	Labeling Deficiency IV:	03-AUG-2001
	CMC Deficiency II:	21-AUG-2001
	Labeling Approval:	02-OCT-2001

10. PHARMACOLOGICAL CATEGORY
CNS Stimulant

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
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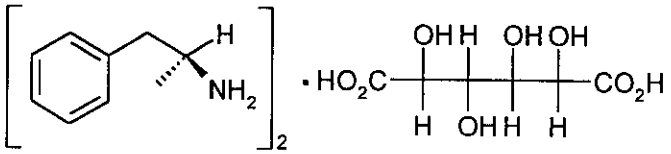
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

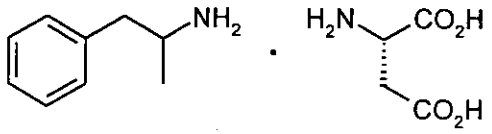
13. DOSAGE FORM
Tablets

14. POTENCY
5 mg, 10 mg, 20 mg, 30 mg

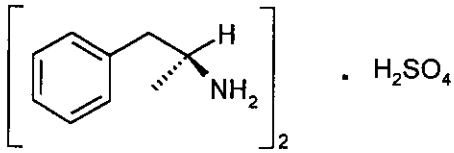
15. CHEMICAL NAME AND STRUCTURE



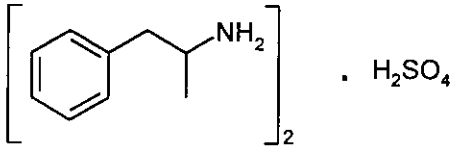
Dextroamphetamine Saccharate
$(C_9H_{13}N)_2 \cdot C_6H_8O_8$ MW=478.53



Amphetamine Aspartate
$C_9H_{13}N \cdot C_4H_7NO_4$ MW=268.31



Dextroamphetamine Sulfate USP
$(C_9H_{13}N)_2 \cdot H_2SO_4$ MW=368.49



Amphetamine Sulfate USP
$(C_9H_{13}N)_2 \cdot H_2SO_4$ MW=368.49

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Approval is recommended.

19. REVIEWER: M. Scott Furness

DATE COMPLETED: 11/16/01

Redacted 31

pages of trade secret and/or confidential commercial information

3/19/01
8/21/01
CMC

Redacted 6

pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-422

BIOEQUIVALENCE REVIEW

APR 30 2001

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 40-422 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCTS:

(dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit detailed information (SOPs) regarding preparation of the standard concentration samples, quality control samples, special 1:1 ratio quality control samples, and the internal standard solution.

2. Please identify samples which were diluted (if any) and the dilution factors. Results of the assay validations for the diluted samples should be also submitted.

3. Please submit the Analytical Raw Data for Study R00-456 summarized in a Table presenting the Drug Area, Internal Standard Area, ratio of Drug Area to the Internal Standard Area, and the corresponding concentration for each assayed sample.

4. Please submit dissolution testing data using the method listed in the USP 24 for Amphetamine Sulfate Tablets and d-Amphetamine Sulfate Tablets.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-422
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-650/Bio Drug File
HFD-658/B. Davit
HFD-658/F. Nouravarsani

V:\FIRMSAM\Barr\ltrs&rev\40422SDW.000

Printed in final on 4/11/2001

Endorsements: (Final with Dates)
HFD-658/F. Nouravarsani /S/ 4/11/2001
HFD-658/B. Davit /S/ 4/11/01
HFD-650/D. Conner for /S/ 4/19/2001

BIOEQUIVALENCY - DEFICIENCY

SUBMISSION DATE:
10/31/2000 (Hard Copy)

OK. **Fasting Study (STF)**
Clinical:

Strength: 30 mg Tablets
Outcome: IC

Analytical:

OK. **DISSOLUTION WAIVER (DIW)**

Strength: 5 mg Tablets
Outcome: IC

OK. **DISSOLUTION WAIVER (DIW)**

Strength: 10 mg Tablets
Outcome: IC

OK. **DISSOLUTION WAIVER (DIW)**

Strength: 20 mg Tablets
Outcome: IC

New Correspondence (NC)
(12/08/2000)

BE Electronic Submission

New Correspondence (NC)
(11/01/2000)

BE Diskettes

New Correspondence (NC)
(11/29/2000)

Correcting the 356h Form

Outcome Decision: IC - Incomplete

WinBio Comments: The application was found incomplete.

BIOEQUIVALENCY AMENDMENT

ANDA 40-422

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APR 30 2001

TO: APPLICANT: Barr Laboratories, Inc.

ATTN: Christine Mundkur

TEL: 914-353-8432

FAX: ~~914~~ 845-353-3859

FROM: Steven Mazzella

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 31, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphatamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

(dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)
Reviewer: F. Nouravarsani
40422SDW.000

Barr Laboratories, Inc.
Pomona, NY
Submission Dates:
10/31/2000 (Hard Copy)
12/08/2000 (EVA)

REVIEW OF A BIOEQUIVALENCE STUDY, DISSOLUTION TESTING, AND WAIVER REQUESTS (ELECTRONIC SUBMISSION)

INTRODUCTION:

- **FIRST GENERIC APPLICATION:** Yes.

- **CONTENTS OF SUBMISSIONS:**
  - Bioequivalence study conducted on 30 mg Tablets under single-dose, fasting conditions
  - Dissolution testing
  - Waiver Requests for 5 mg, 10 mg, and 20 mg Tablets
  - New Correspondence (NC), letter date 11/01/2000: Two Diskettes for BE study.
  - New Correspondence (NC), letter date 11/29/2000: As per the Agency's instructions, Barr corrected the 356h form to state Shire Richwood's Adderall^{R} as the reference listed drug product.
  - New Correspondence (NC), letter date 12/08/2000: Electronic Submission.

- **THE FOLLOWING INFORMATION IS FOUND IN THE PDR, 2001:**

Adderall^{R} is 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.

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

Adderall^{R} is used for Attention Deficit Disorder with Hyperactivity and in Narcolepsy. Regardless of indication, amphetamines should be administered at the lowest effective dosage, and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

BIOEQUIVALENCE STUDY:

A RELATIVE BIOAVAILABILITY STUDY OF 30 MG [redacted] TABLETS UNDER FASTING CONDITIONS (R00-456):

STUDY SPONSOR: Barr Laboratories, Inc.

STUDY OBJECTIVE:

The relative bioavailability (rate and extent of absorption) of 30 mg [redacted] Tablets by Barr Laboratories, Inc. was compared with that of 30 mg Adderall^{R} Tablets by Shire Richwood Inc. following a single oral dose in healthy male volunteers under fasting conditions.

STUDY FACILITY INFORMATION:

Clinical Facility:	[redacted]
Principal Investigator	[redacted]
Clinical Study, Dosing Dates:	Period I: 08/19-21/00 Period II: 08/26-28/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	09/05/00 to 09/18/00

TREATMENT INFORMATION:

Treatment ID:	**TEST (A)**	**REFERENCE (B)**
Product Name:	[redacted]	Adderall^{R}
Manufacturer:	Barr Laboratories, Inc.	Shire Richwood Inc.
Manufacture Date:	5/8/00	N/A
Expiration Date:	N/A	05/02
ANDA Batch Size	[redacted] Tablets	N/A
Batch/Lot Number:	309740003R	B5426
Strength:	30 mg	30 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	30 mg	30 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

RANDOMIZATION:

Randomized:	Y
No. of Sequences:	2
No. of Periods:	2
No. of Treatments:	2

DESIGN:

Design Type:	Two-Way Crossover
Replicated Treatment Design:	N
Balanced:	Y
Washout Period:	7 DAYS

DOSING:

Single or Multiple Dose:	Single
Volume of Liquid Intake:	240 mL
Route of Administration:	Oral

SUBJECTS:

IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	26
No. of Subjects Completing:	26
No. of Subjects Plasma Analyzed:	26
No. of Dropouts:	0
Sex(es) Included:	Male
Healthy Volunteers Only:	Y
Age, Years:	19-45
Height, Cm:	162.6-190.5
Weight, Kg:	62.5-89.2

Dietary Restrictions:	No grapefruit or xanthine containing products were allowed during the confinement part of the study.
Activity Restrictions:	Only non-strenuous activity was permitted during the confinement part of the study.
Blood Sampling:	At 0 hour, and after dose administration at 0.333, 0.667, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 60 hours.
Vital Signs Measurement:	Blood pressure and heart rate were measured prior to dosing, at 8, 12, 24 hours after dosing, and upon completion of the study.

ANALYTICAL METHOD:

Redacted 3

pages of trade secret and/or confidential commercial information

COMMENTS:

1. The plasma samples from 26 subjects were assayed for d-amphetamine and l-amphetamine.

2. The duration of the long-term stability study (33 days) covers the study sample storage.

3. The number of subjects' samples, which were reassayed for d-amphetamine and l-amphetamine are as follows:

1 sample due to "Low Internal Standard"
2 samples due to "Technical Error"
2 samples due to "No Peaks Present"

There were no repeats for pharmacokinetic reasons.

3. PHARMACOKINETIC/STATISTICAL ANALYSES:

ARITHMETIC MEAN PLASMA CONCENTRATIONS (NG/ML) FOR D-AMPHETAMINE, N = 26

TIME (HR)	TEST PRODUCT		REFERENCE PRODUCT		RATIO OF MEANS (TEST/REFERENCE)
	MEAN	%CV	MEAN	%CV	
0.000	0.00	---	0.00	---	---
0.333	0.42	147.27%	0.69	155.95%	0.61
0.667	9.70	81.46%	11.61	67.34%	0.84
1.000	24.93	52.59%	28.06	45.35%	0.89
1.500	38.22	37.30%	40.02	27.96%	0.95
2.000	42.80	29.01%	43.79	18.94%	0.98
2.500	44.72	17.71%	44.79	14.95%	1.00
3.000	44.86	14.36%	45.19	13.31%	0.99
3.500	43.89	12.06%	44.03	13.56%	1.00
4.000	42.35	13.61%	42.80	14.22%	0.99
5.000	41.40	11.85%	41.02	14.25%	1.01
6.000	39.17	10.60%	38.63	14.59%	1.01
8.000	35.46	11.58%	34.40	15.65%	1.03
10.00	30.70	12.04%	30.77	18.60%	1.00
12.00	25.68	15.42%	25.90	21.88%	0.99
16.00	18.84	20.61%	19.33	27.17%	0.97
24.00	10.22	24.01%	10.84	35.48%	0.94
36.00	4.33	33.63%	4.88	52.33%	0.89
48.00	1.82	40.69%	1.98*	60.02%	0.92
60.00	0.74*	71.63%	0.89	88.37%	0.83

*: N = 25

ARITHMETIC MEAN PLASMA CONCENTRATIONS (NG/ML) FOR L-AMPHETAMINE

TIME (HR)	TEST PRODUCT		REFERENCE PRODUCT		RATIO OF MEANS (TEST/REFERENCE)
	MEAN	%CV	MEAN	%CV	
0.000	0.00	---	0.00	---	---
0.333	0.12	150.55%	0.21	161.75%	0.57
0.667	2.69	80.46%	3.38	66.29%	0.79
1.000	6.84	52.11%	8.12	45.08%	0.84
1.500	10.60	37.18%	11.64	27.77%	0.91
2.000	11.95	28.74%	12.88	18.52%	0.93
2.500	12.56	16.97%	13.21	14.64%	0.95
3.000	12.66	13.90%	13.40	12.76%	0.95
3.500	12.50	11.72%	13.10	13.18%	0.95
4.000	12.05	13.14%	12.85	13.22%	0.94
5.000	12.00	11.36%	12.44	13.63%	0.96
6.000	11.51	10.08%	11.87	13.34%	0.97
8.000	10.72	10.70%	10.91	13.82%	0.98
10.00	9.51	11.10%	9.94	16.48%	0.96
12.00	8.13	14.24%	8.60	19.73%	0.95
16.00	6.31	19.53%	6.78	23.99%	0.93
24.00	3.70	22.24%	4.10	31.02%	0.90
36.00	1.78	29.56%	2.07	43.80%	0.86
48.00	0.86	35.44%	0.96*	47.85%	0.89
60.00	0.41*	49.64%	0.52	63.70%	0.79

*: N = 25

MEANS (%CV), PERCENT RATIOS, AND 90% CONFIDENCE INTERVALS FOR PK PARAMETERS OF D-AMPHETAMINE, N = 26

PK PARAMETER	TEST PRODUCT	REFERENCE PRODUCT	PERCENT RATIO OF MEANS (TEST/REF)*100	90% CONFIDENCE INTERVAL
AUC0-T, Hr*ng/mL	753.0 (16)	774.0 (23)		
G. Mean*	743.0	756.0	98.28	94.1 - 103
AUCINF, Hr*ng/mL	767.0 (16)	791.0 (23)		
G. Mean*	757.0	772.0	98.06	93.7 - 103
CMAX, ng/mL	48.13 (17)	47.67 (15)		
G. Mean*	47.47	47.23	100.51	97.1 - 104
TMAX, hr	2.90 (35)	2.73 (32)		
KELM, 1/hr	0.075 (10)	0.073 (17)		
THALF, hr	9.32 (10)	9.81 (19)		

*: Geometric mean based on least square means of log-transformed data

The Root Mean Square Error (Root MSE) for the ln AUC0-T is 0.0923 and for ln CMAX is 0.0730.

MEANS (%CV), PERCENT RATIOS, AND 90% CONFIDENCE INTERVALS FOR PK PARAMETERS OF L-AMPHETAMINE, N = 26

PK PARAMETER	TEST PRODUCT	REFERENCE PRODUCT	PERCENT RATIO OF MEANS (TEST/REF)*100	90% CONFIDENCE INTERVAL
AUC0-T, Hr*ng/mL	246 (15)	265 (21)		
G. Mean*	243	260	93.46	89.1 - 98.1
AUCINF, Hr*ng/mL	253 (16)	275 (22)		
G. Mean*	250	269	92.94	88.2 - 97.7
CMAX, ng/mL	13.62 (17)	14.09 (14)		
G. Mean*	13.45	13.97	96.28	92.9 - 99.7
TMAX, hr	3.27 (41)	2.85 (29)		
KELM, 1/hr	0.063 (13)	0.061 (20)		
THALF, hr	11.10 (13)	11.83 (24)		

*: Geometric mean based on least square means of log-transformed data

The Root Mean Square Error (Root MSE) for the ln AUC0-T is 0.1015 and for ln CMAX is 0.0743.

COMPARISON OF PK PARAMETERS FOR D-AMPHETAMINE AND L-AMPHETAMINE, N = 26

PK PARAMETER	TEST PRODUCT	REFERENCE PRODUCT
L- AUC0-T*	243	260
D- AUC0-T*	743	756
RATIO: L-/D-	0.327	0.344
L- AUCINF*	250	269
D- AUCINF*	757	772
RATIO: L-/D-	0.330	0.348
L- CMAX*	13.45	13.97
D- CMAX*	47.47	47.23
RATIO: L-/D-	0.283	0.296
L- TMAX	3.27	2.85
D- TMAX	2.90	2.73
RATIO: L-/D-	1.13	1.04
L- KELM	0.0634	0.0614
D- KELM	0.0751	0.0728
RATIO: L-/D-	0.844	0.843
L- THALF	11.10	11.83
D- THALF	9.32	9.81
RATIO: L-/D-	1.19	1.21

*: Geometric mean based on least square means of log-transformed data

Plasma concentration-time profiles are found in Figures 1.1 and 1.2 for d-amphetamine, and in Figures 2.1 and 2.2 for l-amphetamine.

COMMENTS:

1. The 90% confidence intervals about the ratio of the test to the reference AUC0-T, AUCINF, and CMAX based on least squares means of log-transformed data are within the 80% - 125% limits for both d-amphetamine and l-amphetamine.

2. The values obtained for the pharmacokinetic parameters of l-amphetamine, d-amphetamine, and the ratio of l-amphetamine to d-amphetamine are similar for the test and reference products.

ASSAY DATA (AS PERCENT OF LABEL CLAIM), %D-AMPHETAMINE, %L-AMPHETAMINE, AND ENANTIOMERIC RATIO:

PRODUCT	5 MG TABLETS	10 MG TABLETS	20 MG TABLETS	30 MG TABLETS
TEST:				
ASSAY	batch No.: 309710003R	batch No.: 309720004R	batch No.: 309730003R	batch No.: 309740003R
%D-AMPHETAMINE				
%L-AMPHETAMINE				
ENANTIOMERIC RATIO: L-/D-				
REFERENCE:				
ASSAY	batch No.: 0B5237	batch No.: B5246	batch No.: B5292	batch No.: B5426
%D-AMPHETAMINE				
%L-AMPHETAMINE				
ENANTIOMERIC RATIO, L-/D-				

COMMENTS:

1. The values reported for the %l-amphetamine, %d-amphetamine, and the ratio of l-amphetamine to d-amphetamine are similar for the test and reference products.

2. The ratios of l-amphetamine to d-amphetamine obtained for AUC0-T, AUCINF, and CMAX for the test product are similar to the l-amphetamine to d-amphetamine ratio

reported for the assayed potency of the test product used in the bio-study.

3. The ratios of l-amphetamine to d-amphetamine obtained for AUC0-T, AUCINF, and CMAX for the reference product are similar to the l-amphetamine to d-amphetamine ratio reported for the assayed potency of the reference product used in the bio-study.

CONTENT UNIFORMITY DATA (AS PERCENT OF LABEL CLAIM), MEAN (CV%), N=10:

PRODUCT	5 MG TABLETS	10 MG TABLETS	20 MG TABLETS	30 MG TABLETS
TEST	— (2.4) batch No.: 309710003R	— (4.1) batch No.: 309720004R	— (3.4) batch No.: 309730003R	— (1.5) batch No.: 309740003R
REFERENCE	— (0.7) batch No.: 0B5237	— (1.0) batch No.: B5246	— (1.7) batch No.: B5292	— (1.2) batch No.: B5426

DISSOLUTION TESTING:

The dissolution testing was conducted using a method proposed by the firm. The method and results are shown in Table 1.

COMMENT:

The following Dissolution testing method is listed in the USP 24 for Amphetamine Sulfate Tablets and d-Amphetamine Sulfate Tablets:

Medium:	Water
Volume:	500 mL
Apparatus:	1
RPM:	100
Specifications:	NLT — (Q) in 45 minutes

FORMULATION COMPARISON OF THE TEST PRODUCTS (NOT TO BE RELEASED UNDER FOI)

INGREDIENT	STRENGTH 5 MG MG/TABLET	STRENGTH 10 MG MG/TABLET	STRENGTH 20 MG MG/TABLET	STRENGTH 30 MG MG/TABLET
AMPHETAMINE ASPARTATE	1.25	2.5	5	7.5
AMPHETAMINE SULFATE, USP	1.25	2.5	5	7.5
DEXTROAMPHETAMINE SACCHARATE	1.25	2.5	5	7.5
DEXTROAMPHETAMINE SULFATE, USP	1.25	2.5	5	7.5
COLLOIDAL SILICON DIOXIDE, NF				
COMPRESSIBLE SUGAR, NF				
MAGNESIUM STEARATE, NF				
MICROCRYSTALLINE CELLULOSE, NF				
SACCHARIN SODIUM, USP				
CORN STARCH, NF				
FD&C BLUE #1 ALUMINUM LAKE				
FD&C YELLOW #6 ALUMINUM LAKE				
TOTAL TABLET WEIGHT	120	240	240	360

FORMULATION COMPARISON OF THE REFERENCE PRODUCTS* (NOT TO BE RELEASED UNDER FOI)

INGREDIENTS	STRENGTH 5 MG MG/TABLET	STRENGTH 10 MG MG/TABLET	STRENGTH 20 MG MG/TABLET	STRENGTH 30 MG MG/TABLET
DEXTROAMPHETAMINE SACCHARATE	1.25	2.5	5.0	7.5
AMPHETAMINE ASPARTATE	1.25	2.5	5.0	7.5
DEXTROAMPHETAMINE SULFATE	1.25	2.5	5.0	7.5
AMPHETAMINE SULFATE	1.25	2.5	5.0	7.5
SUCROSE				
LACTOSE, ANHYDROUS				
CORN STARCH				
ACACIA				
MAGNESIUM STEARATE				
FDC BLUE #1				
FDC YELLOW #6				

*: From COMIS

WAIVERS REQUEST:

The firm requests waivers of in vivo bioequivalence study requirements for its 5 mg, 10 mg, and 20 mg strengths of ——— ™ Tablets based on 21 CFR 320.22(d)(2). The following information was submitted by the firm:

1. In vivo bioequivalence study conducted under fasting conditions for ——— Tablets, 30 mg.

2. Comparative dissolution testing conducted for the test and reference listed products, 5 mg, 10 mg, 20 mg, and 30 mg Tablets.

3. Formulations of ——— Tablets, 5 mg, 10 mg, 20 mg, and 30 mg. The formulation of the 20 mg ——— tablet is "exactly proportional" to the formulation of the 30 mg ——— tablets. The formulations of the 5 mg and 10 mg ——— ™ tablets are "exactly proportional" to one another, and are "proportionally similar" to the formulation of the 30 mg ——— tablet.

DEFICIENCIES OF ANDA 40-422:

1. The firm should submit detailed information regarding preparation of the standard concentration samples, quality control samples, special 1:1 ratio quality control samples, and the internal standard solution.

2. Samples which were diluted (if any) and the dilution factors should be identified. Results of the assay validations for the diluted samples should be submitted.

3. The Analytical Raw Data for the bio-study should be submitted in a Table presenting the Drug Area, Internal Standard Area, ratio of Drug Area to the Internal Standard Area, and the corresponding concentration for each assayed sample.

4. Dissolution testing data should be submitted using the method listed in the USP 24 for Amphetamine Sulfate Tablets and d-Amphetamine Sulfate Tablets.

5. The waivers of bioequivalence study requirements for ——— Tablets, 5 mg, 10 mg, and 20 mg are not granted due to the deficiencies listed above.

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Barr Laboratories, Inc. on its 30 mg ——— Tablets (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, amphetamine sulfate) (lot #309740003R) comparing it to Adderall[R] Tablets, 30 mg (lot #B5426) by Shire Richwood Inc. has been found incomplete by the Division of Bioequivalence.

2. The dissolution testing submitted by Barr Laboratories, Inc. on its ——— Tablets (dxtroamphetamine sccharate, amphetamine aspartate, dextroamphetamine sulfate, amphetamine sulfate), 5 mg (batch #309710003R), 10 mg (batch #309720004R), 20 mg (batch #309730003R), and 30 mg (batch #309740003R) comparing them to Adderall[R] Tablets, 5 mg (batch #0B5237), 10 mg (batch #B5246), 20 mg (batch #B5292), and 30 mg (lot #B5426), respectively, by Shire Richwood Inc. has been found unacceptable by the Division of Bioequivalence.

3. Waiver requests are not granted for ——— Tablets, 5 mg, 10 mg, and 20 mg due to the deficiencies listed under DEFICIENCIES OF ANDA 40-422.

4. The firm should be informed of the DEFICIENCIES.

/S/ , 4/11/2001

Farahnaz Nouravarsani, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED B. Davit /S/ 4/11/01
FT INITIALED B. Davit /S/

Date 4/11/01

Concur: /S/

Date 4/19/2001

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

F. Nouravarsani/Draft: 04-03-2001/40422SDW.000

TABLE 1:

DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)

Method:	**Proposed by the firm**
Analyte:	Amphetamine
Dosage Form and Strength:	Tablets, 5, 10, 20, and 30 mg
No. of Units Tested:	12 Tablets
Medium:	0.1N Hydrochloric Acid
Volume:	500 mL at 37° ± 0.5° C
Apparatus:	USP Apparatus 2 (Paddle)
RPM:	75
Assay Method:	
Proposed Specifications:	NLT ___ (Q) in 45 minutes

RESULTS:

%AMPHETAMINE DISSOLVED

TEST PRODUCT, 5 MG BATCH NO. 309710003R TIME (MINUTES)					REFERENCE PRODUCT, 5 MG BATCH NO. 0B5237 (EXP. 1/2002) TIME (MINUTES)				
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	90	101	101	101	MEAN	72	102	104	104
RSD%	12.9	3.8	3.7	3.7	RSD%	13.3	3.1	2.4	2.1

%AMPHETAMINE DISSOLVED

TEST PRODUCT, 10 MG BATCH NO. 309720004R TIME (MINUTES)					REFERENCE PRODUCT, 10 MG BATCH NO. B5246 (EXP. 2/2002) TIME (MINUTES)				
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	67	98	99	99	MEAN	56	86	103	104
RSD%	15	2.1	2.1	2.0	RSD%	4.9	8.0	1.2	1.0

%AMPHETAMINE DISSOLVED

	TEST PRODUCT, 20 MG BATCH NO. 309730003R TIME (MINUTES)					REFERENCE PRODUCT, 20 MG BATCH NO. B5292(EXP. 02/02) TIME (MINUTES)			
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	60	94	99	100	MEAN	78	100	101	101
RSD%	16.4	5.9	2.0	2.0	RSD%	11.7	1.5	1.2	1.2

%AMPHETAMINE DISSOLVED

	TEST PRODUCT, 30 MG BATCH NO. 309740003R TIME (MINUTES)					REFERENCE PRODUCT, 30 MG BATCH NO. B5426 (EXP. 05/02) TIME (MINUTES)			
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	65	99	103	103	MEAN	58	92	101	102
RSD%	13.9	7.7	5.1	5.1	RSD%	11.9	7.7	2.5	1.0

APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF SUBMISSIONS FOR DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE TABLETS, 5 MG, 10 MG, 20 MG, AND 30 MG:

SUBMISSION	FIRM	DATE	STUDY	DECISION
CC 00-414	[redacted]	10/03/00		
CC 00-314	[redacted]	07/28/00		
CC 00-298	[redacted]	07/21/00		
CC 00-198	[redacted]	05/16/00		
CC 00-056	[redacted]	02/10/00		
CC 00-052	[redacted]	02/18/00		
CC 99-426	[redacted]	11/22/99		
CC 98-279	[redacted]	08/05/98		
P 99-008 (Pilot Study and Protocol)	[redacted]	03/10/99 02/07/00		

Summary of the responses to the above CC and protocol: The Division of Bioequivalence currently requests the following:

- A single-dose, fasting bioequivalence study conducted on the highest strength, 30 mg tablets.
- The plasma levels of racemate and d-amphetamine should be measured in the assessment of bioequivalence study and dissolution testing of amphetamine salt mixture tablets.
- Waivers of bioequivalence study requirements for the lower strengths, 5, 10, and 20 mg may be requested if (i) the bioequivalence study on the 30 mg strength is found acceptable, (ii) all the tablet strengths meet the dissolution requirements, and (iii) the products of lower strengths are formulated proportionally similar to the 30 mg strength.

ANDA 40-422	Barr	10/31/00	STF DIS DIW	Under review

STF: Single-Dose/Fasting
DIS: Dissolution
DIW: Dissolution/Waiver

SUMMARY OF SUBMISSIONS FOR EXTENDED RELEASE ADDERALL[R] CAPSULE (DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE, AND AMPHETAMINE SULFATE), 5 MG, 10 MG, 20 MG, 30 MG, AND 40 MG:

SUBMISSION	FIRM	DATE	STUDY	DECISION

IND [redacted] [redacted] 11/10/99
(General Correspondence)

Biopharmaceutical Requirements: All studies should monitor for both the dextro- and levo-isomers.

IND [redacted] [redacted] 11/30/99
(New Protocol)

Blood samples will be assayed for d-amphetamine and l-amphetamine.

IND [redacted] [redacted] 03/25/99
(30-Day SRD Meeting)

Appendix II: d-amphetamine and l-amphetamine from two experimental formulations of the Capsules were compared with the marketed Adderall[R] Tablets in healthy adult subjects.

Figure 1.1
Mean Plasma Concentration (0 - 60 hours)
d-amphetamine
N=26

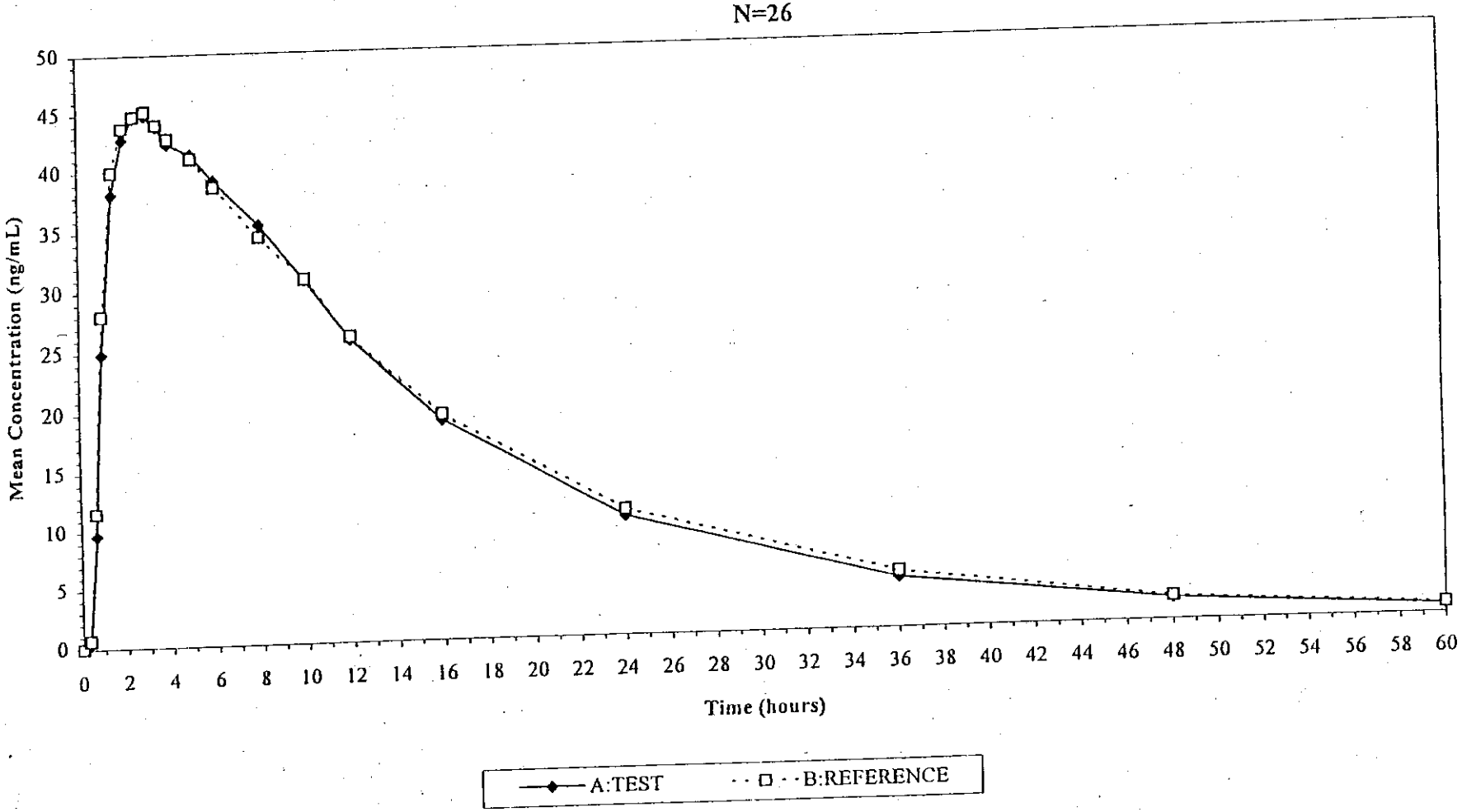


Figure 1.2

Mean Plasma Concentration (0 - 60 hours)

Semi-Logarithmic Scale

d-amphetamine

N=26

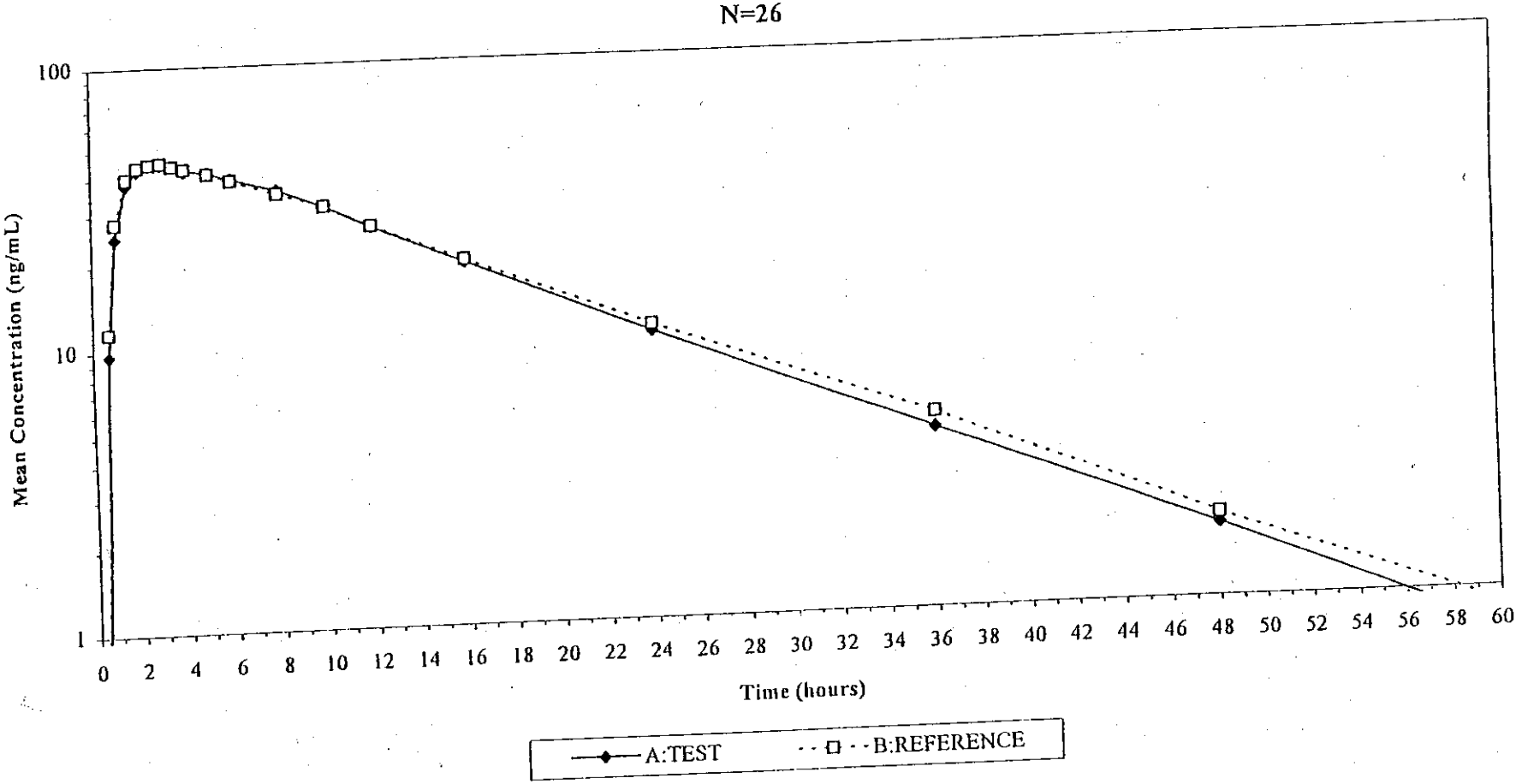


Figure 2.1

Mean Plasma Concentration (0 - 60 hours)

l-amphetamine

N=26

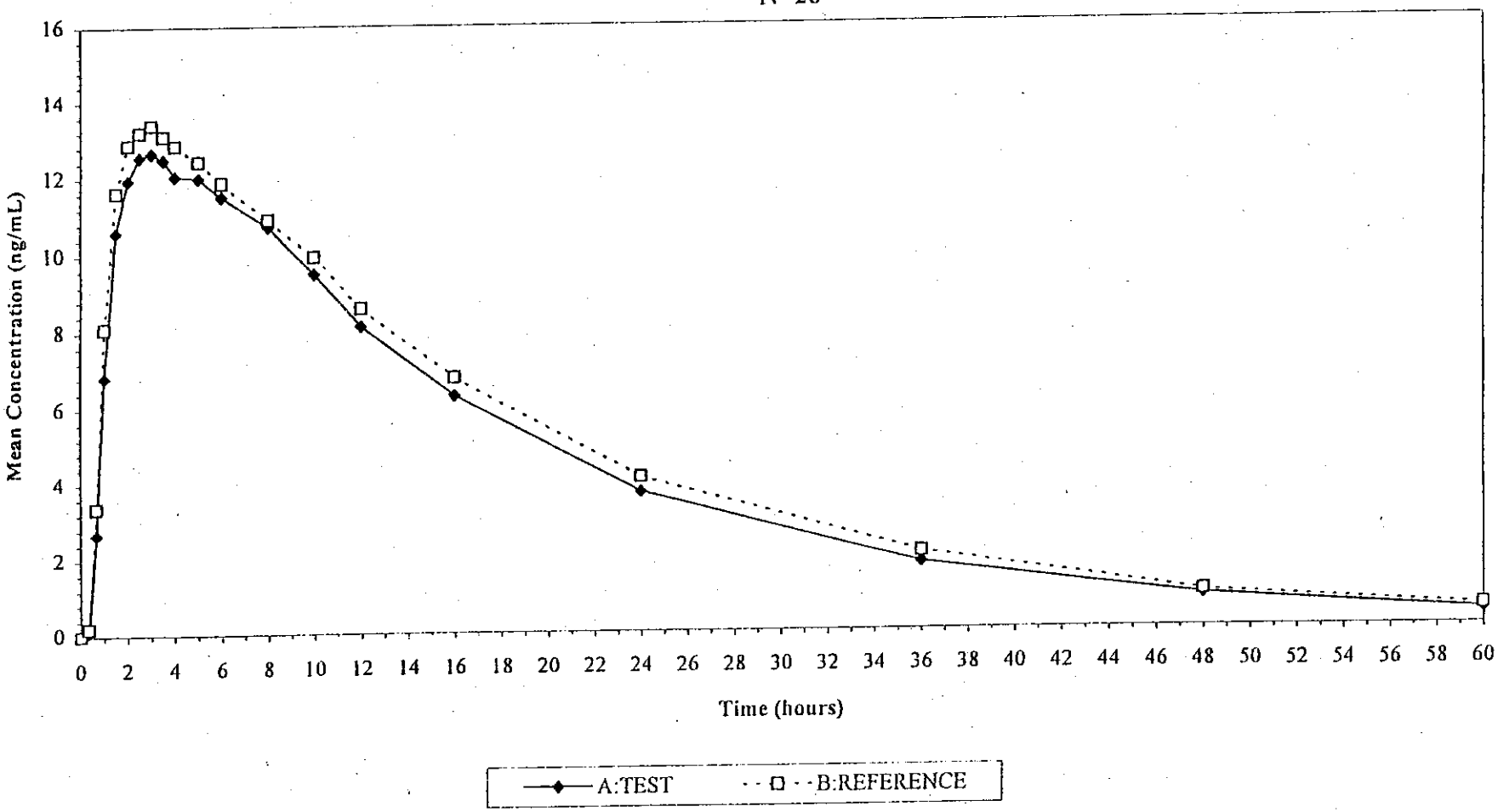
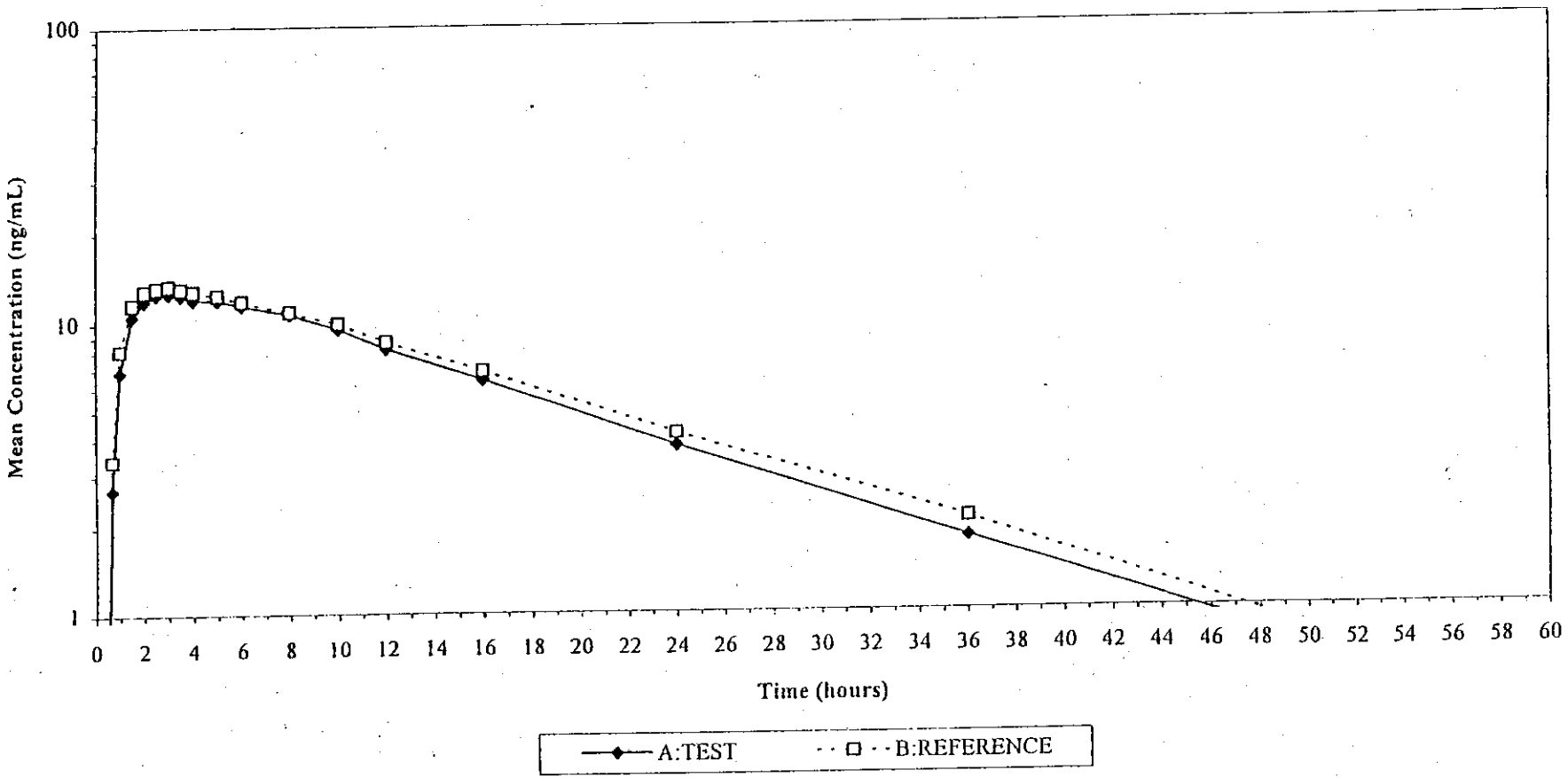


Figure 2.2
Mean Plasma Concentration (0 - 60 hours)
Semi-Logarithmic Scale
l-amphetamine
N=26



(Dextroamphetamine saccharate, Amphetamine aspartate, Dextroamphetamine sulfate, and Amphetamine sulfate tablets)
5 mg, 10 mg, 20 mg, and 30 mg
ANDA #40-422
Reviewer: F. Nouravarsani
40422STA.701

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
July 11, 2001

REVIEW OF AN AMENDMENT

The firm had previously submitted dissolution testing data for the reference listed product, 30 mg Adderall^{R} Tablets, lot B5233. This lot was not used for the bioequivalence study.

The firm was asked to submit dissolution testing data for the 30 mg Adderall^{R} Tablets using the lot that was used in the bioequivalence study.

RESPONSE:

The firm submitted dissolution testing data for lot B5426, which was used in the bioequivalence study. The method (USP 24) and results are shown in Table 1.

The dissolution testing data for both the test and reference products meet the specifications of: "NLT —— (Q) of the labeled amount of drug is dissolved in 45 minutes."

DEFICIENCY OF THE CURRENT SUBMISSION: None.

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Barr Laboratories, Inc. on its 30 mg —— Tablets (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate) (lot #309740003R) comparing it to Adderall^{R} Tablets, 30 mg (lot #B5426) by Shire Richwood Inc. is found acceptable by the Division of Bioequivalence.

2. The dissolution testing submitted by Barr Laboratories, Inc. on its ——— Tablets (dextroamphetamine sccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate), 5 mg (batch #309710003R), 10 mg (batch #309720004R), 20 mg (batch #309730003R), and 30 mg (batch #309740003R) comparing them to Adderall[R] Tablets, 5 mg (batch #0B5237), 10 mg (batch #B5246), 20 mg (batch #B5292), and 30 mg (batch #B5426), respectively, by Shire Richwood Inc. is found acceptable by the Division of Bioequivalence.

3. The waiver of in vivo bioequivalence study requirements is granted for the 5, 10, and 20 mg Tablets of the test products.

/S/ , 7/19/2001

Farahnaz Nouravarsani, Ph.D.
Review Branch III
Division of Bioequivalence

for RD INITIALED B. Davit
FT INITIALED B. Davit /S/ Date 7/19/01

Concur: /S/ Date 7/30/01
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

F. Nouravarsani/Draft: 07-17-2001/40422STA.701

TABLE 1:

DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)

Method:	**USP 24**
Analyte:	Amphetamine
Dosage Form and Strength:	Tablet, 30 mg
No. of Units Tested:	12 Tablets
Medium:	Water
Volume:	500 mL at 37° ± 0.5° C
Apparatus:	USP Apparatus 1 (Basket)
RPM:	100
Specifications:	NLT —— (Q) in 45 minutes

RESULTS:

%AMPHETAMINE DISSOLVED

	TEST PRODUCT, 30 MG BATCH NO. 309740003R TIME (MINUTES)					REFERENCE PRODUCT, 30 MG BATCH NO. B5426 (EXP. 05/02) TIME (MINUTES)			
	15	30	45	60		15	30	45	60
RANGE					**RANGE**				
MEAN	62	104	105	105	**MEAN**	101	102	102	103
RSD%	5.1	2.2	2.4	2.8	**RSD%**	1.2	1.4	1.0	1.2

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-422 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCTS: [redacted] (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets) 5 mg, 10 mg, 20 mg, and 30 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in the USP 24.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-422
DIVISION FILE
HFD-658/ F. Nouravarsani

Endorsements: (Final with Dates)
HFD-658/ F. Nouravarsani /S/ 7/19/2001
for HFD-658/ B. Davit /S/ 7/19/01
HFD-650/ D. Conner /S/ 7/30/01

V:\FIRMSAM\Barr\ltrs&rev\40422STA.701

Printed in final on 7/19/2001

BIOEQUIVALENCY - ACCEPTABLE **SUBMISSION DATE: 7/11/2001**

STUDY AMENDMENT (STA) **Strengths: All**

Outcome: AC

OUTCOME DECISION: AC - Acceptable

WINBIO COMMENTS:
Bio-study is acceptable.
Dissolution testing is acceptable.
Waiver for the lower strengths is granted.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 40-422 **SPONSOR:** Barr Laboratories, Inc.

DRUG AND DOSAGE FORM: ____™ (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets)

STRENGTHS: 5 mg, 10 mg, 20 mg, and 30 mg

TYPE OF STUDY: Fasting study for 30 mg strength

CLINICAL STUDY SITE: _____

ANALYTICAL SITE: _____

STUDY SUMMARY: acceptable.
DISSOLUTION TESTING: acceptable.
WAIVER: is granted for the 5, 10, and 20 mg.

DSI INSPECTION STATUS

Inspection needed: No.	Inspection status:	Inspection results:
First Generic __X___ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Farahnaz Nouravarsani, Ph.D. BRANCH: 3

INITIAL: /S/ DATE: 7/19/2001

TEAM LEADER: Barbara Davit, Ph.D. BRANCH: 3

for INITIAL: /S/ _____ DATE: 7/19/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ _____ DATE: 7/30/01

JUL - 3 2001

BIOEQUIVALENCY DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 40-422 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCTS: [redacted]
(dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets), 5 mg, 10 mg, 20 mg, and 30 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The dissolution testing data submitted by you for the Reference Listed Product, 30 mg Adderall^{R} Tablets, are unacceptable to the Division of Bioequivalence.

Please submit dissolution testing data for the same lot of the 30 mg Adderall^{R} Tablets which was used in the bioequivalence study.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-422
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-658/F. Nouravarsani

V:\FIRMSAM\Barr\ltrs&rev\40422STA.501

Printed in final on 6/14/2001

Endorsements: (Final with
HFD-658/F. Nouravarsani /S/ 6/14/2001
HFD-658/B. Davit /S/ 6/14/01
HFD-650/D. Conner /S/ 6/26/01

BIOEQUIVALENCY - DEFICIENCY

SUBMISSION DATES:
5/17/2001
6/08/2001

OK **1. STUDY AMENDMENT (STA)**

Strengths: 5, 10, 20, and 30 mg

Outcome: IC

OK **2. STUDY AMENDMENT (STA)**

Strengths: 5, 10, 20, and 30 mg

Outcome: IC

OUTCOME DECISION: IC

WINBIO COMMENTS: Bio-study was found acceptable. Dissolution testing was found unacceptable for the 30 mg strength. Waivers were not granted for the lower strengths.

BIOEQUIVALENCY AMENDMENT

ANDA 40-422

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL - 3 2001

TO: APPLICANT: Barr Laboratories, Inc. TEL: 845-353-8432

ATTN: Christine Mundkur FAX: 845-353-3859

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on May 17, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Dextroamphetamine Saccharate, Amphetamine Asparate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg.

Reference is also made to your amendment dated: June 8, 2001.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

[redacted]:
(dextroamphetamine saccharate,
Amphetamine aspartate,
Dextroamphetamine sulfate, and
Amphetamine sulfate tablets,
5 mg, 10 mg, 20 mg, and 30 mg)
ANDA #40-422
Reviewer: F. Nouravarsani
40422STA.501

Barr Laboratories, Inc.
Pomona, NY
Submission Dates:
5/17/2001
6/08/2001

REVIEW OF AMENDMENTS

BACKGROUND:

Barr Laboratories, Inc. had previously submitted a single-dose, fasting bioequivalence study conducted on 30 mg [redacted] Tablets and dissolution testing for review. The firm had requested a waiver of bioequivalence study requirements for its test products, 5, 10, and 20 mg [redacted] Tablets (submission dates: 10/31/2000 [Hard Copy] and 12/08/2000 [EVA]).

DEFICIENCIES AND RESPONSES:

1. Detailed information was requested regarding preparation of the standard concentration samples, quality control samples, special 1:1 ratio quality control samples, and the internal standard solution.

RESPONSE #1:

The firm provided the requested information.

2. The firm was asked to identify samples which were diluted (if any), the dilution factors, and results of the assay validations for the diluted samples.

RESPONSE #2:

The firm responded that there were no diluted samples in the study.

3. Analytical Raw Data was requested for the bioequivalence study in a Table presenting the Drug Area, Internal Standard Area, ratio of Drug Area to the Internal Standard Area, and the corresponding concentration for each assayed sample.

RESPONSE #3:

The firm submitted the Analytical Raw Data.

4. Dissolution testing data was requested using the method listed in the USP 24 for Amphetamine Sulfate Tablets and d-Amphetamine Sulfate Tablets.

RESPONSE #4:

The firm submitted dissolution testing data using the method listed in the USP 24 for Amphetamine Sulfate Tablets and d-Amphetamine Sulfate Tablets. The method and results are shown in Table 1.

COMMENTS TO THE RESPONSE #4:

1. The dissolution testing data for both the test and reference products meet the specifications of: "NLT [redacted] (Q) of the labeled amount of drug is dissolved in 45 minutes."

2. Lot B5233 was used for the dissolution testing for 30 mg Adderall^{R} Tablets. This lot is not the same lot, which was used in the bioequivalence study.

3. The firm was contacted by a telephone communication from DBE on June 07, 2001, and was asked to clarify the reason(s) that a different lot than the one used in the bioequivalence study was used for the dissolution testing of the 30 mg Adderall^{R} Tablets.

The firm responded that "Lot #B5233 was tested using the dissolution method requested in the bioequivalence amendment prior to the selection of the Bio lot."

DEFICIENCY OF THE CURRENT SUBMISSION:

The firm should submit dissolution testing data for the 30 mg Adderall^{R} Tablets using the same lot, which was used in the bioequivalence study.

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Barr Laboratories, Inc. on its 30 mg [redacted] Tablets (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate)

(lot #309740003R) comparing it to Adderall[R] Tablets, 30 mg (lot #B5426) by Shire Richwood Inc. is found acceptable by the Division of Bioequivalence.

2. The dissolution testing submitted by Barr Laboratories, Inc. on its ——— Tablets (dextroamphetamine sccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate), 5 mg (batch #309710003R), 10 mg (batch #309720004R), and 20 mg (batch #309730003R) comparing them to Adderall[R] Tablets, 5 mg (batch #0B5237), 10 mg (batch #B5246), and 20 mg (batch #B5292), respectively, by Shire Richwood Inc. is found acceptable by the Division of Bioequivalence.

3. The dissolution testing submitted by Barr Laboratories, Inc. on its ——— Tablets (dextroamphetamine sccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate), 30 mg (batch #309740003R) comparing it to Adderall[R] Tablets, 30 mg (lot #B5233) by Shire Richwood Inc. is found unacceptable by the Division of Bioequivalence.

4. The firm should be informed of the DEFICIENCY.

/S/ , 6/14/2001

Farahnaz Nouravarsani, Ph.D.
Review Branch III
Division of Bioequivalence

/S/ 6/14/01

RD INITIALED B. Davit
FT INITIALED B. Davi /S/ Date 6/14/01

Concur: /S/ Date 6/26/01

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

F. Nouravarsani/Draft: 06-11-2001/40422STA.501

TABLE 1:

DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)

Method:	**USP 24**
Analyte:	Amphetamine
Dosage Form and Strengths:	Tablets, 5, 10, 20, and 30 mg
No. of Units Tested:	12 Tablets
Medium:	Water
Volume:	500 mL at 37° ± 0.5° C
Apparatus:	USP Apparatus 1 (Basket)
RPM:	100
Specifications:	NLT — (Q) in 45 minutes

RESULTS:

%AMPHETAMINE DISSOLVED

TEST PRODUCT, 5 MG BATCH NO. 309710003R TIME (MINUTES)					REFERENCE PRODUCT, 5 MG BATCH NO. 0B5237 (EXP. 1/2002) TIME (MINUTES)				
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	96	101	101	101	MEAN	96	102	102	102
RSD%	8.7	4.5	4.7	4.6	RSD%	8.2	1.1	1.4	1.3

%AMPHETAMINE DISSOLVED

TEST PRODUCT, 10 MG BATCH NO. 309720004R TIME (MINUTES)					REFERENCE PRODUCT, 10 MG BATCH NO. B5246 (EXP. 2/2002) TIME (MINUTES)				
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	86	101	101	101	MEAN	83	103	104	104
RSD%	10.4	2.2	1.9	2.1	RSD%	11.4	1.0	1.1	1.0

%AMPHETAMINE DISSOLVED

	TEST PRODUCT, 20 MG BATCH NO. 309730003R TIME (MINUTES)					REFERENCE PRODUCT, 20 MG BATCH NO. B5292(EXP. 02/02) TIME (MINUTES)			
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	87	100	100	100	MEAN	100	99	100	100
RSD%	8.9	1.2	1.3	1.4	RSD%	1.7	1.6	1.6	1.5

%AMPHETAMINE DISSOLVED

	TEST PRODUCT, 30 MG BATCH NO. 309740003R TIME (MINUTES)					REFERENCE PRODUCT, 30 MG BATCH NO. B5233 (EXP. 01/02) TIME (MINUTES)			
	15	30	45	60		15	30	45	60
RANGE					RANGE				
MEAN	65	98	99	99	MEAN	100	100	100	100
RSD%	7.4	2.1	2.1	2.3	RSD%	1.1	1.0	1.1	1.0

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 40-422 **SPONSOR:** Barr Laboratories, Inc.

DRUG AND DOSAGE FORM: ~~[redacted]~~ (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets)

STRENGTHS: 5 mg, 10 mg, 20 mg, and 30 mg

TYPE OF STUDY: Fasting study for 30 mg strength

CLINICAL STUDY SITE: ~~[redacted]~~

ANALYTICAL SITE: ~~[redacted]~~

STUDY SUMMARY: acceptable.
DISSOLUTION TESTING: acceptable.
WAIVER: is granted for the 5, 10, and 20 mg.

DSI INSPECTION STATUS

Inspection needed: No.	Inspection status:	Inspection results:
First Generic __X___ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Farahnaz Nouravarsani, Ph.D. BRANCH: 3

INITIAL: /S/ DATE: 7/19/2001

TEAM LEADER: Barbara Davit, Ph.D. BRANCH: 3

for INITIAL: /S/ _____ DATE: 7/19/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ _____ DATE: 7/30/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-422

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-422 Date of Submission: October 31, 2000

Applicant's Name: Barr Laboratories, Inc.

Established Name: Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, & Amphetamine Sulfate, 5 mg , 10 mg, 20 mg, & 30 mg of the combined salts.

Proprietary name: ' ——— '

Labeling Deficiencies:

1. GENERAL COMMENTS:

   Your proposed proprietary name ' ——— ' will be forwarded to the Office of Post-marketing Drug Risk Assessment (OPDRA) for their review and comments. We defer final comments on your proposed proprietary name pending notification of the findings of OPDRA.

2. CONTAINER – 50s, 100s, & 500s

   a. Revise the phrase ' ——— ' to read "Usual Adult Dosage"

   b. Add "[See USP]" to the storage temperature statement.

   c. We strongly recommend that you further differentiate the expression of the strengths using different background color and/or any other means, between 5 mg & 10 mg, and 20 mg & 30 mg.

3. INSERT

   a. GENERAL

      Since you have elected to use a proprietary name throughout the insert labeling, we would like to remind you that the requirements of 21 CFR 201.10(g)(1) must be met. [*i.e.* The established name is to appear at least once in each column in association with the proprietary name.]

   b. TITLE

      We encourage the relocation of "Rx only" to appear immediately beneath the title.

   c. DESCRIPTION

      Revise to read "corn starch" and relocate alphabetically.

   d. INDICATIONS AND USAGE

      ...amphetamine sulfate tablets) is indicated...

e. PRECAUTIONS (Drug Interactions)

i. Haloperidol – Revise to read:

...blocks dopamine and norepinephrine reuptake, thus...

ii. Delete the subsection "[redacted]" in its entirety.

f. HOW SUPPLIED

...amphetamine sulfate tablets) is available as:

Please revise your labels and labeling, as instructed above, and submit in draft. We will not request final printed labeling until we are able to provide adequate resolution for your proposed proprietary name.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-422

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 4, 2002

NEW CORRESP NC

By Hand Delivery

Confidential & Proprietary

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: ANDA 40-422: Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate & Amphetamine Sulfate Tablets 5mg, 10mg, 20mg & 30mg: Barr Laboratories, Inc.

Reference is made to Barr Laboratories, Inc.'s ("Barr") Abbreviated New Drug Application No. 40-422 ("ANDA"), submitted October 31, 2000 under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("the Act").

On December 26, 2001, the agency received a Citizen Petition from Alan Minsk of Arnall Golden Gregory, LLP ("petitioner") requesting that ANDA applicants be required to conduct certain additional testing to establish equivalence of their proposed product to the Reference Listed Drug ("RLD"), Adderall®. Specifically, the petition suggests that "sameness" of the generic drug and the RLD include the traditional pharmacokinetic parameters of both the d- and l-isomers of amphetamine, as well as the early partial AUC and rate of absorption for both isomers during the absorption phase.

Regardless of the scientific validity and appropriateness of the petitioner's requests, Barr hereby voluntarily submits additional data and information to the agency that unequivocally establishes that Barr's product meets the suggested, additional approval standards set forth in the December petition. Barr specifically refers the agency to the bioequivalence section of its original application (6-0090 et al) containing the applicable pharmacokinetic summary, data sets and corresponding traditional statistical analyses for the d- and l- isomers of amphetamine. Barr also refers the agency to the enclosed report compiled by Dr. Sanford Bolton addressing the petitioner's assertions regarding rate of absorption and partial AUC issues. See *Report on Evaluation of Early Time Points In Study R00-456 Comparing Reference Listed Drug, Adderall 30mg, to Barr's Generic Product.* This report clearly demonstrates that: (1) the rate of absorption of Barr's product is similar to, and no greater than, the RLD, and (2) the two products have

similar pharmacokinetic characteristics during the early absorption phase, as they do throughout the conventional pharmacokinetic profile. This submission, in conjunction with Barr's original bioequivalence data, underscores the point that Barr's product should provide the same safety and efficacy profile as that of the RLD. Given this information, Barr respectfully requests that the agency immediately approve ANDA 40-422.

Barr, however, asserts that neither the agency, nor any other state regulatory or formulary body, should construe this data submission as acquiescence to, or concurrence of the scientific validity and appropriateness of the petitioner's suggested approval criteria. Rather, Barr has merely determined that because Barr's product clearly meets the petitioner's suggested, heightened approval criteria, submission of this data package provides the most expeditious resolution of this matter. Should any future issues arise with respect to this application or any other, Barr reserves the right to challenge the scientific validity and appropriateness of the petitioner's suggested approval criteria at that time.

The enclosed data and information responds completely to all of the issues raised by the petitioner. As such, Barr requests immediate approval of the above referenced ANDA.

Thank you for your prompt attention to this matter.

Sincerely,

Christine Mundkur, Esq.
Senior Vice President of Quality &
Regulatory Affairs

cc: Celicia Parise (OGD) (*via hand delivery*)

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 5, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attn: Mark Anderson
Project Manager, Team 6, Division of Chemistry II

NEW CORRESP

VIA FACSIMILE: (301) 443-3839
ORIGINAL VIA FEDERAL EXPRESS

TELEPHONE AMENDMENT

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg.

Reference is also made to the phone conversation between Mark Anderson, Project Manager, Team 6, Division of Chemistry II, OGD and Christine Mundkur, Vice President of Quality and Regulatory Counsel, Barr Laboratories, Inc. on October 4, 2001. Per FDA request, Barr commits to resolve any issues with method validation that the Agency may have regarding this non-compendial product, since the FDA laboratory review will not be completed prior to approval.

An Identical copy of this Telephone Amendment has been sent to the New Jersey and Baltimore district offices of the FDA. A document certification is attached. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

cc: New Jersey and Baltimore District Offices

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 10 2001
OGD

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 11, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT

AB

BIOEQUIVALENCY AMENDMENT

REFERENCE: **ANDA 40-422 — (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets), 5 mg, 10 mg, 20 mg, and 30 mg**

Reference is made to our Abbreviated New Drug Application submitted on October 31, 2000 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for — (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets), 5 mg, 10 mg, 20 mg, and 30 mg.

Reference is also made to the July 03, 2001 Bioequivalency deficiency letter. The deficiency identified in the comment letter and Barr's response are as follows:

COMMENT 1:

The dissolution testing data submitted by you for the Reference Listed Product, 30 mg Adderall® Tablets, are unacceptable to the Division of Bioequivalence.

Please submit dissolution testing data for the same lot of the 30 mg Adderall® Tablets which was used in the bioequivalence study.

RESPONSE:

Barr acknowledges the Agency's request. Enclosed please find a copy of the Dissolution Testing Report for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets, 30 mg which compares Shire Richwood's Adderall Tablets® 30 mg (bio lot # B5426) to Barr's submission batch (Batch No. 309740003R) using the dissolution conditions described in USP 24 for the Amphetamine Sulfate Tablets, USP and Dextroamphetamine Sulfate Tablets USP monographs.

This completes the present Bioequivalency Amendment in response to the Agency's letter dated July 03, 2001. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

JUL 12 2001
OGD
EVALUATION AND RESEARCH

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

This submission is comprised of **Pages 1 through 9.**

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

June 8, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attention: Steven Mazzella

ORIG AMENDMENT
N/AB

BIOEQUIVALENCY PHONE AMENDMENT

REFERENCE: ANDA 40-422
(dextroamphetamine saccharate, amphetamine aspartate, Dextroamphetamine sulfate, and amphetamine sulfate tablets), 5 mg, 10 mg, 20 mg, and 30 mg

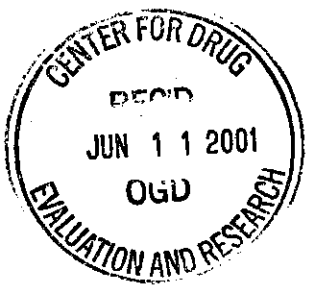
Reference is made to Barr's pending Abbreviated New Drug Application ("ANDA") dated October 31, 2000 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg).

Reference is also made to the phone message left by Steven Mazzella, Division of Bioequivalence, OGD, for Christine Mundkur, Vice President of Quality and Regulatory Counsel, Barr Laboratories on June 7, 2001.

As per the Agency's comments we are responding to the issue that Adderall® 30 mg, Lot #B5233 was used for the dissolution studies in our response dated May 17, 2001 to the Bioequivalency Amendment instead of Adderall® Lot #B5426, which was used in the Biostudy presented in the original application. Please be advised that Lot #B5233 was tested using the dissolution method requested in the bioequivalence amendment prior to the selection of the Bio lot. The report included with our May 17 response is dated May 17, 2001 because this is the date that the report was generated and is not reflective of the date that the data was generated.

This completes the present Bioequivalency Telephone Amendment in response to the message left on June 7, 2001. If you have any questions concerning this correspondence, please contact me at (845) 353-8432 or by fax at (845) 353-3859.

A hard copy of this telephone amendment will follow by courier.



Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 17, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AB

BIOEQUIVALENCY AMENDMENT

REFERENCE: **ANDA 40-422**
——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets), 5 mg, 10 mg, 20 mg, and 30 mg

Reference is made to our Abbreviated New Drug Application submitted on October 31, 2000 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ← (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets), 5 mg, 10 mg, 20 mg, and 30 mg.

Reference is also made to the April 30, 2001 Bioequivalency deficiency letter. The deficiencies identified in the comment letter and Barr's responses are as follows:

COMMENT 1:

Please submit detailed information (SOPs) regarding preparation of the standard concentration samples, quality control samples, special 1:1 ratio quality control samples, and the internal standard solution.

RESPONSE:

A copy of the test method (TM-482, revision original) that was used to complete the validation of the method and the samples analyses is included in Attachment I for your review. All copies of the test method used for daily analysis runs by ——— are numbered, logged, and must be accounted for. Therefore, copies submitted for review purposes only are stamped "unofficial copy". Preparations of all solutions normally used in the assay are included in the method. The preparation of the special 1:1 ratio quality control samples is included on a comment form archived with the validation. A copy of this form is also provided in Attachment II.

COMMENT 2:

Please identify samples which were diluted (if any) and the dilution factors. Results of the assay validations for the diluted samples should be also submitted.

RESPONSE:

There were no diluted samples in the study.

REFERENCE: ANDA 40-422
(dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets), 5 mg, 10 mg, 20 mg, and 30 mg

COMMENT 3:

Please submit the Analytical Raw Data for Study R00-456 summarized in a Table presenting the Drug Area, Internal Standard Area, ratio of Drug Area to the Internal Standard Area, and the corresponding concentration for each assayed sample.

RESPONSE:

Barr acknowledges the Agency's comment. Raw data worksheets for each analytical run, which include the drug area, internal standard area, ratio of the drug area to the internal standard area, and the corresponding concentration for each assayed sample, are archived with the study. Please see Attachment III for a copy of each raw data worksheet for R00-456.

COMMENT 4:

Please submit dissolution testing data using the method listed in the USP 24 for Amphetamine Sulfate Tablets and d-Amphetamine Sulfate Tablets.

RESPONSE:

Barr acknowledges the Agency's comments. Please see Attachment IV for dissolution testing data using the method listed in USP 24 for Amphetamine Sulfate Tablets and d-Amphetamine Sulfate Tablets.

This completes the present Bioequivalency Amendment in response to the Agency's letter dated April 30, 2001. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

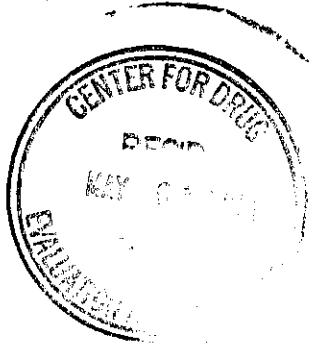
This submission is comprised of **Pages 1 through 118.**

labeling review drafted 5/25/01 /S/

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 2, 2001



Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
7pl
N/AC

MAJOR AMENDMENT

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

Reference is made to our Abbreviated New Drug Application submitted on October 31, 2000 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg.

Reference is also made to the March 19, 2001 Major Deficiency letter. The deficiencies identified in the comment letter and Barr's responses are as follows:

A. Deficiencies:

COMMENT 1:

In the components section it appears that the weight of drug substance used for each strength is inconsistent with regard to significant figures. Please clarify.

RESPONSE:

The composition statement as provided in our original application is based on the label claim for the active ingredients and the theoretical amounts of each ingredient in the unit dose. For example, the label claim for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg is "5 mg" not ' ——— (1.25 mg of each active ingredient) and the label claim for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 30 mg is "30 mg" not ' ——— ("7.5 mg" not ——— mg of each active ingredient). The composition statement for mg/dose is used to calculate the batch formulation that specifies amounts of each ingredient to be weighed out for the batch. Therefore, it is the batch formulation that is specified in significant figures, not the composition statement for mg/dose.

COMMENT 2:

Similarly, the specified weight of ——— used for each strength appears inconsistent with regard to significant figures. Please clarify.

RESPONSE:

Again, the composition statement as provided in our original application is based on the theoretical amounts of each ingredient in the unit dose. The composition statement for mg/dose is used to calculate the batch formulation that specifies amounts of each ingredient to be weighed out for the batch. Therefore, it is the batch formulation that is specified in significant figures, not the composition statement for mg/dose.

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

COMMENT 3:

Please include an [redacted] test in your acceptance criteria for Amphetamine Sulfate USP and Dextroamphetamine Sulfate USP.

RESPONSE:

Barr acknowledges the FDA's comment and has added an [redacted] test to the Raw Material Specifications and Test Record and the Acceptance Tests for the Amphetamine Sulfate, USP and Dextroamphetamine Sulfate, USP Raw Materials.

Please see ATTACHMENT I for the following:

- Revised Blank Raw Material Specifications and Test Record for Amphetamine Sulfate, USP.
- Revised Blank Raw Material Specifications and Test Record for Dextroamphetamine Sulfate, USP.
- Executed Raw Material Specifications and Test Record for Amphetamine Sulfate, USP.
- Executed Raw Material Specifications and Test Record for Dextroamphetamine Sulfate, USP.
- Acceptance Tests for Raw Materials (RM-377A) for Amphetamine Sulfate, USP with the proposed [redacted] method.
- Acceptance Tests for Raw Materials (RM-338I) for Dextroamphetamine Sulfate, USP with the proposed [redacted] method.

COMMENT 4:

[redacted]

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

COMMENT 5:

A specification for pH should be included on your acceptance criteria for Dextroamphetamine Saccharate, Amphetamine Aspartate, and Amphetamine Sulfate, USP.

RESPONSE:

Barr acknowledges the FDA's comment. Barr worked with the vendor to develop specifications and test procedures for pH. Both Barr and Johnson Matthey have incorporated these specifications and test procedures for pH into the Raw Material Specifications and Test Record and the Acceptance Tests for the Dextroamphetamine Saccharate, Amphetamine Aspartate, and Amphetamine Sulfate, USP Raw Materials.

Please see ATTACHMENT I for the following:

- Revised Blank Raw Material Specifications and Test Record for Dextroamphetamine Saccharate.
- Revised Blank Raw Material Specifications and Test Record for Amphetamine Aspartate.
- Revised Blank Raw Material Specifications and Test Record for Amphetamine Sulfate, USP.
- Executed Raw Material Specifications and Test Record for Dextroamphetamine Saccharate.
- Executed Raw Material Specifications and Test Record for Amphetamine Aspartate.
- Executed Raw Material Specifications and Test Record for Amphetamine Sulfate, USP.
- Acceptance Tests for Raw Materials (RM-376D) for Dextroamphetamine Saccharate, USP with the proposed pH method.
- Acceptance Tests for Raw Materials (RM-378D) for Amphetamine Aspartate, USP with the proposed pH method.
- Acceptance Tests for Raw Materials (RM-377A) for Amphetamine Sulfate, USP with the proposed pH method.

COMMENT 6:

Please include a test in your drug substance acceptance criteria that adequately demonstrates that Amphetamine Aspartate is optically inactive.

RESPONSE:

Barr disagrees with the Agency's comment. Amphetamine Aspartate is not optically inactive. This compound consists of two parts: one part amphetamine and one part 1-(+)aspartic acid. The amphetamine anion in amphetamine aspartate is optically inactive. Its counterion, aspartic acid, is optically active, +23°. The resulting specific rotation is not simply a sum of the parts but a function of the molecule itself. According to the drug substance manufacturer, the starting material for the synthesis of amphetamine aspartate is amphetamine sulfate, which is optically inactive and does not undergo racemization under the reactions.

Barr included a specific rotation test in the Amphetamine Aspartate, USP Acceptance Tests for Raw Materials (RM-378D) as an identification test, per USP General Chapter <781>. The specification has been set at [redacted] C based on the data obtained by the drug substance manufacturer.

Redacted 7

pages of trade secret and/or confidential commercial information

REFERENCE: ANDA 40-422
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

RESPONSE:

Acknowledged. Per a phone conversation between Mark Anderson of the FDA and Joseph Greer of Barr Laboratories, Inc. on 05/01/01, bioequivalence comments are forthcoming from the Agency.

In addition, the following LABELING DEFICIENCIES were received:

1. **GENERAL COMMENTS:**

   Your proposed proprietary name " ——— " will be forwarded to the Office of Post-Marketing Drug Risk Assessment (OPDRA) for their review and comments. We defer final comments on your proposed proprietary name pending notification of the findings of OPDRA.

2. **CONTAINER – 50s, 100s, & 500s**

   a. **Revise the phrase " ——— " to read "Usual Adult Dosage"**
   b. **Add "[See USP]" to the storage temperature statement.**
   c. **We strongly recommend that you further differentiate the expression of the strengths using different background color and/or any other means, between mg & 10 mg, and 20 mg & 30 mg.**

3. **INSERT**

   a. **GENERAL**
      Since you have elected to use a proprietary name throughout the insert labeling, we would like to remind you that the requirements of 21 CFR 201.10(g)(1) must be met. [i.e. The established name is to appear at least once in each column in association with the proprietary name.]
   b. **TITLE**
      We encourage the relocation of "Rx only" to appear immediately beneath the title.
   c. **DESCRIPTION**
      Revise to read "corn starch" and relocate alphabetically.
   d. **INDICATIONS AND USAGE**
      ...amphetamine sulfate tablets) is indicated...
   e. **PRECAUTIONS (Drug Interactions)**
      i. **Haloperidol – Revise to read:**
         ...blocks dopamine and norepinephrine reuptake, thus...
      ii. **Delete the subsection " ——— in its entirety.**
   f. **HOW SUPPLIED**
      ...amphetamine sulfate tablets) is available as:

RESPONSE

Barr acknowledges the Agency's request for revising labeling. Revised final print labeling are provided under Attachment VI. In addition, side by side comparisons of the proposed labeling with that of the previously submitted labeling are also provided.

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

Identical copies of this amendment have been sent to the New Jersey and Baltimore district offices of the FDA. A document certification is attached.

If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 12, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MA ORIG AMENDMENT AA

AMENDMENT TO PENDING APPLICATION

REFERENCE: **Abbreviated New Drug Application**
ANDA No. 40-422
[redacted] (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

Reference is made to Barr's pending Abbreviated New Drug Application ("ANDA") dated October 31, 2000 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for [redacted] (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg).

Reference is also made to a January 29, 2001 phone conversation between Ruby Yu, Project Manager, OGD FDA, Dave Gill, Ph.D., Team Leader, Team IV, Div. of Chemistry I, OGD FDA, and Christine Mundkur, Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc. regarding Barr's testing for [redacted] Barr agreed to change their testing limits for [redacted] for all original applications pending approval and for future applications where [redacted] is applicable.

As a result of this conversation, Barr has changed their testing for [redacted] for this product to the following specifications:

Test	Limits
[redacted]	• 3 samples: Between [redacted] • RSD NMT [redacted]
	• 10-12 samples between [redacted] • Mean: 90.0-110.0%* • RSD NMT [redacted]

* of labeled [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 13 2001
OGD

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

Abbreviated New Drug Application
(dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

Attached please find Barr's updated In-Process and Finished Product Test Method, TM-477D and corresponding quality control analytical specification test records.

An identical copy of this Amendment has been provided to the New Jersey and Baltimore District Field Offices. A document certification is attached.

If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

This submission is comprised of Pages 1 through 48

cc: New Jersey and Baltimore District Field Offices

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

December 8, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

40-422 /S/ 12/22/00

NEW CORRESP

NC

REFERENCE: **Amendment to Pending ANDA**
——— [1] (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

CMC and BA/BE Electronic Submission

Reference is made to our Abbreviated New Drug Application submitted October 31, 2000 under 505(j) of the Food, Drug and Cosmetic Act for ——— [1] **(dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)**.

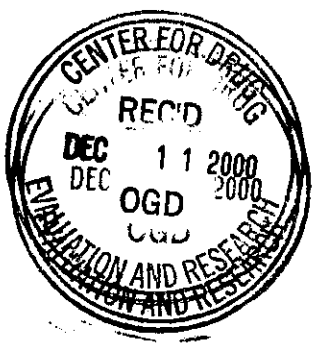
As indicated in our original application, Barr Laboratories, Inc. is amending the above referenced application to provide the CMC and BA/BE electronic submission. The CMC and BA/BE electronic submissions are contained on separate diskettes labeled " CMC ESD & Companion Document" and BA/BE ESD" respectively. Backup diskettes containing identical information for both the CMC section and the BA/BE section are also provided.

The CMC ESD file is named "BRL0017.003" and the MicroSoft Word Companion Document file is named "BRL0017.004". The BA/BE ESD is named "BRL0013.001" and the Microsoft Word Companion Document files are named "BRL0013.002a and BRL0013.002b".

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

A copy of this letter has been forwarded to the Baltimore District Office.

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.



Sincerely,

BARR LABORATORIES, INC.

Joseph Green (for)

Christine Mundkur
Vice President, Quality and Regulatory Counsel

40-422

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 29, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attention: Saundra Middleton, Project Manager

NEW CORRESP
NC

/S/
NAT
12/6/00

VIA FACSIMILE: (301) 594-1174
ORIGINAL VIA FEDERAL EXPRESS

TELEPHONE CORRESPONDENCE

REFERENCE: **Abbreviated New Drug Application**
——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

Reference is made to Barr's pending Abbreviated New Drug Application ("ANDA") dated September 4, 2000 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg).

Reference is also made to the phone conversation between Saundra Middleton, Project Manager, Regulatory Support Branch, OGD and Christine Mundkur, Vice President of Quality and Regulatory Counsel, Barr Laboratories on November 29, 2000.

As per the Agency's instructions, Barr is correcting the 356h form to state Shire Richwood's Adderall® as the reference listed drug.

Identical copies of this Telephone Correspondence have been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes the present Telephone Correspondence to Barr's pending ANDA. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 30 2000
OGD

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

This submission is comprised of **Pages 1 through 5**.

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 14, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attn: Mark Anderson
Project Manager, Team 6, Division of Chemistry II

N/AMA
ORIG AMENDMENT

VIA FACSIMILE: (301) 443-3839
ORIGINAL VIA FEDERAL EXPRESS

TELEPHONE AMENDMENT

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg.

Reference is also made to the phone conversation between Mark Anderson, Project Manager, Team 6, Division of Chemistry II, OGD and Christine Mundkur, Vice President of Quality and Regulatory Counsel, Barr Laboratories, Inc. on November 5, 2001. Per the phone conversation, the FDA has requested the following:

[redacted]

Vendor Lot #	Barr Lot #	Melting Range °C	Notebook Ref	Test Date
B1097-990901	LC10083		B2507/p.282	11/14/01
B1097-991001	LC10084		B2507/p.278	11/14/01
B1097-991001	LC10088		B2507/p.279	11/14/01
B1097-991002	LC10089		B2507/p.280	11/14/01
B1097-011001	LC10094		B2507/p.281	11/14/01

Please see Attachment I for the following:

- **Revised Blank Raw Material Specifications and Test Record**

2.

Please see Attachment II for the following:

- **Current Revised Blank Finished Product and Stability Specifications and Test Records.**

An Identical copy of this Telephone Amendment has been sent to the New Jersey and Baltimore district offices of the FDA. A document certification is attached. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and Regulatory Counsel

cc: New Jersey and Baltimore District Offices

Noted:
To Scott Furness

/S/ 11/31/01

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 31, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/AM
ORIG AMENDMENT

MINOR AMENDMENT

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg

Reference is made to our Abbreviated New Drug Application submitted on October 31, 2000 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg.

Reference is also made to the August 21, 2001 Minor deficiency letter. The deficiencies identified in the comment letter and Barr's response are as follows:

A. Deficiencies

[redacted]

COMMENT 2:

Acceptable room temperature stability study conditions are either 25-30°C/ambient humidity or 25°C ± 2° C/60% RH ± 5 % RH and acceptable accelerated stability conditions are 40°C ± 2°C/75% RH ± 5 % RH. Although your stability protocol included those conditions, please include the appropriate temperature and humidity ranges on your stability report forms.

RESPONSE 2:

The referenced room temperature stability and accelerated stability conditions have been incorporated in our Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg Stability Testing Summaries. Please see Attachment II for the updated stability reports.

COMMENT 3:

Please include the manufacturer of the drug substances and the corresponding lot (s) used on your drug product stability report forms.

RESPONSE 3:

The manufacturer and the corresponding lot (s) have been incorporated into our uupdated stability Summary Testing Summaries. Please refer again to Attachment II for the updated stability reports.

COMMENT 4:

Please update your list of test methods for drug product release and stability to include the dissolution methodology approved by the Division of Bioequivalence in your 7/11/01 amendment.

RESPONSE 4:

Barr acknowledges the Agency's comment. The test methods and drug product release specifications have been updated to reflect the change in the dissolution methodology as approved by the Division of Bioequivalence in the 7/11/01 amendment. The updated methods and specification sheets are provided in Attachment III.

A. **In addition to responding to the deficiencies presented above, please note and acknowledge The following comment in your response:**

COMMENT 1:

The Drug Master Files (DMFs) [redacted] have been reviewed and remain inadequate. The DMF holders have been informed of the deficiencies. Please be aware that the application cannot be approved until the deficiencies regarding these DMFs have been addressed satisfactorily by the holders.

RESPONSE 1:

Barr acknowledges that the DMFs remain inadequate [redacted] is diligently working to respond to the deficiencies and will do so in a timely manner.

COMMENT 2:

Please provide updated long-term stability data using the dissolution methodology submitted in your 7/11/01 amendment.

RESPONSE 2:

The updated long-term stability data using the dissolution methodology submitted in the 7/11/01 amendment is provided in Attachment II.

COMMENT 3:

Please acknowledge that a satisfactory methods evaluation and validation for the methods used to analyze the drug product is required to support the ANDA.

RESPONSE 3:

Barr acknowledges that a satisfactory methods evaluation and validation for the methods used to analyze the drug product is required to support the ANDA. All reports will be made available to the field investigators during inspections.

Identical copies of this amendment have been sent to the New Jersey and Baltimore district offices of the FDA. A document certification is attached.

If you have any questions concerning this correspondence, please contact me by phone (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice Presidient, Quality and Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 31, 2001

William L. Bargo
Baltimore District
Food and Drug Administration
900 Madison Avenue
Baltimore, Maryland 21201

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg
MINOR AMENDMENT (Field Copy)

In accordance with 21 CFR §314.96 (b), Barr Laboratories, Inc. is submitting a Field Copy of an Amendment to the pending Abbreviated New Drug Application filed under § 505 (j) of the Federal Food, Drug and Cosmetic Act for the above referenced product.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and Regulatory Counsel

Barr Laboratories, Inc.

Document Certification

Barr Laboratories, Inc. hereby certifies that field copies of this Minor Amendment for **Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg** are being submitted to the New Jersey and Baltimore district offices of the FDA. Barr Laboratories, Inc. further certifies that the field copies are true copies of the material submitted to the Agency.

Christine Mundkur
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

8/31/01
Date

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 31, 2001

Regina Brown
Pre-Approval Coordinator
Food and Drug Administration
120 North Center Drive
North Brunswick, NJ 08902

REFERENCE: **ANDA 40-422**
Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg, and 30 mg
MINOR AMENDMENT (Field Copy)

In accordance with 21 CFR §314.96 (b), Barr Laboratories, Inc. is submitting a Field Copy of an Amendment to the pending Abbreviated New Drug Application filed under § 505(j) of the Federal Food, Drug and Cosmetic Act for the above referenced product.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and Regulatory Counsel

150

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 1, 2000

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

40-420

NEW CORRESP
NC/BIO

CORRESPONDENCE

REFERENCE: **Abbreviated New Drug Application**
——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

Reference is made to our Abbreviated New Drug Application for ——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg) submitted on October 31, 2000.

During the submission of the original application, the diskette containing data regarding the Bioequivalence study was inadvertently left out. Attached please find two (2) copies of the diskette for your review.

We apologize for any inconvenience that this may have caused. If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Joseph Green (By)
Christine Mundkur
Vice President, Quality and Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV - 2 2000
OGD

ANDA 40-422

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. BOX 2900
Pomona, NY 10970-0519

NOV 30 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated November 29, 2000 and your correspondence dated November 29, 2000.

NAME OF DRUG: Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate Tablets, 5 mg, 10 mg, 20 mg and 30 mg (Mixed salts)

DATE OF APPLICATION: October 31, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 1, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

/S/ for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-422
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSR /S/ date 30-NOV-2
HFD-615/SMiddleton, CSO /S/ date 11/30/02
Word File
V:\FIRMSAM\BARR\LTRS&REV\40422.ACK
F/T StM 11/30/00
ANDA Acknowledgment Letter!

40-422

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 29, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773
Attention: Saundra Middleton, Project Manager

NEW CORRESP
NC
/S/
NAT
12/6/00

VIA FACSIMILE: (301) 594-1174
ORIGINAL VIA FEDERAL EXPRESS

TELEPHONE CORRESPONDENCE

REFERENCE: **Abbreviated New Drug Application**
——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

Reference is made to Barr's pending Abbreviated New Drug Application ("ANDA") dated September 4, 2000 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg).

Reference is also made to the phone conversation between Saundra Middleton, Project Manager, Regulatory Support Branch, OGD and Christine Mundkur, Vice President of Quality and Regulatory Counsel, Barr Laboratories on November 29, 2000.

As per the Agency's instructions, Barr is correcting the 356h form to state Shire Richwood's Adderall® as the reference listed drug.

Identical copies of this Telephone Correspondence have been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes the present Telephone Correspondence to Barr's pending ANDA. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 30 2000
OGD

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

This submission is comprised of **Pages 1 through 5**.

ACK for Fil... JST 505(b)(2)(A) 11/30/00

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 31, 2000

Name of Drug nomenclature on ack. letter confirmed w/ C. Hoppes 30-NOV-2000

OK! 30-NOV-2000 JST

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **Abbreviated New Drug Application**
——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg)

In accordance with the regulations promulgated under 505 (j) of the Food, Drug and Cosmetic Act, and as amended, Barr Laboratories, Inc. is submitting this Abbreviated New Drug Application for ——— (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate tablets, 5 mg, 10 mg, 20 mg, and 30 mg).

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 10 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 7 volumes as well as two additional sets of two volumes each containing Section XV, Analytical Methods since the drug product is not a USP article. The bioequivalence part of the review copy is contained in orange binders and consists of 4 volumes.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, is a Debarment Certification Statement. Field Copies of this application has been forwarded to the New Jersey and Baltimore District Offices. A Field Copy Certification is also provided in this application.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The CMC and Bioequivalence Sections of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will at that time provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel