CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074479

Trade Name : ALPRAZOLAM TABLETS

Generic Name: Alprazolam Tablets

Sponsor : Royce Laboratories, Inc.

Approval Date: January 21, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074479

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074479

APPROVAL LETTER

ANDA 74-479

1/21/97

Royce Laboratories, Inc.
Attention: Loren Gelber, Ph.D.
16600 NW 54 Avenue
Miami, FL 33014

Dear Madam:

This is in reference to your abbreviated new drug application dated March 24, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Alprazolam Tablets USP, 0.25 mg, 0.5 mg and 1 mg.

Reference is also made to your amendments dated November 5 and December 23, 1996, and January 8, and 15, 1997.

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 Alprazolam Tablets USP, 0.25 mg, 0.5 mg and 1 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Xanax Tablets, 0.25 mg, 0.5 mg and 1 mg, respectively, of Pharmacia and Upjohn Company. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, 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. 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 which 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-240). 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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-479
Division File
Field Copy
HFD-600/Reading File
HFD-92
HFD-600/Reading File
HFD-8/PSavino
HFD-610/JPhillips

Endorsements:

HFD-625/SSherken/11/22/96
HFD-625/MSmela/11/25/96
HFD-617/SO'Keefe/12/31/96
HFD-613/CHolquist/12/30/96
HFD-613/JGrace/ 1/3/9
X:\NEW\FIRMSNZ\RO CE\LTRS&RI
F/t: gp/1/2/97
APPROVAL

/S/

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074479

FINAL PRINTED LABELING

mrgo

Each Tablet Contains:
Alprazolam, USP ..... 1 mg

USUAL ADULT DOSAGE:
See package insert for dosage information.

Store at controlled room temperature,
15°-30°C (59°-86°F). Protect from moisture.
Dispense in a tight, light-resistant container
as specified in the USP.

Royce™

NDC 51875-0365-4

ALPRAZOLAM TABLETS, USP

C IV

1 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Rx Only

Batch No.:

Exp. Date: JAN 21 1997

N 3 51875-0365-4 1

Each Tablet Contains:
Alprazolam, USP ..... 1 mg

USUAL ADULT DOSAGE:
See package insert for dosage information.

Store at controlled room temperature,
15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container
as specified in the USP.

NDC 51875-0365-2

Royce™

ALPRAZOLAM TABLETS, USP

(IV)

1 mg

Caution: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Lot No.: 0365

Batch No.:

Exp. Date: JAN 21 1997

N 3 51875-0365-2 7

MAMG 2

Each Tablet Contains:
Alprazolam, USP ..... 1 mg
USUAL ADULT DOSAGE:
See package insert for dosage information.
Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture.
Dispense in a tight, light-resistant container as specified in the USP.

Royce™

NDC 51875-0365-1

ALPRAZOLAM TABLETS, USP

(C IV)

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No:
Exp. JAN 21 1997

N 3 51875-0365-1 0

Each Tablet Contains:
Alprazolam, USP ..... 0.5 mg

USUAL ADULT DOSAGE:
See package insert for dosage information.

Store at controlled room temperature,
15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container
as specified in the USP.

Royce™

NDC 51875-0364-4

ALPRAZOLAM TABLETS, USP

C IV

0.5 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

APPROVED
Lot No.
Exp. Date: JAN 21 2007

N 3 51875-0364-4 2

Each Tablet Contains:
Alprazolam, USP ..... 0.5 mg

USUAL ADULT DOSAGE:
See package insert for dosage information.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container as specified in the USP.

Royce™

NDC 51875-0364-2

ALPRAZOLAM TABLETS, USP

C IV

0.5 mg

Caution: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

APPROVED
Batch No:
Exp JAN 21 1997

N 3 51875-0364-2 8

MAR 80

Each Tablet Contains:
Alprazolam USP ..... 0.5 mg

USUAL ADULT DOSAGE:
See package insert for dosage information.

Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture.
Dispense in a tight, light-resistant container as specified in the USP.

Royce™

NDC 51875-0364-1

ALPRAZOLAM TABLETS, USP

0.5 mg

(IV)

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:

Exp. Date: JAN 21 1007

N 3 51875-0364-1 1

MTH 50

Each Tablet Contains:
Alprazolam, USP ..... 0.25 mg

USUAL ADULT DOSAGE:
See package insert for dosage information.

Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container as specified in the USP.

Royce™

NDC 51875-0363-4

ALPRAZOLAM TABLETS, USP

(IV)

0.25 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

APPROVED

Code No. 0363
Batch No.
Exp. Date

N 3 51875-0363-4 3

Each Tablet Contains:
Alprazolam, USP ..... 0.25 mg

USUAL ADULT DOSAGE:
See package insert for dosage information.

Store at controlled room temperature,
15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container
as specified in the USP.

NDC 51875-0363-2

Royce™

ALPRAZOLAM TABLETS, USP

C IV

0.25 mg

Caution: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

APPROVED

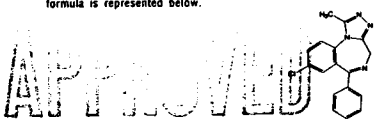
Catalog No. 0363
Batch No.
Exp. Date

N 3 51875-0363-2 9

ALPRAZOLAM TABLETS, USP (C-IV)

DESCRIPTION

Alprazolam is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds. The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4*H*-s-triazolo[4,3-α][1,4] benzodiazepine. The structural formula is represented below.



$C_{17}H_{13}ClN_4$ MW= 308.77

Alprazolam is a white to off-white crystalline powder, which is soluble in alcohol but which has no appreciable solubility in water at physiological pH.

Each tablet, for oral administration, contains 0.25, 0.5, or 1 mg of alprazolam, USP.

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, docusate sodium, sodium starch glycolate, sodium benzoate, colloidal silicon dioxide, and magnesium stearate. In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 1.

CLINICAL PHARMACOLOGY

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3 mg, peak levels of 8.0 to 37 ng/ml were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3-26.9 hours) in healthy adults.

The predominant metabolites are α-hydroxy-alprazolam and a benzophenone derived from alprazolam. The biological activity of α-hydroxy-alprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as that of alprazolam. Alprazolam and its metabolites are excreted primarily in the urine.

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

In vitro, alprazolam is bound (80 percent) to human serum protein.

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0-26.9 hours, n=16) compared to 11.0 hours (range: 6.3-15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean: 21.8, n=12) as compared to between 6.3 and 15.8 hours (mean: 10.6 hours, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

INDICATIONS AND USAGE

Alprazolam tablets are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances, for a period of six months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: *Motor Tension* (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); *Autonomic Hyperactivity* (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or light-headedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or 'lump in throat'); *Vigilance and Scanning* (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or 'mind going blank' because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to alprazolam.

Demonstrations of the effectiveness of alprazolam by systematic clinical study are limited to four months duration for anxiety disorder. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam is contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Alprazolam may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

Alprazolam is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP 3A) (see **WARNINGS** and **PRECAUTIONS–Drug Interactions**).

WARNINGS

Dependence and withdrawal reactions, including seizures:

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see **DRUG ABUSE AND DEPENDENCE**). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (i.e., 0.75 to 4 mg per day), there is some risk of dependence. Post-marketing surveillance data suggest that the risk of dependence and its severity appear to be greater in patients treated with relatively high doses (above 4 mg per day) and for long periods (more than 8-12 weeks).

Status epilepticus and its treatment:

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well. Ordinarily, the treatment of status epilepticus of any etiology involves use of intravenous benzodiazepines plus phenytoin or barbiturates, maintenance of a patent airway and adequate hydration. For additional details regarding therapy, consultation with an appropriate specialist may be considered.

Risk of dose reduction:

Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (e.g., the patient forgets, the patient is admitted to a hospital, etc.). Therefore, the dosage of alprazolam should be reduced or discontinued gradually (See DOSAGE AND ADMINISTRATION).

Alprazolam is not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment of psychosis. Because of its CNS depressant effects, patients receiving alprazolam should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam.

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Alprazolam interaction with drugs that inhibit metabolism via cytochrome P450 3A: The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP 3A. With drugs inhibiting CYP 3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP 3A.

Potent CYP 3A inhibitors: Azole antifungal agents–Although *in vivo* interaction data with alprazolam are not available, ketoconazole and itraconazole are potent CYP 3A inhibitors and the coadministration of alprazolam with them is not recommended. Other azole-type antifungal agents should also be considered potent CYP 3A inhibitors and the coadministration of alprazolam with them is not recommended (see **CONTRAINDICATIONS**).

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs):

Nefazodone–Coadministration of nefazodone increased alprazolam concentration two-fold.

Fluvoxamine–Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine–Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

Other drugs possibly affecting alprazolam metabolism: Other drugs possibly affecting alprazolam metabolism by inhibition of CYP 3A are discussed in the **PRECAUTIONS** section (see **PRECAUTIONS–Drug Interactions**).

PRECAUTIONS

General: If alprazolam is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines (See **Drug Interactions**). As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See **DOSAGE AND ADMINISTRATION**). The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam. A decreased systemic alprazolam elimination rate (e.g., increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam (See **CLINICAL PHARMACOLOGY**).

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

Information for Patients:

For all users of Alprazolam:

To assure safe and effective use of benzodiazepines, all patients prescribed alprazolam should be provided with the following guidance.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without prescription. Alcohol should generally not be used during treatment with benzodiazepines.
2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
3. Inform your physician if you are nursing.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

Laboratory Tests: Laboratory tests are not ordinarily required in otherwise healthy patients.

Drug Interactions: The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of alprazolam in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Drugs that inhibit alprazolam metabolism via cytochrome P450 3A: The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see **CONTRAINDICATIONS** and **WARNINGS** for additional drugs of this type).

Drugs demonstrated to be CYP 3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam):

Fluoxetine–Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene–Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives–Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of *in vitro* studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam): Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see **WARNINGS**).

Drug/Laboratory Test Interactions: Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy: *Teratogenic Effects:* Pregnancy Category D: (See WARNINGS Section)

Nonteratogenic Effects: It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery: Alprazolam has no established use in labor or delivery.

Nursing Mothers: Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

Pediatric Use: Safety and effectiveness in individuals below the age of 18 years have not been established.

ADVERSE REACTIONS

Side effects to alprazolam, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, e.g., drowsiness or light-headedness.

The data cited in the table below are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (i.e., four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety).

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-

drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, for anxiety disorders the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (e.g., increased surveillance, decreased dosage or discontinuation of therapy) may be necessary because of the untoward clinical event.

ANXIETY DISORDERS

	Treatment-Emergent Symptom Incidence†		Incidence of Intervention Because of Symptom
	ALPRAZOLAM	PLACEBO	ALPRAZOLAM
Number of Patients	565	685	565
% of Patients Reporting:			
Central Nervous System			
Drowsiness	41.0	21.6	15.1
Light-headedness	20.8	19.3	1.2
Depression	13.9	18.1	2.4
Headache	12.9	19.6	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.9	16.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	*
Dizziness	1.8	0.8	2.5
Akathisia	1.6	1.2	*
Tiredness/Sleepiness	*	*	1.8
Gastrointestinal			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	2.4	*
Cardiovascular			
Tachycardia/Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	*
Sensory			
Blurred Vision	6.2	6.2	0.4
Musculoskeletal			
Rigidity	4.2	5.3	*
Tremor	4.0	8.8	0.4
Cutaneous			
Dermatitis/Allergy	3.8	3.1	0.6
Other			
Nasal Congestion	7.3	9.3	*
Weight Gain	2.7	2.7	*
Weight Loss	2.3	3.0	*

**None reported*

†Events reported by 1% or more of alprazolam patients are included.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated in the table above on Anxiety Disorders, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (See **WARNINGS**).

To discontinue treatment in patients taking alprazolam, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every three days (See **DOSAGE AND ADMINISTRATION**). Some patients may require an even slower dosage reduction.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

Laboratory analyses were performed on all patients participating in the clinical program for alprazolam. The following incidences of abnormalities shown below were observed in patients receiving alprazolam and in patients in the corresponding placebo group. Few of these abnormalities were considered to be of physiological significance.

General Treatment of Overdose: Overdosage reports with alprazolam tablets are limited. As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.
Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** should be consulted prior to use.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who require higher doses. In such cases, dosage should be increased cautiously to avoid adverse effects.

Anxiety disorders and transient symptoms of anxiety:

Treatment for patients with anxiety should be initiated with a dose of 0.25 to 0.5 mg given three times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg, given two or three times daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose may be lowered.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

HOW SUPPLIED

Alprazolam Tablets, USP, 0.25 mg, are white, oval, biconvex, scored tablets upper debossed with 363 above the score and 0.25 below, and lower debossed with Royce logo. They are supplied in bottles of:

SIZE	ROYCE NDC NUMBER
100	51875-0363-1
500	51875-0363-2
1000	51875-0363-4

Alprazolam Tablets, USP, 0.5 mg, are peach, oval, biconvex, scored tablets upper debossed with 364 above the score and 0.5 below, and lower debossed with Royce logo. They are supplied in bottles of:

SIZE	ROYCE NDC NUMBER
100	51875-0364-1
500	51875-0364-2
1000	51875-0364-4

Alprazolam Tablets, USP, 1 mg, are blue, oval, biconvex, scored tablets upper debossed with 365 above the score and 1 below, and lower debossed with Royce logo. They are supplied in bottles of:

SIZE	ROYCE NDC NUMBER
100	51875-0365-1
500	51875-0365-2
1000	51875-0365-4

STORAGE

Store at controlled room temperature, 15-30°C (59-86°F); protect from moisture.
Dispense in a tight, light-resistant container as specified in the USP.
Caution: Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY

Animal Studies

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

CLINICAL STUDIES

Alprazolam tablets were compared to placebo in double blind clinical studies (doses up to 4 mg/day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. Alprazolam was significantly better than placebo at each of the evaluation periods of these four week studies as judged by the following psychometric instruments: Physician's Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions and Self-Rating Symptom Scale.

Royce Laboratories, Inc.
16600 NW 54 Avenue, Miami, Florida 33014

Revised December 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074479

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW: Addendum #1 to Chemistry Review #5

2. ANDA # 74-479

3. NAME AND ADDRESS OF APPLICANT

Royce Laboratories Inc.
Miami, FL 33014

4. LEGAL BASIS FOR ANDA SUBMISSIONS

505(j)

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Alprazolam Tablets USP

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

N/A

9. AMENDMENTS AND OTHER DATES

Original Application 3/24/94; RTF 4/20/94; Amend 4/27/94; AFF 4/28/94; AL 5/11/94; NA 9/21/94, Major Amend 12/15/94 NA (minor) 6/16/95, Tel memo 6/20/95, Amend (minor) 7/11/95; NA 7/31/95 NC 1/25/96; Tel Amend; 3/7/96; Tel Amend 4/1/96*; Tel Amend 8/20/96; Amendment (Minor) 11/5/96; Tel Memo 1/7/97; Telephone Amendment* 1/8/97.

* Amendments Reviewed

10. PHARMACOLOGICAL CATEGORY

Tranquilizer (a controlled drug)

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM

14. POTENCY

a. White, oval, biconvex, scored tablets. — 0.25 mg

b. Peach, oval, biconvex, scored tablets. — 0.50 mg

c. Blue, oval, biconvex, scored tablets. — 1 mg

15. CHEMICAL NAME AND STRUCTURE

See review #1

16. RECORDS AND REPORTS

N/A

17. COMMENTS

On June 5, 1996 (b)4 - Confidential Business

On October 16, 1996 OGD found (b)4 - Confidential Business adequate.

18. CONCLUSIONS AND RECOMMENDATIONS

(b)4 - Confidential Business

Chemistry, manufacturing, stability and testing are satisfactory Royce has added the current impurity/degredant test currently in the Stability test to the product release method.

Bio found acceptable on 5/31/96.

Labeling found acceptable 7/29/95.

EER remains outstanding.

Approve ANDA 74-479 pending satisfactory EER.

19. REVIEWER: — DATE COMPLETED:

/S/ — 1/9/97

Stephen Sherken — Janurary 9, 1997

/S/

1/9/97

1. CHEMISTRY REVIEW #5

2. ANDA # 74-479

3. NAME AND ADDRESS OF APPLICANT

Royce Laboratories Inc.
Miami, FL 33014

4. LEGAL BASIS FOR ANDA SUBMISSIONS

505(j)

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Alprazolam Tablets USP

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

N/A

9. AMENDMENTS AND OTHER DATES

Original Application 3/24/94; RTF 4/20/94; Amend 4/27/94; AFF 4/28/94; AL 5/11/94; NA 9/21/94, Major Amend 12/15/94 NA (minor) 6/16/95, Tel memo 6/20/95, Amend (minor) 7/11/95; NA 7/31/95 NC 1/25/96; Tel Amend; 3/7/96; Tel Amend 4/1/96*; Tel Amend 8/20/96; Amendment (Minor) 11/5/96*

* Amendments Reviewed

10. PHARMACOLOGICAL CATEGORY

Tranquilizer (a controlled drug)

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM	14. POTENCY
a. White, oval, biconvex, scored tablets.	0.25 mg
b. Peach, oval, biconvex, scored tablets.	0.50 mg
c. Blue, oval, biconvex, scored tablets.	1 mg

15. CHEMICAL NAME AND STRUCTURE

See review #1

16. RECORDS AND REPORTS

N/A

17. COMMENTS

(b)4 - Confidential Business

18. CONCLUSIONS AND RECOMMENDATIONS

(b)4 - Confidential Business

Chemistry, manufacturing, stability and testing are satisfactory.

Bio found acceptable on 5/31/96.

Labeling found acceptable 7/29/95.

EER remains outstanding.

Approve ANDA 74-479 pending satisfactory EER.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken November 22, 1996

cc: ANDA 74-479
Field Copy
Division File
Endorsements:

/S/ 1/7/97

HFD-625/SSherken/11/22/96
HFD-625/MSmela/11/25/96
X:\NEW\FIRMSNZ\ROYCE\LTRS&REV\74479.RV5
F/t by: gp/1/2/97

/S/ 1/7/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074479

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-479 SPONSOR: Royce Laboratories
DRUG: Alprazolam
DOSAGE FORM: Tablets
STRENGTH(s): 1mg
TYPE OF STUDY: (Single)/Multiple (Fasting)/Fed
STUDY SITE: Pharmakinetics

STUDY SUMMARY: The study compare the bio availability of two formulations under fasting conditions. The study was acceptable. The waiver for 0.25 and 0.5 mg Tablets was granted based upon formula proportionality to 1 mg Tab.

DISSOLUTION: The dissolution was conducted in 500 ml of PO4 buffer pH 6.0 at 37°C using USP XXII apparatus I (Basket) at 100 rpm. The tablet meets the dissolution specifications

PRIMARY REVIEWER: BRANCH:

INITIAL: /S/ DATE: 1/19/95

BRANCH CHIEF: BRANCH:

INITIAL: /S/ DATE: 1/19/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 1/19/95

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: /S/ DATE: 2/28/95

JAN 12 1995

Alprazolam Tablets
0.25 mg, 0.5 mg, and 1.0 mg
ANDA # 74-479
Reviewer: Man M. Kochhar
74479SDW.394

Royce Laboratories
Miami, Florida
Submission Date:
March 24, 1994

Review of a Bioequivalence Study, Waiver Requests and Dissolution Data

INTRODUCTION:

Alprazolam is a triazolobenzodiazepine used in the treatment of generalized anxiety, panic disorder, and depression. The drug effect is dose-related. The average daily dose is 1.5 to 4.0 mg. Alprazolam is currently available as Xanax (Upjohn Pharmaceuticals) in 0.25mg, 0.5mg, 1.0 mg and 2.0 mg tablets for oral administration.

Alprazolam is readily absorbed after oral administration. The mean plasma elimination half-life of alprazolam is about 11 hours (range 6.3 to 26.9 hours). The rate of drug absorption is slower when alprazolam is taken after a meal than on an empty stomach; however, the total absorption is same in both cases.

OBJECTIVES:

1. The objective of this study was to compare the bioavailability of two formulations of alprazolam 1.0 mg tablets of test and reference products under fasting conditions.

2. The sponsor has requested a waiver for their 0.25 mg and 0.5 mg tablets based upon the proportionality to their 1.0 mg tablet which underwent a bioequivalence study.

IN-VIVO STUDY:

The bioequivalence study

(b)4 - Confidential Business

STUDY DESIGN:

The study was designed as a randomized, single dose, two-way crossover bioequivalence study in 24 healthy volunteers under fasting conditions.

Subjects:

The study employed twenty-four (24) healthy male volunteers between the ages of 18-55, whose weight did not deviate by more than ±15% of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin,1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular,

hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications and/or OTC preparations for atleast 7 days prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing until after completion of the study. Each subject signed a written informed consent.

The subjects remained in the clinic from 12 hours before and 24 hours after the drug administration.

Methods:

The product and dosage employed in this study were as follows:

A. Test: One 1.0 mg tablet Alprazolam (test drug), lot # KH-1152 with 240 mL of water
Batch size: [redacted] (b)4 - [redacted] Expiry Date: N/A
Content Uniformity: 98.1 %

B. Reference: One 1.0 mg Xanax tablet (Upjohn), lot # 278 YH with 240 mL of water. Expiry Date: 3-98.
Content Uniformity: 101.7 %

The subjects fasted from 10 hours before until 4 hours following drug administration. No meals were served within 4 hours of any dose. Water ad lib was allowed except within 2 hours of the drug administration.

10 mL of venous blood were drawn in Vacutainers with no anticoagulant at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48 and 60 hours. The serum was separated and promptly frozen for analysis.

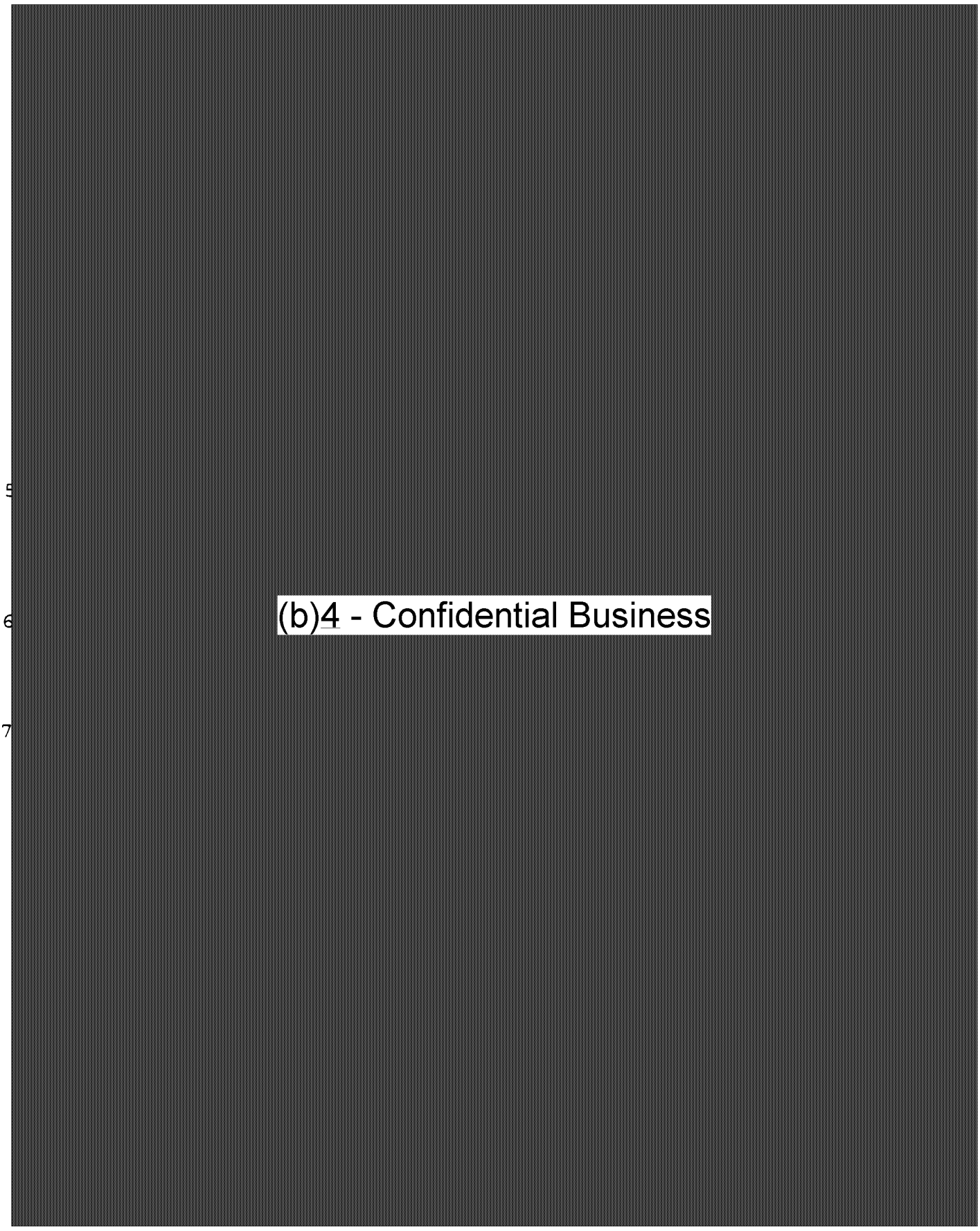
WASHOUT PERIOD: one week

ANALYTICAL METHODOLOGY:

Alprazlamo in serum was measured by a [redacted] (b)4 - [redacted] method developed by the company.

ASSAY VALIDATION:

[redacted] (b)4 - Confidential Business


(b)4 - Confidential Business

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, and sequence) were carried out to compare serum levels at each sampling time, AUCo-t, AUCinf, Cmax, Tmax, t1/2, Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for alprazolam pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the twenty-four (24) subjects, 23 completed the crossover. The serum samples from 23 subjects were assayed for alprazolam as per the protocol. The results of the study comparing the bioavailability of alprazolam test and reference products are given in Table 1, 2, and 3. The mean serum alprazolam concentrations for test and reference treatments are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Alprazolam (N= 23)

Time (hours)	Royce's Alprazolam Lot # KH-1152 ng/mL (CV%)	Upjohn's Xanax Lot # 278 YH ng/mL (CV%)	T/R
0.00	0.0	0.08 (360)	0.0
0.25	1.71 (104)	3.65 (103)	0.47
0.50	8.90 (75)	11.77 (46)	0.76
0.75	10.88 (54)	14.22 (33)	0.76
1.00	10.73 (44)	13.50 (23)	0.79
1.33	10.66 (38)	12.94 (22)	0.82
1.67	11.77 (30)	13.38 (15)	0.88
2.00	12.60 (25)	13.49 (19)	0.93
2.50	12.28 (24)	12.89 (17)	0.95
3.00	12.10 (24)	12.57 (19)	0.96
4.00	11.89 (21)	11.84 (20)	1.00
6.00	9.24 (23)	9.22 (22)	1.00
9.00	7.42 (28)	7.44 (26)	1.00
12.00	5.98 (30)	5.97 (28)	1.00
24.00	3.42 (42)	3.44 (45)	1.00
36.00	1.74 (65)	1.84 (60)	0.94
48.00	1.06 (86)	1.14 (73)	0.93
60.00	0.49 (142)	0.46 (107)	1.06

TABLE 2

A Summary of Pharmacokinetic Parameters for 23 Subjects (CV%)

Parameters	Royce's Alprazolam	Upjohn's Xanax	T/R	90% Confidence Interval
AUC_{0-60} ng.hr/mL	218.6 (37)	226.1 (31)	0.97	93; 100
AUC_{inf} ng.hr/mL	239.0 (41)	248.9 (37)	0.96	93; 99
C_{max} ng/mL	14.8 (28)	16.1 (22)	0.92	83; 102
T_{max} hours	1.8 (62)	1.1 (55)	1.64	
K_{el} 1/hr	0.054 (27)	0.051 (28)	1.06	
$t_{1/2}$ hours	13.78 (27)	14.58 (26)	0.94	
Ln AUC_{0-60} ng.hr/mL	5.33 (6)	5.38 (5)	0.99	92; 99
Ln AUC_{inf} ng.hr/mL	5.42 (6)	5.46 (6)	0.99	92; 99
Ln C_{max} ng/mL	2.66 (10)	2.75 (7)	0.97	83; 100

TABLE 3

Test Product/Reference Product Ratios

Subject	AUCo-60	AUCinf	Cmax	Tmax
1				
2				
3				
4				
5.				
6				
7				
9				
10				
11				
12				
13				
14		(b)4 - Confidential Business		
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				

The alprazolam AUC_{0-60} and AUC_{inf} produced by Royce formulation are 3.32% and 3.98% lower than the respective values for the reference drug. The C_{max} is 8.07% lower than the reference. The K_{el} and $t_{1/2}$ values differ by 5.88% and 5.49% respectively. The firm did calculate Ln AUC and Ln Cmax for alprazolam and the 90% confidence intervals for log-transformed parameters were 92 to 99 for Ln AUCo-t, 92 to 99 for Ln AUCinf and 83 to 100 for Ln Cmax.

The 90% confidence intervals for untransformed alprazolam AUCo-t, AUCinf and C_{max} were well within ±20% limits set for defining product bioequivalence.

The alprazolam concentration/time profiles of the two products were superimposable with less than 20% difference between the products being observed at each of the timed collection points except from 0.75 to 1.67 hours after dosing.

One subject #8 was withdrawn after 3 hours sample time because of personal reasons.

15 subjects experienced drowsiness during the study which was an expected effect of the drug product. Drowsiness was reported

evenly in both phases of the study. The number of subjects were almost evenly divided among test and reference products who experienced drowsiness. No serious adverse event was observed during the study.

On the basis of fasting in vivo bioavailability data it is determined that Royce's alprazolam tablets and Upjohn's Xanax 1 mg tablets are bioequivalent.

The sponsor has requested for a waiver for 0.25 and 0.5 mg tablets based upon the proportionality to their 1.0 mg tablet. The formulation for all three strengths of tablet is given in Table 5.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 500 mL of Phosphate buffer, pH 6.0 at 37°C using USP XXII apparatus 1 (Basket) at 100 rpm. Results are presented in Table 4. Both the test and reference products meet the dissolution specifications of not less than (b)(4) of the labeled amount of the drug dissolved from the tablet in 30 minutes. USP method is same as described in this submission.

The sponsor has not sampled at the 45 minutes point because the USP method testing time is 30 minutes. Since almost all the active ingredient dissolves as early as 5 minutes, the 45 minutes time point is not important.

The batch size was [redacted] (b)(4) - [redacted]

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

COMMENTS:

1. 24 subjects enrolled in the study. Subject # 8 dropped after 3 hour sample time because of personal reasons. The data from 23 subjects were assayed as per the protocol, comparing the serum concentrations from Royce's alprazolam, 1 mg tablet to that of reference Xanax, 1 mg tablet manufactured by Upjohn.

The alprazolam AUC_{0-60}, AUC_{inf}, and C_{max} of Royce's formulation were 3.32% lower, 3.98% lower and 8.07% lower respectively than the corresponding Upjohn's reference values. The differences were not statistically significant. The 90% confidence intervals for log transformed parameters were 92 to 99 for Ln AUCo-t, 92 to 99 for Ln AUCinf and 83 to 100 for Ln Cmax. The 90% confidence intervals for untransformed alprazolam AUC and Cmax were well within ±20% limits set for defining product bioequivalence. These results indicate that the test drug is bioequivalent to the reference product under fasting conditions. Both treatments

yielded similar mean serum alprazolam concentration-time profiles.

2. Analysis of variance indicated no statistically significant treatment or sequence differences for AUC and C_{max}.

3. No serious side effects were observed.

4. The in vitro dissolution testing conducted on both the test and reference products show greater than 80% of the labeled amount of alprazolam dissolved in 30 minutes.

5. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

6. The in vivo fasting bioequivalence study and in vitro dissolution testing are acceptable.

7. The sponsor has conducted an acceptable biostudy on their 1 mg tablet. Therefore the waiver for 0.25 mg and 0.5 mg tablets can be granted based upon the formulation proportionality to their 1.0 mg tablet.

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by Royce Laboratories on its alprazolam tablets, lot # KH-1152, comparing it to Xanax tablets, lot # 278 YH manufactured by Upjohn has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Royce's Alprazolam tablets, 1 mg are bioequivalent to the reference product, Xanax tablets, 1 mg manufactured by Upjohn.

2. The in vitro dissolution testing conducted for 1 mg, 0.5 mg and 0.25 mg tablets for test and reference products is acceptable. The formulations for 0.25 mg and 0.5 mg alprazolam tablets are proportionally similar to 1 mg tablets which underwent an acceptable bioequivalence study. The waiver of in vivo bioequivalence study requirement for Royce's Alprazolam 0.5 mg and 0.25 mg tablet is granted. The 0.5 mg and 0.25 mg alprazolam tablets from Royce are, therefore, deemed bioequivalent to 0.5 mg and 0.25 mg Xanax tablets manufactured by Upjohn based on 21 CFR 320.22 (d)(2).

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of Phosphate buffer, pH 6.0 at 37°C using USP XXII apparatus 1 (Basket) at 100 rpm. The test should meet the following specifications:

Not less than (b)(4) of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution testing and the study is acceptable.

The firm should be informed of the recommendations.

/S/

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/

Concur: /S/ Date: 1/12/95
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMKochhar/mmk/6-23-94; 12-14-94; 74-479 BIO

cc: ANDA # 74-479 original, HFD-230, HFD-604 (Hare), HFD-658 (Mhatre, Kochhar), Drug File.

TABLE 5

FORMULATIONS

INGREDIENTS	Tablets 0.25 mg	0.5 mg	1.0 mg
Alprazolam, USP micronized)	0.255	0.51	1.02
Microcrystalline Cellulose, NF Docusate Sodium (b)4 and Sodium Benzoate Lactose Monohydrate NF Sodium Starch Glycolate NF FD & C Yellow # 6 Aluminum Lake FD & C Blue # 1 Aluminum Lake Colloidal Silicon Dioxide NF Magnesium stearate NF	(b)4 - Confidential Business		
TOTAL WEIGHT (mg)	120.00	120.00	120.00

(Please select Typeover for Input.)

Table 4 . In Vitro Dissolution Testing

Drug (Generic Name): Alprazolam
Dose Strength: 1 mg
ANDA No.: 74-479
Firm: Royce Laboratories
Submission Date: March 24, 1994
File Name:

I. Conditions for Dissolution Testing: UV

USP XXII Basket:X Paddle: RPM: 100
No. Units Tested: 12
Medium: Volume: 500 Phosphate Buffer, pH 6.0
Specifications: NLT (b)4 in 30 minutes
Reference Drug: Xanax
Assay Methodology: (b)4 -

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # KH-1152 Strength(1 mg)			Reference Product Lot # 278 YH Strength(1 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	101.5	(b)4 - Confidential Business	1.0	104.4	(b)4 - Confidential Business	1.8
20	101.3		2.0	104.8		1.0
30	101.5		1.9	105.1		1.6
45	103.7		2.2	106.3		2.2

Sampling Times (Minutes)	Test Product Lot # KH-1150 Strength(0.5 mg)			Reference Product Lot # 583 YF Strength(0.5 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
05	101.5	(b)4 - Confidentia Business	1.5	97.8	(b)4 - Confidentia Business	1.3
10	104.0		1.8	96.7		2.1
15	103.8		1.8	97.4		2.1
30	104.2		1.8	97.4		1.7
45	104.2		1.8	see note		--

Sampling Times (Minutes)	Test Product Lot # KH-1149 Strength(0.25 mg)			Reference Product Lot # 575 YD Strength(0.25 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
05	101.5	(b)4 - Confidential Business	1.5	101.3	(b)4 - Confidential Business	1.4
10	104.0		1.8	101.5		1.7
15	103.8		1.8	101.7		1.5
30	104.2		1.8	101.7		1.1
45	104.2		1.8	--		--

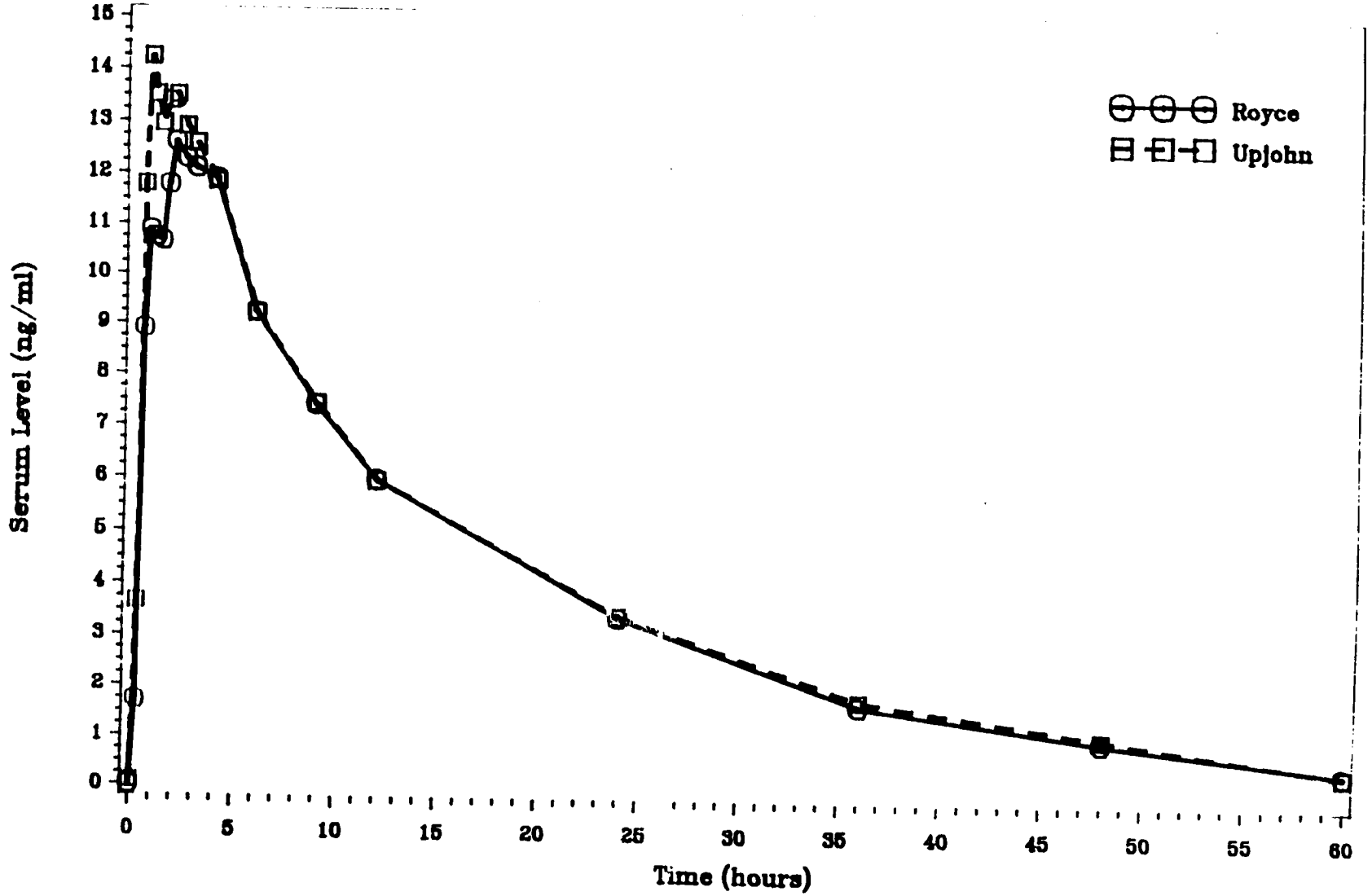
Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

FIGURE 1

Mean Alprazolam Serum Levels

n = 23



2.J

ANDA 74-479

Royce Laboratories, Inc.
Attention: Loren Gelber, Ph.D.
16600 NW 54 Avenue
Miami FL 33014

MAY 31 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Alprazolam Tablets USP, 0.25 mg, 0.5 mg and 1 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 mL of phosphate buffer, pH 6.0 at 37°C using USP 23 apparatus 1 (Basket) at 100 rpm. The test should meet the following specifications:

   Not less than (b)4 of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

D,V

MAY 24 1996

Alprazolam Tablets
0.25 mg, 0.5 mg and 1 mg
ANDA # 74-479
Reviewer: Man M. Kochhar
74479W.496

Royce Laboratories, Inc.
Miami, Florida
Submission Date:
April 1, 1996

REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

The firm with an acceptable bioequivalence study has submitted the dissolution data for 1 mg tablets, in support for a waiver request for bioequivalence study for a change in the source of raw material alprazolam [redacted](b)4 - Confidential Business[redacted](b)4 -[redacted]

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 500 mL of phosphate buffer, pH 6.0 at 37°C using USP XXIII apparatus 1 (Basket) at 100 rpm. Results are presented in Table 1. Both the test and reference products (The old batch, KH 1152 on which bioequivalence study was conducted) meet the dissolution specifications of not less than (b)4 of the labeled amount of drug dissolved from the tablets in 30 minutes.

The batch size was [redacted](b)4 -[redacted]

COMMENTS:

1. The firm is changing the source of their alprazolam from [redacted](b)4 - Confidential Business[redacted] This change in the source of raw material should not effect the bioavailability of the product provided the dissolution profile is similar.

2. The in vitro dissolution testing conducted for 1 mg tablets of the test and reference products (old product batch # KH 1152 on which the sponsor has conducted an acceptable biostudy) shows greater than (b)4 of the labeled amount of the alprazolam dissolved in 30 minutes.

3. The waiver of in vivo bioequivalence study requirement for 1 mg tablet is granted based on 21 CFR 320.22 (d)(4).

DEFICIENCY: None

RECOMMENDATIONS:

1. The dissolution testing conducted by Royce Laboratories on its new material (different source) Alprazolam, 1 mg tablets is acceptable. The firm has previously conducted an acceptable fasting bioequivalence study on its 1 mg tablets. Therefore, the waiver of in vivo bioequivalence study requirement for Royce Laboratories 1 mg tablet is granted. The 1 mg Alprazolam tablet from Royce Laboratories are, therefore, deemed bioequivalent to

1 mg tablet of Alprazolam (old source) manufactured by Royce Laboratories based on 21 CFR 320.22 (d)(4).

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of phosphate buffer, pH 6.0 at 37°C using USP XXIII apparatus 1 (Basket) at 100 rpm. The test should meet the following specifications:

> Not less than (b)4 of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

The firm should be informed of the recommendations.

/S/

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE 5/22

/S/

Concur: Date: 5/24/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/4-22-96; 5-22-96; 74479 W

cc: ANDA # 74-479 original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Kochhar), Drug File, Division File.

TABLE 1

IN VITRO DISSOLUTION TESTING

DRUG: Alprazolam 1 mg Tablets
ANDA # 74-479
Firm: Royce Laboratories

Conditions for dissolution:
USP XXIII, Apparatus 1 (Basket) at 100 rpm
Number of Units Tested : 12
Medium: 500 mL of Phosphate Buffer, pH 6.0
Specifications: NLT (b)4 in 30 minutes
Reference Drug: Old Batch KH 1152 on which an acceptable biostudy was conducted.
Assay Methodology: (b)4 -

RESULTS

Sampling Time Minutes	**Test Product Lot # KH-1151 Strength (1 mg)**			**Reference Product Lot # KH-1152 Strength (1 mg)**		
	Mean%	Range	%RSD	Mean	Range	%RSD
10	103	(b)4 -	1.8	101	(b)4 -	1.0
15	103	onfidentia	1.4	101	onfidenti	2.0
30	104		1.6	101		1.9
45	104	Business	1.4	104	Business	2.2