

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

74-951

APPLICATION NUMBER:

APPROVAL LETTER

ANDA 74-951

AUG 31 1998

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald Steinlauf
Sixty DaVinci Drive
Bohemia, NY 11716

|||||

Dear Sir:

This is in reference to your abbreviated new drug application dated August 29, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg.

Reference is also made to your amendments dated April 2 and April 10, 1997; June 4, July 27, and August 26, 1988.

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 Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Fiorinal® with Codeine Capsules USP, 50 mg/325 mg/40 mg/30 mg, of Novartis Pharmaceuticals Corporation). 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 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 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-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.

Sincerely yours,



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

8-31-98

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

74-951

APPLICATION NUMBER:

APPROVED DRAFT LABELING

MINI GRAPHICS INC.

SPECIALIZING IN PHARMACEUTICAL PACKAGE INSERTS AND ROLL LABELS

Tel.: (516) 223-6464
Fax: (516) 223-6486

45 St. John's Place
Freeport, New York 11520

CUSTOMER: <u>JSP</u> PLATE #: <u>4155-1</u> JOB #: <u>6284</u> P.O. #: <u>TO COME</u> MISC. CODE #: <u>-</u> ATTN: <u>PATTI DIMEGLIO</u>	PROOF #: <u>1</u> LABEL SIZE: <u>2.0" X 5.0"</u> PROOF SIZE (%): <u>100</u> DATE PROOF OUT: <u>05/29/98</u> PREPARED BY: <u>Steve Z.</u>	UPC CODE SPECS. <u>100 %</u> <u>- 0.002 B.W.A.</u>	<table border="1"> <thead> <tr> <th>COLORS</th> <th>PLATES NEEDED</th> </tr> </thead> <tbody> <tr> <td><input checked="" type="checkbox"/> PMS BLACK</td> <td><input checked="" type="checkbox"/></td> </tr> <tr> <td><input checked="" type="checkbox"/> PMS COOL GRAY 3C</td> <td><input checked="" type="checkbox"/></td> </tr> <tr> <td><input checked="" type="checkbox"/> PMS 285 BLUE</td> <td><input checked="" type="checkbox"/></td> </tr> <tr> <td><input type="checkbox"/> SPOT VARNISH</td> <td><input checked="" type="checkbox"/></td> </tr> </tbody> </table> <p>This color proof does not represent actual printed colors. Refer to PMS Book for actual color.</p>	COLORS	PLATES NEEDED	<input checked="" type="checkbox"/> PMS BLACK	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> PMS COOL GRAY 3C	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> PMS 285 BLUE	<input checked="" type="checkbox"/>	<input type="checkbox"/> SPOT VARNISH	<input checked="" type="checkbox"/>
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NO VARNISH

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APPROVED

JSP INC.

NDC 50564-507-01

BUTALBITAL, ASPIRIN, CAFFEINE AND CODEINE PHOSPHATE CAPSULES USP.

50 mg/325 mg/40 mg/30 mg

R ONLY

100 CAPSULES

Each Capsule Contains:
 Codeine Phosphate, USP
 Aspirin, USP
 Butalbital, USP
 Caffeine, USP

Usual Adult Dosage: 1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules. See package insert for additional information.

Pharmacist: Store and Dispense below 25°C (77°F) in a light-resistant container.

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- O.K. TO PRINT
- SUBMIT ADDITIONAL PROOFS

Production delivery 2 - 3 weeks from receipt of O.K. TO PRINT.

AUTHORIZED BY: _____ DATE: _____

AUG 31 1998 BUTALBITAL,
ASPIRIN,
CAFFEINE AND
CODEINE
PHOSPHATE
CAPSULES, USP III

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy

Teratogenic Effects:

Pregnancy Category C. Animal reproduction studies have not been conducted with butalbital, aspirin, caffeine and codeine. It is also for known whether this combination product can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity and should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects:

Although Butalbital, Aspirin, Caffeine with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Butalbital, Aspirin, Caffeine with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death, or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery

Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers

Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from this product, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

Commonly Observed

The most commonly reported adverse events associated with the use of butalbital, aspirin, caffeine and codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation

Of the 382 patients treated with Butalbital, Aspirin, Caffeine and Codeine in controlled clinical trials, three (0.8%) discontinued treatment because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials

The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Butalbital, Aspirin, Caffeine and Codeine treated patients in controlled clinical trials comparing the combination product to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Butalbital, Aspirin, Caffeine and Codeine Treated Patients During Placebo Controlled Clinical Trials

Body System/ Adverse Event	Incidence Rate of Adverse Events	
	Butalbital, Aspirin, Caffeine and Codeine (N=382)	Placebo (N=377)
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to butalbital, aspirin, caffeine and codeine while participating in controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving the combination product, the adverse events were not necessarily caused by butalbital, aspirin, caffeine and codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Butalbital, Aspirin, Caffeine and Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with the combination product, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of this product. Potential effects of high dosage are listed in the **OVERDOSAGE** section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE

Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules are controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Barbiturates

Barbiturates may be habit-forming. Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

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OVERDOSAGE

The toxic effects of acute overdosage of Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from this combination product is unlikely.

Signs and Symptoms.

Symptoms attributable to **acute barbiturate poisoning** include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to **acute aspirin poisoning** include hyperpnea, acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus; hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. **Acute caffeine poisoning** may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles. Symptoms of **acute codeine poisoning** include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment

The following paragraphs describe one approach to the treatment of overdose with this combination product. However, because strategies for the management of an overdose continually evolve, consultation with a regional Poison Control Center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levaterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses

Butalbital: toxic dose 1 g (adult); lethal dose 2 g to 5 g

Aspirin: toxic blood level greater than 30 mg/100 mL;
lethal dose 10 to 30 g (adult)

Caffeine: toxic dose greater than 1 g; lethal dose unknown

Codeine: lethal dose 0.5 to 1 g (adult)

DOSAGE AND ADMINISTRATION

1 or 2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED

Each yellow and blue Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsule USP 50 mg/325 mg/40 mg/30 mg is imprinted JSP 507

Bottles of 100 NDC 50564-507-01

Bottles of 500 NDC 50564-507-05

Store and Dispense

Below 25°C (77°F); in a tight, light resistant container.

Manufactured by:
Jerome Stevens Pharmaceuticals
Bohemia, NY 11716

Rev. 8/97
MG #11583

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**BUTALBITAL,
ASPIRIN,
CAFFEINE AND
CODEINE
PHOSPHATE
CAPSULES, USP** 

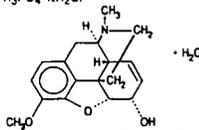
Rx ONLY

DESCRIPTION

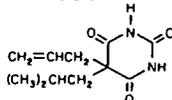
Each capsule for oral administration contains:

codeine phosphate, USP	30 mg (1/2 gr)
butalbital, USP	50 mg
caffeine, USP	40 mg
aspirin, USP	325 mg

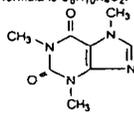
Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is 7,8-didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol phosphate (1:1) (salt) hemihydrate. Its molecular weight is 406.37 and its molecular formula is $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$.



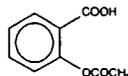
Butalbital, 5-allyl-5-isobutyl-barbituric acid, a white odorless crystalline powder, is a short- to intermediate-acting barbiturate. Its molecular weight is 224.26 and its molecular formula is $C_{11}H_{16}N_2O_3$.



Caffeine, 1,3,7-trimethylxanthine, is a central nervous stimulant which occurs as a white powder or white glistening needles. Its molecular weight is (anhydrous) 194.19 and its molecular formula is $C_8H_{10}N_4O_2$.



Aspirin is benzoic acid, 2-(acetyloxy)-, with a molecular formula of $C_9H_8O_4$ and its molecular weight is 180.16.



Inactive ingredients: D&C Yellow #10, D&C Yellow #10 Aluminum Lake, D&C Red #33, D&C Red #28, FD&C Blue #1, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Blue #10 Aluminum Lake, FD&C Red #40 Aluminum Lake, gelatin, microcrystalline cellulose, pregelatinized starch, talc, titanium dioxide, stearic acid, colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules is a combination drug product intended as a treatment for tension headache.

Pharmacokinetics

Bioavailability: The bioavailability of the components of the fixed combination of butalbital, aspirin, caffeine and codeine is identical to their bioavailability when butalbital, aspirin, caffeine and codeine is administered separately in equivalent molar doses.

The behavior of the individual components is described below.

Aspirin

The systemic availability of aspirin after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacids, buffering agents, and particle size. These factors affect not necessarily the extent of absorption of total salicylates but more the stability of aspirin prior to absorption.

During the absorption process and after absorption, aspirin is mainly hydrolyzed to salicylic acid and distributed to all body tissues and fluids, including fetal tissues, breast milk, and the central nervous system (CNS). Highest concentrations are found in plasma, liver, renal cortex, heart, and lung. In plasma, about 50%-80% of the salicylic acid and its metabolites are loosely bound to plasma proteins.

The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are still a good approximation for doses up to 650 mg. The plasma half-life for aspirin is about 12 minutes and for salicylic acid and/or total salicylates is about 3.0 hours.

The elimination of therapeutic doses is through the kidneys either as salicylic acid or other biotransformation products. The renal clearance is greatly augmented by an alkaline urine as is produced by concurrent administration of sodium bicarbonate or potassium citrate.

The biotransformation of aspirin occurs primarily in the hepatocytes. The major metabolites are salicylic acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acid (1%). The bioavailability of the component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent to that of a solution except for a slower rate of absorption. A peak concentration of 8.80 mcg/mL was obtained at 40 minutes after a 650 mg dose.

See **OVERDOSAGE** for toxicity information.

Codeine

Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen, and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. Codeine is not bound to plasma proteins and does not accumulate in body tissues.

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide-conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

The bioavailability of the codeine component is equivalent to that of a solution. Peak concentrations of 198 ng/mL were obtained at 1 hour after a 60 mg dose.

See **OVERDOSAGE** for toxicity information.

Butalbital

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most of the tissues in the body. Barbiturates, in general, may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59%-88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products included parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5-(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% was conjugated.

The bioavailability of the component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent to that of a solution except for a decrease in the rate of absorption. A peak concentration of 2020 ng/mL is obtained at about 1.5 hours after a 100 mg dose.

See **OVERDOSAGE** for toxicity information.

Caffeine

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared rapidly through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methyl-xanthine and 1-methyluric acid. Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug.

The bioavailability of the component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent to that of a solution except for a slightly longer time to peak. A peak concentration of 1660 ng/mL was obtained in less than an hour for an 80 mg dose.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules are indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy of butalbital, aspirin, caffeine and codeine phosphate capsules is derived from 2 multi-clinic trials that compared patients with tension headache randomly assigned to 4 parallel treatments: 1) butalbital, aspirin, caffeine and codeine; 2) codeine; 3) butalbital, aspirin and caffeine; 4) placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. The combination product of butalbital, aspirin, caffeine and codeine proved statistically significantly superior to each of its components and to placebo on measures of pain relief.

Evidence supporting the efficacy and safety of butalbital, aspirin, caffeine and codeine in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because codeine and butalbital are habit-forming and potentially abusable.

CONTRAINDICATIONS

Barbiturates, in general, may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59%-88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products included parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% was conjugated.

The bioavailability of the component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent to that of a solution except for a decrease in the rate of absorption. A peak concentration of 2020 ng/mL is obtained at about 1.5 hours after a 100 mg dose.

See **OVERDOSAGE** for toxicity information.

Caffeine

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared rapidly through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methyl-xanthine and 1-methyluric acid. Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug.

The bioavailability of the component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent to that of a solution except for a slightly longer time to peak. A peak concentration of 1660 ng/mL was obtained in less than an hour for an 80 mg dose.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules are indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy of butalbital, aspirin, caffeine and codeine phosphate capsules is derived from 2 multi-clinic trials that compared patients with tension headache randomly assigned to 4 parallel treatments: 1) butalbital, aspirin, caffeine and codeine; 2) codeine; 3) butalbital, aspirin and caffeine; 4) placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. The combination product of butalbital, aspirin, caffeine and codeine proved statistically significantly superior to each of its components and to placebo on measures of pain relief.

Evidence supporting the efficacy and safety of butalbital, aspirin, caffeine and codeine in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because codeine and butalbital are habit-forming and potentially abusable.

CONTRAINDICATIONS

This combination product is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS

Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure the signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS

General

Butalbital, aspirin, caffeine and codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients

Patients should be informed that this combination product contains aspirin and should not be taken by patients with an aspirin allergy. Butalbital, aspirin, caffeine and codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with this product, and should be avoided. Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Butalbital, aspirin, caffeine and codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing to an additive effect, if dosage of this product exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Butalbital, aspirin, caffeine and codeine may diminish the effects of:

Uricosuric agents such as probenecid and sulfipyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxaloacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxy-indoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-951

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3
2. ANDA #: 74-951
3. NAME AND ADDRESS OF APPLICANT
Jerome Stevens Pharmaceuticals, Inc.
Sixty DaVinci Drive
Bohemia, NY 11716
4. LEGAL BASIS FOR SUBMISSION
The reference Listed Drug is Fiorinal® with Codeine Capsules (Sandoz Pharmaceutical Corp.) The applicant certified that there are no relevant patents for the listed drug and that the period of marketing exclusivity for the listed drug expired on October 26, 1993.
5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME:
Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules USP
8. SUPPLEMENT(s) PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: August 29, 1996
New Corresp. (Environmental): September 30, 1996
New Corresp. (CGMP): October 16, 1996
Amendment: (Field Copy): November 26, 1996
New Corresp. (Bio): April 2, 1997
New Corresp. (Bio): April 10, 1997
Major Amendment: September 29, 1997 (Subject of this review)
Minor amendment: June 4, 1998 (Subject of this review)

FDA:
Telecon (A. Weikel): September 30, 1996
Telecon (C. Parise): October 16, 1996
Refusal to File Letter: November 20, 1996
Acceptance Letter: December 27, 1996
Method Verification: January 6, 1997
Label Review: April 21, 1997
Bio Letter & Review: May 2, 1997
Letter, C.R. # 1: June 9, 1997
Letter; C.R. # 2: May 4, 1998
Memo (Dissolution testing): May 18, 1998
Telecon (T. Ames/J. Stevens): May 20, 1998
10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

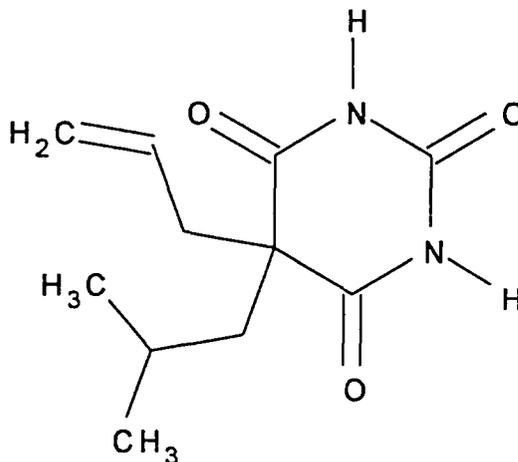
DMF 4164 Cotton (Personna Medical)
 LOAs included

13. DOSAGE FORM
 Capsule (Hard Gelatin)

14. POTENCY
 Butalbital: 50 mg
 Aspirin: 325 mg
 Caffeine: 40 mg
 Codeine Phosphate: 30 mg

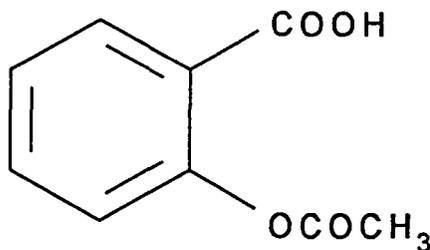
15. CHEMICAL NAME AND STRUCTURE

Butalbital USP
 $C_{11}H_{16}N_2O_3$; M.W. = 224.26



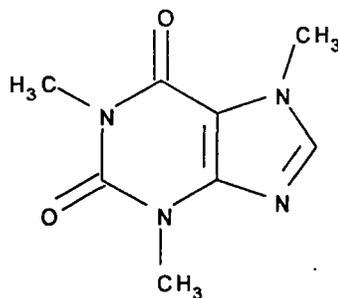
5-Allyl-5-isobutyl barbituric acid. CAS [77-26-9]

Aspirin USP
 $C_9H_8O_4$; M.W. = 180.16



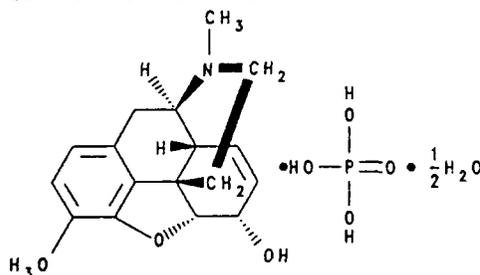
Salicylic acid acetate. CAS [50-78-2]

Caffeine USP
 $C_8H_{10}N_4O_2$; M.W. = 194.19



1,3,7-Trimethylxanthine. CAS [58-08-2]

Codeine Phosphate USP
 $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$; M.W. = 406.37



7,8-Didehydro-4-5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol
 phosphate (1:1) (salt) hemihydrate. CAS [41444-62-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

- a. CMC issues are satisfactory
- b. Label review acceptable; A. Vezza 8/4/98.
- c. Bio review is satisfactory - 5/2/97.
- d. Drug substances and product are USP - methods validation not required. Methods verification performed on drug product 1/6/97 by the New York Regional Laboratory and is satisfactory.
- e. There is currently only one generic approval for this drug product - ANDA 74-359 (Watson Labs, approved ca. 8/95).
- f. EIR acceptable 8/3/98.

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is approved

19. <u>REVIEWER:</u>	<u>DATE COMPLETED:</u>
Donald Shostak	July 20, 1998

Page(s) 13

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Information and are not

releasable.

Chem Rev 3

7/20/98

ANDA 74-951

1. CHEMISTRY REVIEW NO. 2
2. ANDA #: 74-951
3. NAME AND ADDRESS OF APPLICANT
Jerome Stevens Pharmaceuticals, Inc.
Sixty DaVinci Drive
Bohemia, NY 11716
4. LEGAL BASIS FOR SUBMISSION
The reference Listed Drug is Fiorinal® with Codeine Capsules (Sandoz Pharmaceutical Corp.) The applicant certified that there are no relevant patents for the listed drug and that the period of marketing exclusivity for the listed drug expired on October 26, 1993.
5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME:
Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules USP
8. SUPPLEMENT(s) PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: August 29, 1996
New Corresp. (Environmental): September 30, 1996
New Corresp. (CGMP): October 16, 1996
Amendment: (Field Copy): November 26, 1996
New Corresp. (Bio): April 2, 1997
New Corresp. (Bio): April 10, 1997
Major Amendment: September 29, 1997 (Subject of this review)

FDA:
Telecon (A. Weikel): September 30, 1996
Telecon (C. Parise): October 16, 1996
Refusal to File Letter: November 20, 1996
Acceptance Letter: December 27, 1996
Method Verification: January 6, 1997
Label Review: April 21, 1997
Bio Letter & Review: May 2, 1997
Letter, C.R. # 1: June 9, 1997
10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

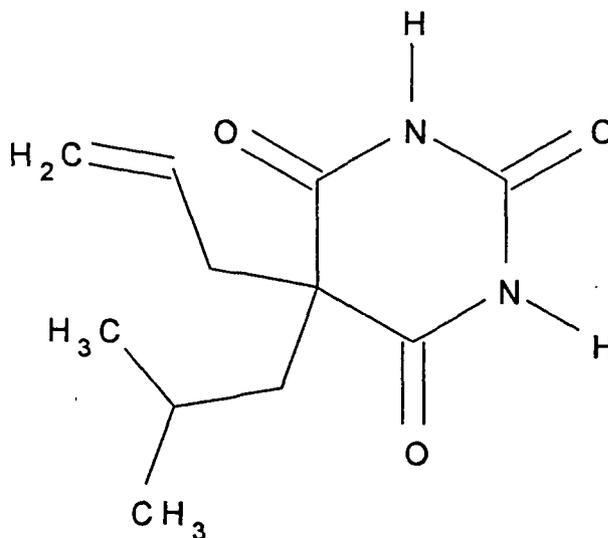
13. DOSAGE FORM
Capsule (Hard Gelatin)

14. POTENCY
Butalbital: 50 mg
Aspirin: 325 mg
Caffeine: 40 mg
Codeine Phosphate: 30 mg

15. CHEMICAL NAME AND STRUCTURE

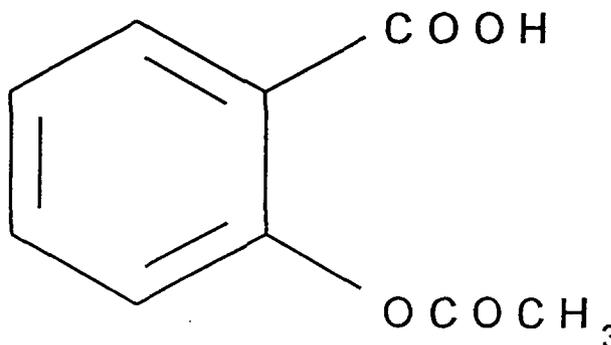
Butalbital USP

C₁₁H₁₆N₂O₃; M.W. = 224.26



5-Allyl-5-
isobutyl
barbituric acid.
CAS [77-26-9]

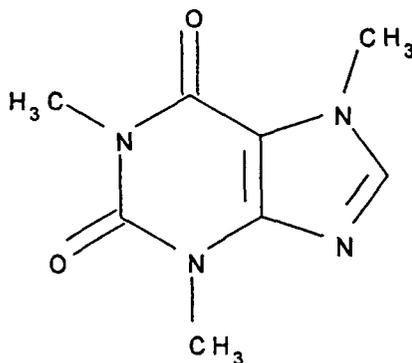
Aspirin USP
C₉H₈O₄; M.W. =
180.16



Salicylic acid acetate. CAS [50-78-2]

Caffeine USP

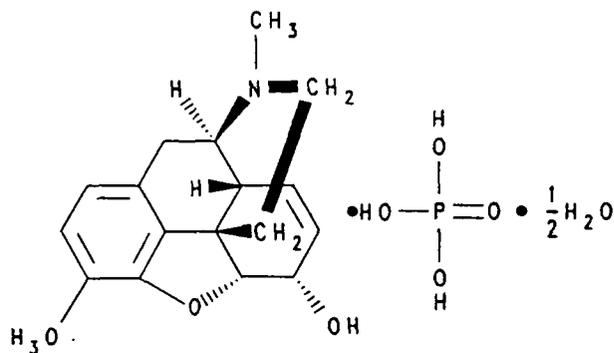
$C_8H_{10}N_4O_2$; M.W. = 194.19



1,3,7-Trimethylxanthine. CAS [58-08-2]

Codeine Phosphate USP

$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$; M.W. = 406.37



7,8-Didehydro-4-5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol phosphate (1:1) (salt) hemihydrate. CAS [41444-62-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

- a. Minor deficiencies remain regarding the container/closure system.
- b. Label review pending for 9/29/97 amendment.
- c. Bio review is satisfactory - 5/2/97.
- d. EIR pending for Jerome Stevens; satisfactory for all other firms per EES 3/16/98.
- e. Drug substances and product are USP - methods validation not required. Methods verification performed on drug product 1/6/97 by the New York Regional Laboratory and is satisfactory.
- f. There is currently only one generic approval for this drug product - ANDA 74-359 (Watson Labs, approved ca. 8/95).

18. CONCLUSIONS AND RECOMMENDATIONS

This application is NOT APPROVABLE. The amendment will be ^{AJ}MINOR.

19. REVIEWER:

Donald Shostak

DATE COMPLETED:

March 20, 1998

Page(s) 16

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releasable.

Chem Rev 2

3/20/98

ANDA 74-951

1. CHEMISTRY REVIEW NO. 1
2. ANDA #: 74-951
3. NAME AND ADDRESS OF APPLICANT
Jerome Stevens Pharmaceuticals, Inc.
Sixty DaVinci drive
Bohemia, NY 11716
4. LEGAL BASIS FOR SUBMISSION
The reference Listed Drug is Fiorinal® with Codeine Capsules (Sandoz Pharmaceutical Corp.) The applicant certified that there are no relevant patents for the listed drug and that the period of marketing exclusivity for the listed drug expired on October 26, 1993.
5. SUPPLEMENT(s):N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME:
Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules USP
8. SUPPLEMENT(s) PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: August 29, 1996
New Corresp. (Environmental): September 30, 1996
New Corresp. (CGMP): October 16, 1996
Amendment: (Field Copy): November 26, 1996
New Corresp. (Bio): April 2, 1997
New Corresp. (Bio): April 10, 1997

FDA:
Telecon (A. Weikel): September 30, 1996
Telecon (C. Parise): October 16, 1996
Refusal to File Letter: November 20, 1996
Acceptance Letter: December 27, 1996
Method Verification: January 6, 1997
Label Review: April 21, 1997
Bio Letter & Review: May 2, 1997
10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
DMF
DMF
DMF
DMF
DMF
DMF
DMF

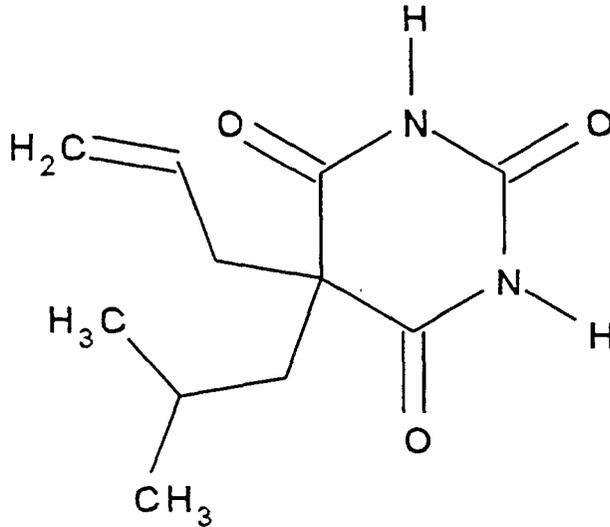
13. DOSAGE FORM
 Capsule (Hard Gelatin)

14. POTENCY
 Butalbital: 50 mg
 Aspirin: 325 mg
 Caffeine: 40 mg
 Codeine Phosphate: 30 mg

15. CHEMICAL NAME AND STRUCTURE

Butalbital USP

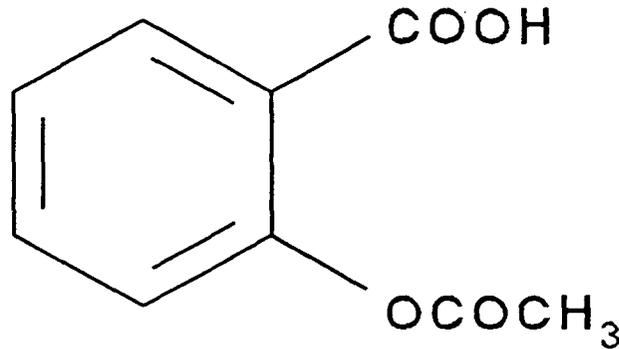
$C_{11}H_{16}N_2O_3$; M.W. = 224.26



5-Allyl-5-isobutyl barbituric acid. CAS [77-26-9]

Aspirin USP

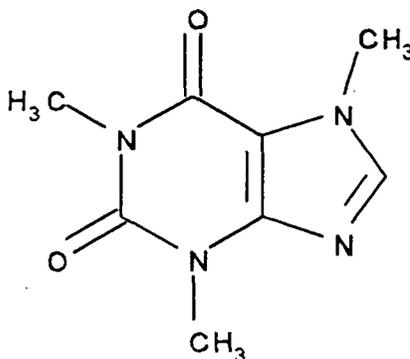
$C_9H_8O_4$; M.W. = 180.16



Salicylic acid acetate. CAS [50-78-2]

Caffeine USP

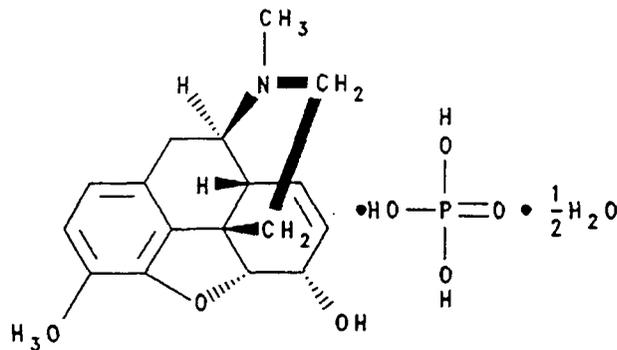
$C_8H_{10}N_4O_2$; M.W. = 194.19



1,3,7-Trimethylxanthine. CAS [58-08-2]

Codeine Phosphate USP

$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$; M.W. = 406.37



7,8-Didehydro-4-5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol phosphate (1:1) (salt) hemihydrate. CAS [41444-62-6]

16. RECORDS AND REPORTS: N/A17. COMMENTS

- a. ANDA 74-951 contains significant deficiencies regarding chemistry, manufacturing and controls procedures, container/closure issues and stability testing and protocol procedures.
- b. Label review is unsatisfactory - 4/21/97.
- c. Bio review is satisfactory - 5/2/97.
- d. EIR unsatisfactory for Jerome Stevens; satisfactory for all other firms 4/30/97.
- e. Drug substances and product are USP - methods validation not required. Methods verification performed on drug product 1/6/97 by the New York Regional Laboratory and is satisfactory.
- f. There is currently only one generic approval for this drug product - ANDA 74-359 (Watson Labs, approved ca. 8/95).

18. CONCLUSIONS AND RECOMMENDATIONS

ANDAs 74-951 is NOT APPROVABLE. The amendment will be MAJOR.

19. REVIEWER:

Donald Shostak

DATE COMPLETED:

May 13, 1997

Page(s)

16

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Chem Rev 1

5/13/97

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-951

BIOEQUIVALENCE

APR 30 1997

Aspirin/Butalbital/Caffeine/Codeine Phosphate
Capsules (325/50/40/30 mg)
ANDA # 74-951
Reviewer: Hoainhon Nguyen
WP # 74951sd.896

Jerome Stevens Pharmaceuticals
Bohemia, NY
Submission Date:
August 29, 1996
April 2, 1997
April 10, 1997

Review of a Fasting Bioequivalence Study and Dissolution Data

I. Background:

The combination drug product of Aspirin/Butalbital/Caffeine/Codeine Phosphate Capsules (325/50/40/30 mg) is used for the relief of the symptom complex of tension (or muscle contraction) headache. Aspirin, the prototype of the salicylates, is a nonsteroidal anti-inflammatory agent, slightly soluble in water with pKa of 3.5. Butalbital is a short- to intermediate-acting barbiturate. Caffeine is a central nervous stimulant. Codeine phosphate is a phenanthrene-derivative opiate agonist, freely soluble in water.

The systemic availability of aspirin after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacids, buffering agents, and particle size. These factors affect not necessarily the extent of absorption of total salicylates but more the stability of aspirin prior to absorption. During the absorption process and after absorption, aspirin is mainly hydrolyzed to salicylic acid and distributed to all body tissues and fluids with highest concentrations found in plasma, liver, renal cortex, heart, and lung. In plasma, about 50-80% of the salicylic acid and its metabolites are loosely bound to plasma proteins. The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are still a good approximation for doses up to 650 mg. The plasma half-life for aspirin is about 12 minutes and for salicylic acid and/or total salicylates is about 3.0 hours. The elimination of therapeutic doses is through the kidneys either as salicylic acid or other biotransformation products. The biotransformation of aspirin occurs primarily in hepatocytes. The major metabolites are salicylic acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acid (1%). The bioavailability of the aspirin component of the studied combination product is

equivalent to that of a solution except for a slower rate of absorption. A peak concentration was obtained at 40 minutes after a 650 mg dose.

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most of the tissues in the body. They are bound to plasma and tissue proteins to a varying degree. Elimination of butalbital is primarily via the kidney (59%-88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products included parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydropropyl) barbituric acid (about 24%), 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid (4.8%), products with the barbituric acid ring hydrolyzed with excretion of urea (14%), as well as unidentified materials. Of the material excreted in the urine, 32% was conjugated. The bioavailability of the butalbital component of the studied combination drug product is equivalent to that of a solution except for a decrease in the rate of absorption. A peak concentration is obtained at about 1.5 hours after a 100 mg dose.

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids. Caffeine is cleared rapidly through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methyl-xanthine and 1-methyluric acid. Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug. The bioavailability of the caffeine component of the studied combination drug product is equivalent to that of a solution except for a slightly longer time to peak. A peak concentration was obtained in less than an hour for an 80 mg dose.

Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as liver, spleen, and kidney. Codeine is not bound to plasma proteins and does not accumulate in body tissues. The plasma half-life is about 2.9 hours. The elimination of codeine is mainly via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide-conjugated codeine (about 10%), free and conjugated morphine (10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in feces. At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours. The bioavailability

of the codeine component of the studied combination drug product is equivalent to that of a solution. Peak concentrations were obtained at 1 hour after a 60 mg dose.

The most commonly reported adverse events associated with the use of this combination drug product are nausea and/or abdominal pain, drowsiness, and dizziness.

Recommended dosage is one or 2 capsules every 4 hours with total daily dosage not exceeding 6 capsules.

The reference listed drug product is Fiorinal® with Codeine Capsules USP, manufactured by Sandoz.

The Division of Bioequivalence requires measurement of only two components of the product, Butalbital and Codeine, for satisfying the bioequivalence approval criteria.

The firm has submitted the results of a single-dose, two-way crossover, fasting bioequivalence study comparing its test product with the RLD product. Comparative dissolution data were also submitted.

II. Bioequivalence Study: (Protocol No. 960366)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Jerome-Stevens' Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg) capsules and Sandoz's Fiorinal® with Codeine Capsules, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at Phoenix Clinical Research Center, Quebec, Canada, between April 11 and May 9, 1996. The principal investigator was Pierre Geoffroy, M.D.. Plasma samples were assayed by _____, under the supervision of _____, between May 20 and May 29, 1996.

Demographics:

Twenty-four and 2 alternate normal, healthy male volunteers between 18-45 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 61.5 - 88.2 kg and 162 - 187 cm, respectively.

Inclusion/exclusion criteria:

Subjects did not have any history of: hypersensitivity to aspirin or any other nonsteroidal anti-inflammatory drugs, caffeine or other xanthines, codeine or other narcotics, butalbital or other barbiturates; alcoholism or drug abuse; cardiovascular, pulmonary, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric.

Restrictions:

They were free of all medications at least 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed 24 hours prior to their check-in appointment and throughout the period of sample. The subjects fasted for overnight prior to and 4 hours after each drug administration. The washout duration between the two phases was 28 days. Duration of confinement was 12 hours pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 2-capsule dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Jerome-Stevens' Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg) capsules, lot # 015395 (Batch size of units, potency of 101.5/99.6/100.2/100.4% (Aspirin/Butalbital/Caffeine/Codeine).

Reference product: Sandoz's Fiorinal® with Codeine capsules, lot # 589X9300 (Potency of 100.2/99.3/100.7/99.5% (Aspirin/Butalbital/Caffeine/Codeine)).

Blood samples were collected at predose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 48, 72, 96, 120 and 144 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -12°C until shipping to the analytical laboratory.

Assay Methodology:

The analytical method was developed by

A. Butalbital:

Assay Specificity:

The assay was specific for butalbital with no significant interferences seen at the retention time of the drug and internal standard in the of the predose subject samples and blank plasma standards. (Interferences seen at the retention time of butalbital in 12 and 7 of the predose samples and blank standards, respectively, were less than 47% in peak height of the LOQ standard of the same run.)

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 0.100 to 9.978 µg/ml of butalbital.

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 6.9% at 0.300 $\mu\text{g/ml}$, 3.7% at 3.995 $\mu\text{g/ml}$ and 6.1% at 7.99 $\mu\text{g/ml}$.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 0.100 $\mu\text{g/ml}$ for butalbital (CV% = 11.3). Any level below this limit was reported as zero.

The prestudy assay validation data showed CV% for the quality control of 0.100 $\mu\text{g/ml}$ was 5.9 (n=10).

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: 100% at 0.300 $\mu\text{g/ml}$, 98.8% at 3.995 $\mu\text{g/ml}$ and 96.6% at 7.990 $\mu\text{g/ml}$.

Stability:

Long-term stability of frozen samples was demonstrated in a pre-study validation study using frozen control samples which were prepared, stored at -22C, analyzed on Day 65 and compared with freshly prepared control samples. Ratio of mean responses was within 0.96-1.01. The actual plasma samples were first collected and stored frozen (-22C) on 04/11/96 and last analyzed on 05/29/96 (Total of 48 days).

Short-term stability (10.1 hours at room temperature), freeze-thaw stability (3 cycles), autosampler stability (2.9 hours at room temperature) and stock solution (in methanol at -22°C for 78 days) were evaluated and acceptable.

B. Codeine:

Assay Specificity:

The assay was specific for codeine with no significant interferences seen at the retention time of the drug and internal standard in the pre-dose subject samples and blank plasma standards. (Interferences were seen at the retention time of codeine in 2 of the blank standards; however, these standards were not included in the calibration and the quality controls of these runs were acceptable.)

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 10.0 to 1000.8 ng/ml of codeine.

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 6.9% at 30.1 ng/ml, 3.8% at 401.7 ng/ml and 3.2% at 803.4 ng/ml.

Sensitivity:

(Based on actual study back-calculate standard data)

Sensitivity limit was 10.0 ng/ml for codeine (CV% = 11.3). Any level below this limit was reported as zero.

Prestudy assay validation data showed that CV% for the quality control of 10.0 ng/ml was 12.3 (n=9)

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: 99.4% at 30.1 ng/ml, 99.8% at 401.7 ng/ml and 98.2% at 803.4 ng/ml.

Stability:

Long-term stability of frozen samples was demonstrated in a pre-study validation study using frozen control samples which were prepared, stored at -22°C, analyzed on Day 65 and compared with freshly prepared control samples. Ratio of mean responses was within 0.93-1.01. The actual plasma samples were first collected and stored frozen (-22°C) on 04/11/96 and last analyzed on 05/29/96 (Total of 48 days).

Short-term stability (10.1 hours at room temperature), freeze-thaw stability (3 cycles), autosampler stability (3.1 hours at room temperature) and stock solution (in methanol at -22°C for 78 days) were evaluated and acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by: $AUC(0-\infty) = AUC(0-T) + [last\ measured\ concentration / KEL]$. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares

means, using the two, one-sided t-test.

Results:

Twenty-five of 26 enrolled volunteers completed the clinical portion of the study. Subject # 6 was withdrawn from the study 25.2 days after Period I dosing for personal reasons. The statistical analysis was performed using 24 (balanced) data sets per protocol.

A. Butalbital:

There was no significant difference ($\alpha=0.05$) between treatments for AUC (0-T), AUC (0-Infinity), \ln AUC(0-T), \ln AUC(0-Infinity) and \ln C_{MAX}. There was a significant difference between treatments for C_{MAX} ($p=0.0479$) and T_{MAX} ($p=0.0432$). The results are summarized in the tables below:

Table I
Butalbital Comparative Pharmacokinetic Parameters
Dose=2 capsules*; n=24

<u>Parameters</u>	<u>Jerome-Stevens'</u> <u>Mean (CV%)</u>	<u>Fiorinal®</u> <u>Mean (CV%)</u>	<u>90%</u> <u>C.I.</u>	<u>Ratio</u> <u>T/R</u>
AUC (0-T) μg.hr/ml	101.9**	100.4**	[0.99;1.04]	1.02
AUC (0-Inf) μg.hr/ml	112.7**	110.5**	[0.99;1.06]	1.02
C _{MAX} (μg/ml)	2.170**	2.100**	[1.00;1.06]	1.03
T _{MAX} (hrs)	1.264(58)	1.854(88)		
K _{EL} (1/hrs)	0.018(20)	0.018(19)		
T _{1/2} (hrs)	40.73(22)	38.68(19)		

*One capsule= Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)

**Geometric LSMeans

Table II
Comparative Mean Plasma Levels of Butalbital
Dose=2 capsules* ; n=24
μg/ml(CV%)

<u>Hour</u>	<u>Jerome-Stevens'</u>	<u>Fiorinal®</u>
0	0	0
0.25	0.178(171)	0.173(173)
0.5	1.351(46)	1.086(52)
0.75	1.807(24)	1.664(29)
1	1.998(15)	1.826(18)
1.33	1.937(11)	1.964(10)
1.67	1.944(11)	1.958(10)
2	1.904(11)	1.890(12)
2.5	1.867(12)	1.868(10)
3	1.838(12)	1.841(11)
4	1.792(14)	1.785(14)
6	1.702(12)	1.699(12)
9	1.570(12)	1.645(12)
12	1.540(12)	1.540(13)
16	1.457(14)	1.462(12)
24	1.323(14)	1.312(13)
48	0.856(19)	0.856(18)
72	0.562(22)	0.543(26)
96	0.373(32)	0.368(36)
120	0.246(35)	0.225(46)
144	0.154(61)	0.133(73)
AUC(0-T) _{μg.hr/ml}	103.1(15)	101.8(17)
AUC(0-Inf) _{μg.hr/ml}	114.4(17)	112.3(18)
C _{MAX}	2.183(11)	2.108(9)

*One capsule = Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)

(NOTE: ANOVA for Butalbital was repeated with Subject # 20 dropped from the

data set due to his CMAX being the first plasma concentration (under Test Treatment). 90% confidence intervals for log-transformed AUCT, AUCI and CMAX without this subject were within [0.80;1.25] (They were [0.99;1.04], [0.99;1.06, and [[1.01;1.07], respectively).)

B. Codeine:

There was no significant difference ($\alpha=0.05$) between treatments for all analyzed parameters. The results are summarized in the tables below:

Table III
Codeine Comparative Pharmacokinetic Parameters
Dose=2 capsules*; n=24

<u>Parameters</u>	<u>Jerome-Stevens'</u> <u>Mean (CV%)</u>	<u>Fiorinal®</u> <u>Mean (CV%)</u>	<u>90%</u> <u>C.I.</u>	<u>Ratio</u> <u>T/R</u>
AUC (0-T) ng.hr/ml	235.2**	234.9**	[0.92;1.08]	1.00
AUC (0-Inf) ng.hr/ml	292.2**	294.0**	[0.93;1.06]	0.99
CMAX(ng/ml)	74.98**	70.50**	[0.99;1.14]	1.06
TMAX (hrs)	1.264(58)	1.854(88)		
KEL (1/hrs)	0.018(20)	0.018(19)		
T1/2 (hrs)	40.73(22)	38.68(19)		

*One capsule=Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)

**Geometric LSMeans

Table IV
Comparative Mean Plasma Levels of Codeine
Dose=2 capsules* ; n=24
ng/ml(CV%)

<u>Hour</u>	<u>Jerome-Stevens'</u>	<u>Fiorinal®</u>
0	0	0
0.25	0	0
0.5	32.39(95)	28.33(112)
0.75	57.72(42)	60.37(50)
1	67.65(24)	64.37(23)
1.33	66.61(20)	64.37(23)
1.67	62.57(22)	62.14(21)
2	56.75(20)	56.06(22)
2.5	48.37(32)	48.13(29)
3	42.70(26)	43.10(23)
4	34.01(25)	34.40(28)
6	17.90(33)	20.33(53)
9	3.05(179)	2.92(179)
12	0	0
16	0	0
24	0	0
AUC(0-T) _{ng.hr/ml}	243.7(28)	246.3(32)
AUC(0-Inf) _{ng.hr/ml}	300.1(24)	304.1(26)
C _{MAX}	76.86(22)	73.42(31)

*One capsule=Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)

(NOTE: ANOVA for Codeine was repeated with Subjects # 1, 16, 18 and 20 dropped from the data set due to their C_{MAX}'s being the first plasma concentration (under Reference Treatment for Subjects # 1 and 20; and under Test Treatment for Subjects #16,20 and 18). 90% confidence intervals for log-transformed AUC_T, AUC_I and C_{MAX} without these subjects were within [0.80;1.25] (They were [0.91;1.11], [0.92;1.06, and [[0.98;1.16], respectively).)

2. Butalbital:

Strength (mg) 50

Strength (mg) 50

	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
<u>15</u>	<u>74.1</u>		(6.9%)	<u>68.5</u>		(7.4%)
<u>30</u>	<u>92.2</u>		(3.8%)	<u>78.4</u>		(5.7%)
<u>45</u>	<u>97.7</u>		(2.2%)	<u>84.1</u>		(4.7%)
<u>60</u>	<u>99.6</u>		(1.6%)	<u>88.3</u>		(4.2%)

Sampling
Times
(min.)

Test Product
Lot # 015395

Reference Product
Lot # 589X9300

3. Caffeine:

Strength (mg) 40

Strength (mg) 40

	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
<u>15</u>	<u>84.3</u>		(8.8%)	<u>57.1</u>		(14.6%)
<u>30</u>	<u>97.5</u>		(3.3%)	<u>73.9</u>		(10.1%)
<u>45</u>	<u>99.4</u>		(1.3%)	<u>82.7</u>		(7.0%)
<u>60</u>	<u>99.6</u>		(1.1%)	<u>88.7</u>		(5.6%)

4. Codeine:

Strength (mg) 30

Strength (mg) 30

	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
<u>15</u>	<u>85.7</u>		(9.7%)	<u>56.8</u>		(15.4%)
<u>30</u>	<u>98.5</u>		(3.0%)	<u>77.1</u>		(9.5%)
<u>45</u>	<u>99.8</u>		(1.1%)	<u>87.1</u>		(5.8%)
<u>60</u>	<u>99.9</u>		(0.9%)	<u>93.1</u>		(4.1%)

USP Current Specification:

NLT 75% (all components) dissolved in 60 minutes

IV. Comments:

1. The single-dose, fasting bioequivalence study conducted by Jerome-Stevens on the test product, Aspirin/Butalbital/Caffeine/Codeine, 325/50/40/30 mg, lot # 015395, comparing it with the reference product, Fiorinal®with Codeine Capsules, lot # 589X9300, demonstrates that the test product is equivalent to the reference product in their rate and extent of absorption as measured by $\ln C_{MAX}$, $\ln AUC(0-T)$ and $\ln AUC(0-\infty)$ of butalbital and codeine.
2. The in vitro dissolution data for the test and reference products are acceptable.

V. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Jerome-Stevens on the test product, Aspirin/Butalbital/Caffeine/Codeine Capsules, 325/50/40/30 mg, lot # 015395, comparing it with the reference product, Sandoz's Fiorinal®with Codeine Capsules, lot # 589X9300, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Jerome-Stevens' Aspirin/Butalbital/Caffeine/Codeine Capsules, 325/50/40/30 mg, is bioequivalent to the reference product, Sandoz's Fiorinal®with Codeine Capsules, under fasting conditions.
2. The in-vitro dissolution testing conducted by Jerome-Stevens on its Aspirin/Butalbital/Caffeine/Codeine Capsules (325/50/40/30 mg), has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 1000 ml of water at 37C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

Not less than 75% of the labeled amount of aspirin, butalbital, caffeine and codeine in the dosage form is dissolved in 60 minutes.



Hoainhon Nguyen
Division of Bioequivalence

Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

Y. Huang 4/24/97

Concur: N. Balucik

Date: 4/30/97

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

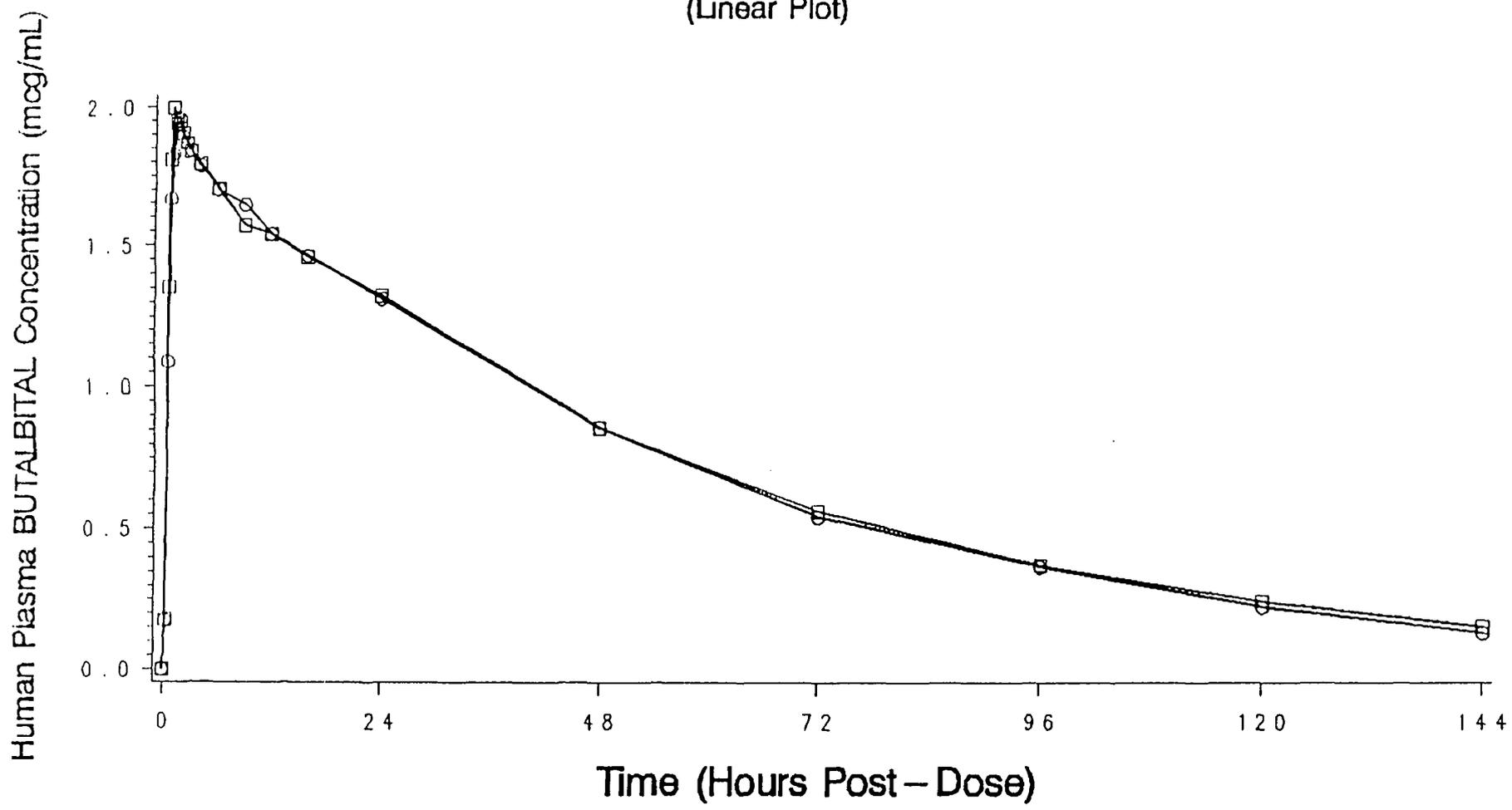
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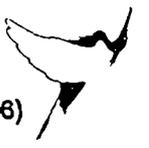
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ANDA # 749515d. 896 Attachment 1 of 3

Figure 4
Project No. 960366
Mean Human Plasma Butalbital Concentrations
(Linear Plot)

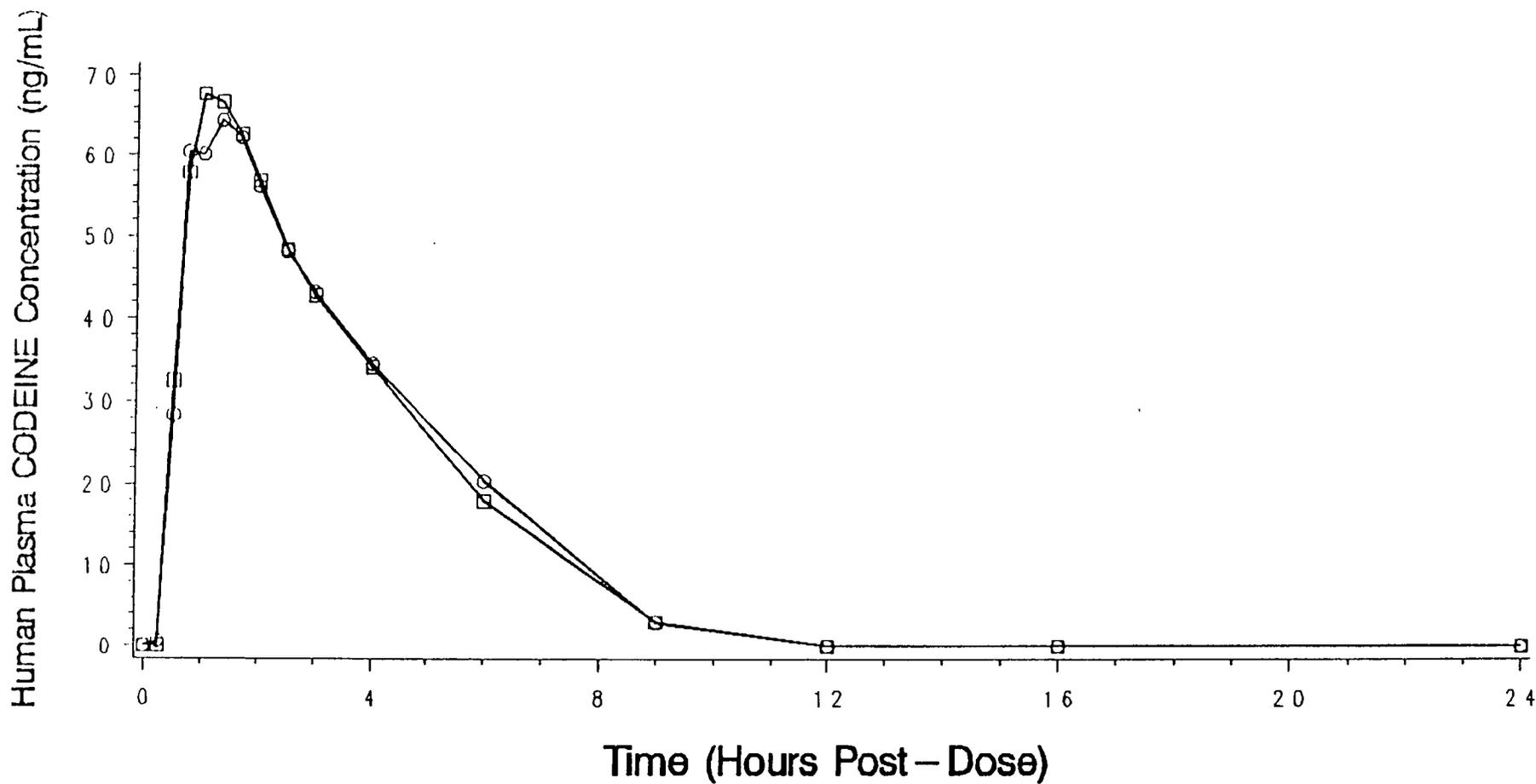


Formulation □-□-□ Jerome-Stevens ○-○-○ Sandoz



ANDA # 74951 sd. 896 Attachment 2 of 3

Figure 2
Project No. 960366
Mean Human Plasma Codeine Concentrations
(Linear Plot)



Formulation □-□-□ Jerome-Stevens ○-○-○ Sandoz



ANDA #74951sd.896 Attachment 3 of 3

Components and Composition Statements

<u>COMPONENTS</u>	<u>mg/Capsule</u>
a. Aspirin	325.0
b. Butalbital	50.0
c. Caffeine	40.0
d. Codeine Phosphate	30.0
e. Starch)
f. Microcrystalline Cellulose)
g. Talc)
h. Colloidal Silicon Dioxide	3
i. Stearic Acid	2
j.	1) 0mg (approx.)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-951

ADMINISTRATIVE DOCUMENTS

CDER Establishment Evaluation Report
for August 28, 1998

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: _____ DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **06-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Establishment: _____ DMF No: _____
AADA No: _____

RD
340

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **06-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Establishment: _____ DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **13-FEB-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

CDER Establishment Evaluation Report
for August 10, 1998

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

MF No:
ADA No:

Profile: CSN OAI Status: NONE
Last Milestone: **OC RECOMMENDATION**
Milestone Date **06-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: **OC RECOMMENDATION**
Milestone Date **06-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: **OC RECOMMENDATION**
Milestone Date **13-FEB-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**



Memorandum

Date . JUN 10 1998
From Consumer Safety Officer, Investigations &
Preapproval Compliance Branch/DMPQ (HFD-324)
Subject Concurrence with District Withhold
Recommendation, ANDAs 74-988, 74-951 & 63-298
To Pat Beers-Block, Chief
Review Support Branch, HFD-617

Applicant: Jerome Stevens
Pharmaceuticals, Inc.
60 DaVinci Drive
Bohemia, NY 11716
CFN 2431950

Division of Manufacturing and Product Quality (HFD-320) has completed review of the Establishment Inspection Report (EIR) of the subject ANDAs. The products for these ANDAs are:

&

ANDA 74-951; Aspirin 325 mg/Butalbital 50 mg/Caffeine
40 mg/Codeine Phosphate Capsules, 30mg

The EIR covers a physical inspection conducted at the applicant's facility from March 23 - April 6, 1998. The ANDAs identify this site to perform finished product manufacture and testing on the subject ANDAs.

DMPQ concurs with the District's recommendation to withhold approval of these ANDAs. Our concurrence with NYK-DO's withhold recommendation is based on the following significant GMP observations relative to the referenced ANDAs:

- Failure to document when samples were placed onto accelerated and long term stability studies for the following products and lots #'s:

ANDA 74-951; Aspirin 325 mg/Butalbital 50 mg/Caffeine 40mg/Codeine Phosphate 30mg Capsules - lot #'s 015395 and 007196

- Failure to document any investigation of dissolution test failures in accelerated stability study samples in the following product and lot #'s: Aspirin 325 mg/Butalbital 50 mg/Caffeine 40mg/Codeine Phosphate 30mg Capsules - lot #'s 015395 and 007196. Note that a statement did appear in the ANDA on page 219, that states that this drug product "exhibits gelatine capsule pellicle formation during dissolution testing."

- Failure to maintain a system for recording temperature and relative humidity conditions in the accelerated stability chamber to assure that it meets specifications.

- Several discrepancies were observed in raw material inventory records.

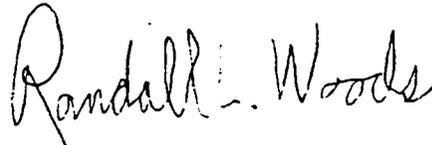
- Failure to perform five replicate injections during system suitability evaluation as required by current USP.

Additionally, numerous minor GMP deficiencies were noted during the inspection.

Finally, in regard to

NYK-DO was contacted on June 10, 1998 and as of this date no response has been received from the applicant.

A copy of the EIR and exhibits are attached for your review. If you have questions, please contact me at (301)-827-0065.

A handwritten signature in cursive script that reads "Randall L. Woods". The signature is written in dark ink and is positioned above the printed name.

Randall L. Woods

Attachments - EIR and Exhibits

ANDA APPROVAL SUMMARY

ANDA: 74-951

DRUG PRODUCT: Butalbital, Aspirin, Caffeine and Codeine Capsules

FIRM: Jerome Stevens Pharmaceuticals, Inc.

DOSAGE FORM: Hard gelatin capsule

STRENGTH: 50 mg Butalbital, 325 mg Aspirin, 40 mg Caffeine,
30 mg Codeine Phosphate

CGMP STATEMENT: Included - New Correspondence, 10/16/96.

EIR STATUS UPDATE: Acceptable EIR issued 8/3/98.

BIO STUDY: Bio study and dissolution testing found satisfactory
4/30/97 - H. Nguyen.

VALIDATION: Drug substance and drug product are compendial. The New
York Regional Laboratory indicated acceptable methods
verification for compendial tests, 1/6/97.

STABILITY: 3 month accelerated (40°C/75% RH) and 12 month room
temperature data submitted for drug product packaged in
the proposed market container/closure systems. Testing
included appearance, assay, dissolution and free
salicylic acid. A 24 month expiration date was proposed
which was supported by the data submitted.

LABELING: Labeling satisfactory for approval, A. Vezza, 8/4/98.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: The bio study was performed on lot #015395,
capsules.

SIZE OF STABILITY BATCHES: Stability testing was performed on the
two test batches, Lot #015395,
capsules and Lot #007196,
capsules.

PROPOSED PRODUCTION BATCH: The proposed production batch sizes is
capsules.

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

ANDA Number: **74-951** Dates of Submission: **June 4 and July 27, 1998**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s and 500s
Satisfactory as of June 4, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of July 27, 1998 submission.

Revisions needed post-approval: Container labels - "Total daily dosage ..." rather than "... dose ..." PI - include 2nd sentence in CLIN PHARM section "The role butalbital, aspirin, and caffeine plays in the relief of the complex of symptoms known as tension headache is incompletely understood." Also PI has FDAMA changes in it but has rev date of 8/97 (we did not make an issue of this)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Fiorinal with Codeine Capsules

NDA Number: 19-429

NDA Drug Name: Fiorinal (Butalbital/Aspirin/Caffeine) with Codeine Capsules USP, 50 mg/325 mg/40 mg/30 mg

NDA Firm: Novartis

Date of Approval of NDA Insert and supplement #: 4-29-91 (S-001)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: label on file and side-by-sides submitted

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?	X		
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	

	Yes	No	N.A.
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? Exceeds NDA but meets USP requirements.		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of the listed drug (Fiorinal with Codeine; Approved April 29, 1991, Revised November 1, 1990). Since recent changes approved for Fiorinal (NDA 17-534) and Fioricet with Codeine (NDA 20-232) should apply to this drug product, PM, Deborah Gunter, has been asked to include this labeling in her analysis. She has responded to an E-mail sent to her concerning this and is in the process of trying to consolidate the insert labeling for all three products.

2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

NDA: Store and dispense below 77°F (25°C) in a tight container.

ANDA: Store and dispense below 77°F (25°C) in a tight, light-resistant container.

USP: Preserve in tight, light-resistant containers.

4. Product Line:

The innovator markets their product in bottles of 100s and unit-dose containers of 25s.

The applicant proposes to market their product in bottles of 100s and 500s.

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 129.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 55.

7. All manufacturing will be performed by Jerome Stevens Pharmaceuticals. No outside firms are utilized. See pages 118 and 123.

8. Container/Closure:

This product will be packaged in white HDPE containers with a screw cap.

Date of Review: 7-30-98 Dates of Submission: 6-4 & 7-27-98

Primary Reviewer: Adolph Vezza Date:

A. Vezza

8/4/98

Team Leader: Charlie Hoppes Date:

Ch Hoppes

8/4/98

M E M O R A N D U M

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

DATE: May 18, 1998

FROM: Don Shostak, HFD-647 *D. Shostak 5/18/98*

THRU: U. Venkataram, HFD-647 *U.V. Venkataram 5/18/98*

SUBJECT: ANDA 74-951 (Dissolution Testing Waiver)

TO: Timothy Ames

UV, Florence and I discussed Jerome Stevens' dissolution waiver request in their 5/13/98 correspondence. It was decided that we would ask Jerome Stevens to commit to placing the first production batch under accelerated storage conditions (40°C/75% RH) and to perform dissolution testing according to the ANDA procedure followed by the method published in USP 23, Supplement 8 if necessary. We also agreed that if the applicant agrees to this request, we will reclassify the deficiencies to MINOR.

74951.2mem

74-951 5/18/98
Tim: Done 5/20/98
you can inform the applicant of the above in regard to their dissolution waiver requests they can submit the results when they obtain them
Don S

Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

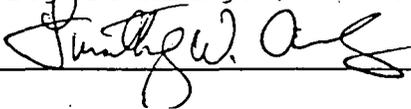
PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens
Tim Ames, FDA

PHONE NUMBER: 516-567-1113

DATE: 5/20/98

Called firm to relate decision regarding Item 3 of the May 4, 1998 Major deficiency fax. It was decided by Ffang, Uvenkataram and Dshotak to request the firm to commit to placing the first production batch under accelerated storage conditions (0° C/75% RH) and to perform dissolution testing according to the ANDA procedure followed by the method published in the USP 23, Supplement 8. This request was related to the firm and it was also related that the amendment would now be considered a MINCR amendment and should be designated as such referencing this teleconference.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD



phone.174

Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens
Tim Ames, FDA

PHONE NUMBER: 516-567-1113

DATE: 5/12/98

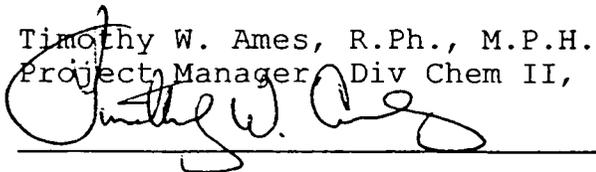
Called firm to relate clarification of Item 3 "Please perform dissolution testing at accelerated conditions using the procedure specified in the 20th IRA to USP 23 published in the Pharmacopeial Forum, Volume 23, # 6, Nov. - Dec. 1997 in the last facsimile deficiency.

I explained that this question was asked as a result of the accelerated stability sample failures at 60 and 90 days. The firm's assertion that this was due to pellicle formation was unsubstantiated and by requesting this testing be performed it would determine if pellicle formation was the actual problem.

The firm countered by indicating that this was unnecessary as their RT data was acceptable and all that was needed to establish an expiry date and all that was necessary for approval. They further claimed that this was a known problem with the RLD and only generic on the market. They explained they felt they were being held to an unnecessarily higher standard since they were a small firm and that this was a disproportionate burden on them. They also claimed that this may effect the classification to a MAJOR AMENDMENT status of this deficiency fax.

I indicated I would discuss their issues with the Chemistry Team Leader and Division Director.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD



M E M O R A N D U M

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

DATE: May 18, 1998

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74951.2mem

Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

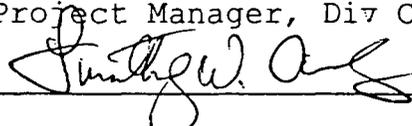
PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens
Tim Ames, FDA

PHONE NUMBER:

DATE: 5/20/98

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Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD



Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens
Tim Ames, FDA

PHONE NUMBER: 516-567-1113

DATE: 5/12/98

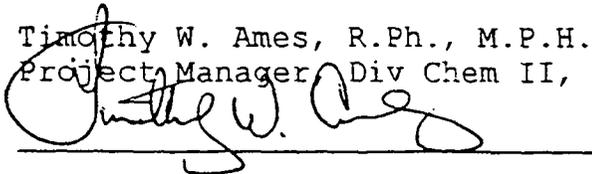
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I explained that this question was asked as a result of the accelerated stability sample failures at 60 and 90 days. The firm's assertion that this was due to pellicle formation was unsubstantiated and by requesting this testing be performed it would determine if pellicle formation was the actual problem.

The firm countered by indicating that this was unnecessary as their RT data was acceptable and all that was needed to establish an expiry date and all that was necessary for approval. They further claimed that this was a known problem with the RLD and only generic on the market. They explained they felt they were being held to an unnecessarily higher standard since they were a small firm and that this was a disproportionate burden on them. They also claimed that this may effect the classification to a MAJOR AMENDMENT status of this deficiency fax.

I indicated I would discuss their issues with the Chemistry Team Leader and Division Director.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD



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

ANDA Number: **74-951** Date of Submission: **September 29, 1997**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and
Codeine Phosphate Capsules USP,
50 mg/325 mg/40 mg/30 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "R only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: <http://www.fda.gov/cder/guidance/index.htm> for guidance.
- b. The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement from your labels and labeling.

2. CONTAINER 100s and 500s

- a. See GENERAL COMMENTS above.
- b. Usual Adult Dosage - Revise to read as follows:

1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules. [N.B. not "1-2"]

3. INSERT

a. GENERAL COMMENT

Please improve the print quality, especially of the subscripts, throughout the text of the insert.

b. DESCRIPTION

- i. See GENERAL COMMENTS [under (1)] above.
- ii. Please note you have failed to provide all of the dyes and colorants found in the capsule (omissions include: D&C Red and D&C Red and all the dyes found in the imprinting ink (omissions include: FD&C Blue FD&C Red D&C Blue , and D&C Yellow . Please revise the inactive listing to include these.

c. INDICATIONS AND USAGE

Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for... (rather than "...is indicated for...")

d. DRUG ABUSE AND DEPENDENCE

Butalbital, aspirin, caffeine and codeine phosphate capsules are controlled... (rather than "This product is controlled...")

e. HOW SUPPLIED

- i. Delete all the terminal zeros in this section (i.e., "greater than 1 g" rather than "greater than 1.0 g" and "lethal dose 0.5 to 1 g" rather than "lethal dose 0.5-1.0 g")
- ii. Replace all the hyphens in this section with the word "to" (e.g., "0.5 to 1 g")
- iii. Each yellow and blue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsule USP, 50 mg/325 mg/40 mg/30 mg is... (delete the

word "capsule" after "30 mg")

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
 If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Fiorinal with Codeine Capsules

NDA Number: 19-429

NDA Drug Name: Fiorinal (Butalbital/Aspirin/Caffeine) with Codeine Capsules USP, 50 mg/325 mg/40 mg/30 mg

NDA Firm: Sandoz Pharmaceuticals Corporation

Date of Approval of NDA Insert and supplement #: 4-29-91 (S-001)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: label on file and side-by-sides submitted

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO		X	

	Yes	No	N.A.
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? See note to chemist.	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X

	Yes	No	N.A.
USP Issues: (PTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? Exceeds NDA but meets USP requirements.		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: PTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

*****NOTE TO PROJECT MANAGER*****

Please ensure the note to the chemist is answered prior to faxing the labeling review. Thanks.

*****NOTE/QUESTION TO THE CHEMIST:*****

See comment (b) (ii) under INSERT. Do you concur?

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of the listed drug (Fiorinal with Codeine; Approved April 29, 1991, Revised November 1, 1990). Since recent changes approved for Fiorinal (NDA 17-534) and Fioricet with Codeine (NDA 20-232) should apply to this drug product, PM, Deborah Gunter, has been asked to include this labeling in her analysis. She has responded to an E-mail sent to her concerning this and is in the process of trying to consolidate the insert labeling for all three products.
2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this drug product.
3. Storage/Dispensing Conditions:

NDA: Store and dispense below 77°F (25°C) in a tight container.

ANDA: Store and dispense below 77°F (25°C) in a tight, light-resistant container.

USP: Preserve in tight, light-resistant containers.

4. Product Line:

The innovator markets their product in bottles of 100s and unit-dose containers of 25s.

The applicant proposes to market their product in bottles of 100s and 500s.

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 129.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 55. See note to chemist and comment (b)(ii) under INSERT.

7. All manufacturing will be performed by Jerome Stevens Pharmaceuticals. No outside firms are utilized. See pages 118 and 123.

8. Container/Closure:

This product will be packaged in white HDPE containers with a screw cap.

9. Review done with red jacket.

Date of Review: 4-24-98 Date of Submission: 9-29-97

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

5/7/98

Team Leader: Charlie Hoppes

Date:

Charlie Hoppes

5/7/98

cc:

74951NA2.L

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

ANDA Number: **74-951** Date of Submission: **September 29, 1997**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and
Codeine Phosphate Capsules USP,
50 mg/325 mg/40 mg/30 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "R only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: <http://www.fda.gov/cder/guidance/index.htm> for guidance.
- b. The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement from your labels and labeling.

2. CONTAINER 100s and 500s

- a. See GENERAL COMMENTS above.
- b. Usual Adult Dosage - Revise to read as follows:

1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules. [N.B. not "1-2"]

3. INSERT

a. GENERAL COMMENT

Please improve the print quality, especially of the subscripts, throughout the text of the insert.

b. DESCRIPTION

- i. See GENERAL COMMENTS [under (1)] above.
- ii. Please note you have failed to provide all of the dyes and colorants found in the capsule

clude

c. INDICATIONS AND USAGE

Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for... (rather than "...is indicated for...")

d. DRUG ABUSE AND DEPENDENCE

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e. HOW SUPPLIED

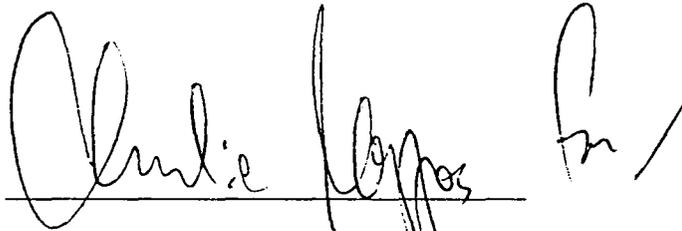
- i. Delete all the terminal zeros in this section (i.e., "greater than 1 g" rather than "greater than 1.0 g" and "lethal dose 0.5 to 1 g" rather than "lethal dose 0.5-1.0 g")
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To facilitate review of your next submission, and in accordance with 21 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.

A handwritten signature in black ink, appearing to read "Jerry Phillips", is written over a horizontal line. To the right of the signature, there is a large, stylized flourish or mark.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CDER Establishment Evaluation Report
for April 30, 1997

Application: **ANDA 74951/000**
Stamp: **30-AUG-1996** Regulatory Due:
Applicant: **JEROME STEVENS**
60 DAVINCI DR
BOHEMIA, NY 11716

Priority:
Action Goal:
Brand Name:
Established Name: **BUTALBITAL;ASPIRIN;CAFFEINE;**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **50MG/32MG/40MG/30MG**

Org Code: **600**
District Goal: **30-OCT-1997**

FDA Contacts: **T. AMES (HFD-617)**
J. SIMMONS (HFD-647)

301-594-0305 , Project Manager
301-594-0305 , Team Leader

Overall Recommendation:

Establishment:

DMF No:

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATIO 04-FEB-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **2431950**

DMF No:

JEROME STEVENS PHARMACEUTI
60 DA VINCI DR
BOHEMIA, NY 11716

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO DO 06-JAN-1997**

Responsibilities:

FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATIO 09-APR-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:

INC

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATIO 06-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

*CMP
QUEST*

CDER Establishment Evaluation Report
for April 30, 1997

Establishment:

DMF No:

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Profile: CSN

OAI Status: NONE

Last Milestone: OC RECOMMENDATIO 06-JAN-1997

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment:

DMF No:

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Profile: CSN

OAI Status: NONE

Last Milestone: OC RECOMMENDATIO 13-FEB-1997

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One) <input checked="" type="checkbox"/> Original <input type="checkbox"/> FollowUp <input type="checkbox"/> FUR	DATE December 24, 1996	PHONE NO. 594-0305	EER ID #
REQUESTORS NAME: Tim Ames	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-951			
BRAND NAME:	ESTABLISHED NAME: Aspirin 325 mg/Butalbital 50 mg/Caffeine 40 mg/Codeine Phosphate 30 mg Capsule		
DOSAGE STRENGTH:	STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
PROFILE CLASS.: CHG	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)		
APPLICANT'S NAME: Jerome Stevens Pharmaceuticals, Inc.			
APPLICANT'S ADDRESS: 60 DaVinci Dr. Bohemia, NY 11716			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

RESPONSIBILITY

DMF NUMBER/
PROFILE CODE

FKEY
CIRTS ID

HFD-324 USE ONLY

1.		Drug Substance Supplier (Aspirin)	CSN			
2.	F	nisco) Drug Substance Supplier (Butalbital)	CSN			
3.		Drug Substance Supplier (Caffeine)	CSN			
4.		4 Drug substance Supplier (Caffeine)	CSN			
5.	Germany	Drug Product Manufacturer	CHG			

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

OHM FDA 3274 (8/92)

Distribution: Original and Yellow Copy: HFD-324.

c: ANDA 74-951 HFD-647/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-647/JSimmons HFD-647/GJSmith

Handwritten notes: REPLY TO REQUEST ?? continue 12/26/96 to ?? See EER 4/30/97

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

ANDA Number: 74-951 Date of Submission: November 26, 1996

Applicant's Name: Jerome Stevens Pharmaceuticals Inc.

Established Name: Butalbital, Aspirin, Caffeine, and
Codeine Phosphate Capsules USP,
50 mg/325 mg/40 mg/30 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. Revise the established name on all labels and labeling to read as follows:

Butalbital, Aspirin, Caffeine and Codeine
Phosphate Capsules USP

- b. Revise to read "mcg" rather than "µg" throughout the text of the insert.

2. CONTAINER

- a. See GENERAL COMMENTS a above.
- b. Include the product strength on the main panel to appear in conjunction with the established name.
- c. Usual Adult Dosage - Revise to read as follows:
1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules.
- d. 25°C(77°F)
- e. Place an asterisk after "BUTALBITAL" and after "PHOSPHATE" in the established name.

3. INSERT

- a. TITLE

See GENERAL COMMENTS a.

b. DESCRIPTION

- i. Revise the first sentence to read:
Each capsule for oral administration contains...
- ii. Revise to read "molecular formula" rather than "empirical formula". [2 places].
- iii. Include the molecular formulas, structural formulas and molecular weights of each active ingredient.
- iv. Inactive Ingredients - Revise to read "pregelatinized starch" rather than "starch" and "colloidal silicon dioxide" rather than "silicon dioxide".

c. CLINICAL PHARMACOLOGY

- i. Pharmacokinetics - Insert the following text to appear as the first paragraph:

Bioavailability: The bioavailability of the components of the fixed combination of butalbital, aspirin, caffeine and codeine is identical to their bioavailability when butalbital, aspirin, caffeine and codeine is administered separately in equivalent molar doses.
- ii. Aspirin - Revise the penultimate sentence of the penultimate paragraph to read as follows:

...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...
- iii. Butalbital - Revise the first sentence of the penultimate paragraph to read as follows:

...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...
- iv. Caffeine - Revise the first sentence of the penultimate paragraph to read as follows:

...component for butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

d. INDICATIONS

- i. Revise this section heading to read:

INDICATIONS AND USAGE

- ii. Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for...

- iii. Insert the following text to appear as the second paragraph:

Evidence supporting the efficacy of butalbital, aspirin, caffeine and codeine phosphate capsules is derived from 2 multi-clinic trials that compared patients with tension headache randomly assigned to 4 parallel treatments: 1) butalbital, aspirin, caffeine and codeine; 2) codeine; 3) butalbital, aspirin, and caffeine; 4) placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. The combination product of butalbital, aspirin caffeine, and codeine proved statistically significantly superior to each of its components and to placebo on measures of pain relief.

- iv. Revise the last paragraph to read as follows:

...safety of butalbital, aspirin, caffeine, and codeine in the treatment of...

e. CONTRAINDICATIONS

This combination product...

f. PRECAUTIONS

- i. General - Revise the first sentence of paragraph one to read as follows:

Butalbital, aspirin, caffeine, and codeine should be prescribed with caution for...

- ii. Information for Patients

A) Paragraph one - ...that this combination product contains...

- B) Paragraph two - Butalbital, aspirin, caffeine, and codeine may impair...

iii. Drug Interactions

- A) Revise paragraph three to read:

Butalbital, aspirin, caffeine, and codeine may...

- B) Penultimate paragraph - Butalbital, aspirin, caffeine, and codeine may diminish...

iv. Usage in Pregnancy

- A) Revise this subsection heading to read "Pregnancy" rather than "Usage in Pregnancy".

- B) Teratogenic Effects - Revise to read as follows:

...conducted with butalbital, aspirin, caffeine, and codeine. It is...this combination product...

- C) Nonteratogenic Effects - Place a period following the last sentence of the second paragraph.

v. Pediatric Use - Revise to read:

...in pediatric patients below the...

g. ADVERSE REACTIONS

- i. Commonly Observed - Replace "this product" with "butalbital, aspirin, caffeine and codeine".

ii. Incidence in Controlled Clinical Trials

- A) Paragraph one - ...comparing the combination product to placebo...

- B) Paragraph two, last sentence - ...obtained from other clinical...

- iii. Insert the following text to appear as the first paragraph following the table:

**Other Adverse Events Reported During
Controlled Clinical Trials**

The listing that follows represents the proportion of the 382 patients exposed to butalbital, aspirin, caffeine, and codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving the combination product, the adverse events were not necessarily caused by butalbital, aspirin, caffeine, and codeine.

iv. Miscellaneous, second paragraph - ...patients treated with the combination product, are...

h. DRUG ABUSE AND DEPENDENCE

Butalbital, aspirin, caffeine and codeine phosphate capsules are controlled...

i. OVERDOSAGE

i. Revise paragraph one to read as follows:

...overdosage of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules are attributable...toxicity from this combination product is unlikely.

ii. Treatment

A) Paragraph one, first sentence - ...with this combination product.

B) Paragraph four - ...intravenous administration.

C) Paragraph five, second sentence - ...a dose of 0.4 mg to 2 mg...

iii. Toxic and Lethal Doses - Delete the terminal zeros from "1 g", "2 g" and "5 g".

j. HOW SUPPLIED

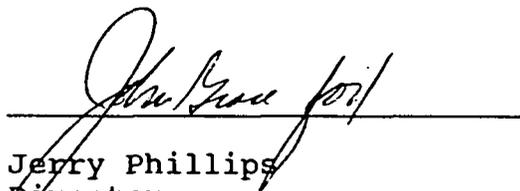
i. Each yellow and blue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsule USP, 50 mg/325 mg/40 mg/30 mg is...

ii. See comment 2(d).

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

A handwritten signature in cursive script, appearing to read "Jerry Phillips", is written over a horizontal line.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: **74-951** Date of Submission: **November 26, 1996**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and Codeine
Phosphate Capsules USP,
50 mg/325 mg/40 mg/30 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. Revise the established name on all labels and labeling to read as follows:

Butalbital, Aspirin, Caffeine and Codeine
Phosphate Capsules USP

- b. Revise to read "mcg" rather than "µg" throughout the text of the insert.

2. CONTAINER

- a. See GENERAL COMMENTS a above.

- b. Include the product strength on the main panel to appear in conjunction with the established name.

- c. Usual Adult Dosage - Revise to read as follows:

1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules.

- d. 25°C (77°F)

- e. Place an asterisk after "BUTALBITAL" and after "PHOSPHATE" in the established name.

3. INSERT

- a. TITLE

See GENERAL COMMENTS a.

b. DESCRIPTION

- i. Revise the first sentence to read:

Each capsule for oral administration contains...

- ii. Revise to read "molecular formula" rather than "empirical formula". [2 places].
- iii. Include the molecular formulas, structural formulas and molecular weights of each active ingredient.
- iv. Inactive Ingredients - Revise to read "pregelatinized starch" rather than "starch" and "colloidal silicon dioxide" rather than "silicon dioxide".

c. CLINICAL PHARMACOLOGY

- i. Pharmacokinetics - Insert the following text to appear as the first paragraph:

Bioavailability: The bioavailability of the components of the fixed combination of butalbital, aspirin, caffeine and codeine is identical to their bioavailability when butalbital, aspirin, caffeine and codeine is administered separately in equivalent molar doses.

- ii. Aspirin - Revise the penultimate sentence of the penultimate paragraph to read as follows:
- ...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

- iii. Butalbital - Revise the first sentence of the penultimate paragraph to read as follows:
- ...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

- iv. Caffeine - Revise the first sentence of the penultimate paragraph to read as follows:
- ...component for butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

d. INDICATIONS

- i. Revise this section heading to read:

INDICATIONS AND USAGE

- ii. Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for...

- iii. Insert the following text to appear as the second paragraph:

Evidence supporting the efficacy of butalbital, aspirin, caffeine and codeine phosphate capsules is derived from 2 multi-clinic trials that compared patients with tension headache randomly assigned to 4 parallel treatments: 1) butalbital, aspirin, caffeine and codeine; 2) codeine; 3) butalbital, aspirin, and caffeine; 4) placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. The combination product of butalbital, aspirin caffeine, and codeine proved statistically significantly superior to each of its components and to placebo on measures of pain relief.

- iv. Revise the last paragraph to read as follows:

...safety of butalbital, aspirin, caffeine, and codeine in the treatment of...

e. CONTRAINDICATIONS

This combination product...

f. PRECAUTIONS

- i. General - Revise the first sentence of paragraph one to read as follows:

Butalbital, aspirin, caffeine, and codeine should be prescribed with caution for...

- ii. Information for Patients

A) Paragraph one - ...that this combination product contains...

- B) Paragraph two - Butalbital, aspirin, caffeine, and codeine may impair...

iii. Drug Interactions

- A) Revise paragraph three to read:

Butalbital, aspirin, caffeine, and codeine may...

- B) Penultimate paragraph - Butalbital, aspirin, caffeine, and codeine may diminish...

iv. Usage in Pregnancy

- A) Revise this subsection heading to read "Pregnancy" rather than "Usage in Pregnancy".

- B) Teratogenic Effects - Revise to read as follows:

...conducted with butalbital, aspirin, caffeine, and codeine. It is...this combination product...

- C) Nonteratogenic Effects - Place a period following the last sentence of the second paragraph.

v. Pediatric Use - Revise to read:

...in pediatric patients below the...

g. ADVERSE REACTIONS

- i. Commonly Observed - Replace "this product" with "butalbital, aspirin, caffeine and codeine".

ii. Incidence in Controlled Clinical Trials

- A) Paragraph one - ...comparing the combination product to placebo...

- B) Paragraph two, last sentence - ...obtained from other clinical...

- iii. Insert the following text to appear as the first paragraph following the table:

**Other Adverse Events Reported During
Controlled Clinical Trials**

The listing that follows represents the proportion of the 382 patients exposed to butalbital, aspirin, caffeine, and codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving the combination product, the adverse events were not necessarily caused by butalbital, aspirin, caffeine, and codeine.

iv. Miscellaneous, second paragraph - ...patients treated with the combination product, are...

h. DRUG ABUSE AND DEPENDENCE

Butalbital, aspirin, caffeine and codeine phosphate capsules are controlled...

i. OVERDOSAGE

i. Revise paragraph one to read as follows:

...overdosage of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules are attributable...toxicity from this combination product is unlikely.

ii. Treatment

A) Paragraph one, first sentence - ...with this combination product.

B) Paragraph four - ...intravenous administration.

C) Paragraph five, second sentence - ...a dose of 0.4 mg to 2 mg...

iii. Toxic and Lethal Doses - Delete the terminal zeros from "1 g", "2 g" and "5 g".

j. HOW SUPPLIED

i. Each yellow and blue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsule USP, 50 mg/325 mg/40 mg/30 mg is...

ii. See comment 2(d).

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP Z3	X		
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAM stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD? Product is a capsule.			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? See note to chemist.	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? Exceeds NDA but meets USP requirements.		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		

Patent/Exclusivity Issues?: FIR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.

X

*****NOTE TO PROJECT MANAGER*****

Please ensure the notes to the chemist are answered prior to faxing the labeling review. Thanks.

*****NOTES/QUESTIONS TO THE CHEMIST:*****

1. See comment b(iv) under INSERT. Do you concur? *Concur D. Hestak 5/12/9*
2. The firm lists "D&C Yellow #10, FD&C Blue #1 and FD&C Yellow #6" as inactive ingredients. I believe they are the dyes used in the capsule color. I was unable to find the components of the capsule in the raw materials section of the jacket. Can you verify these ingredients? *Applicant to provide this information. See Chem Rev. D. Hestak 5/12/9*

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Fiorinal with Codeine; Approved April 29, 1991, Revised November 1, 1990).
2. Patent/ Exclusivities:
There are no patents or exclusivities that pertain to this drug product.
3. Storage/Dispensing Conditions:
NDA: Store and dispense below 77°F (25°C) in a tight container.
ANDA: Store and dispense below 77°F (25°C) in a tight, light-resistant container.
USP: Preserve in tight, light-resistant containers.
4. Scoring:
Not applicable. This product is a capsule.
5. Product Line:
The innovator markets their product in bottles of 100s and unit-dose containers of 25s.
The applicant proposes to market their product in bottles of 100s and 500s.
6. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products

for Human Use; Final Rule, effective 9/13/95). See page 129.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 55. See note to chemist.

8. All manufacturing will be performed by Jerome Stevens Pharmaceuticals. No outside firms are utilized. See pages 118 and 123.

9. Container/Closure:

This product will be packaged in white containers with a screw cap.

Date of Review: March 24, 1997 for Jackie White

Date of Submission: November 26, 1996

Primary Reviewer:

Date:

Secondary Reviewer:

Date:

Team Leader:

Date:

cc:

L

lallncrodt Chemical Inc.
.O. Box 5432
t. Louis, MO 63147

Drug Substance Manufacturer
(codeine)

4839
CSN

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One) <input checked="" type="checkbox"/> Original <input type="checkbox"/> FollowUp <input type="checkbox"/> FUR	DATE October 9, 1996	PHONE NO.	EER ID #
REQUESTORS NAME: Tim Ames	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-951			
BRAND NAME:	ESTABLISHED NAME: Aspirin 325 mg/Butalbital 50 mg/Caffeine 40 mg/Codeine Phosphate 30 mg Capsule		
DOSAGE STRENGTH:			STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
PROFILE CLASS.: CHG	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)		
APPLICANT'S NAME: Jerome Stevens Pharmaceuticals, Inc.			
APPLICANT'S ADDRESS: 60 DaVinci Dr. Bohemia, NY 11716			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

RESPONSIBILITY

DMF NUMBER/
PROFILE CODE

FKEY
CIRTS ID

HFD-324 USE ONLY

(Name and Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY
	Drug Substance Supplier (Aspirin)	CSN		
2. (sco)	Drug Substance Supplier (Butalbital)	CSN		
	Drug Substance Supplier (Caffeine)	CSN		
	Drug substance Supplier (Caffeine)	CSN		
3. Applicant	Drug Product Manufacturer	CHG		

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

EROME STEVENS
0 DAVINCI DR
OHEMIA

NY 11716

NDA #: N074951

Dear Sir/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 for the following:

NAME OF DRUG:
MUTALBITAL;ASPIRIN;CAFFEINE;CODEINE PHOSPHATE
Dosage Form: CAP Potency: 50MG/32MG/40MG/30MG USP: Y

USP,

DATE OF APPLICATION: 29-AUG-96

DATE OF RECEIPT: 30-AUG-96

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

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

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

Sincerely yours,

*Simmons
Rendon VII
HFD-647*

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION/MEETING

I conveyed to Mr. Steinlauf that the application was lacking a few items before we could accept it for filing. I explained that he should provide this informatin to us within 10 working days. The following items were requested:

- a signed certification of compliance with environmental laws
- a written explanation of the annotated portions of the side-by-side labeling comparisons
- a signed CGMP certification

He promised to fax these items in right away.

DATE

September 30,
1996

ANDA NUMBER

74-951

IND NUMBER

TELECON

INITIATED BY MADE
 _ APPLICANT/ X BY
 SPONSOR TELE.

_ X FDA _ IN
 PERSON

PRODUCT NAME

Butalbital/
Aspirin/Caffeine/
Codeine Capsules

FIRM NAME

Jerome Stevens
Pharms

NAME AND TITLE OF
PERSON WITH WHOM
CONVERSATION WAS HELD

Ronald Steinlauf
Vice President

TELEPHONE NUMBER

(516) 567-1113

SIGNATURE



RECORD OF TELEPHONE CONVERSATION

Requested that they submit a certification that Jerome Stevens is in compliance with current good manufacturing practices under 21 CFR parts 210 and 211.

DATE

October 16, 1996

APPLICATION NUMBER

74-95

IND NUMBER

TELECON

INITIATED BY MADE
_ APPLICANT/ _ BY
SPONSOR TELE.

X _ FDA _ IN
 PERSON

PRODUCT NAME
Butalbital, Aspirin,
Caffeine, and
Codeine Phosphate

FIRM NAME
Jerome Stevens

NAME AND TITLE OF
PERSON WITH WHOM
CONVERSATION WAS HELD

Ronald Steinlauf

TELEPHONE NUMBER

516-567-1113

SIGNATURE

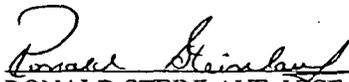
Cecelia Parise

SEPTEMBER 30, 1996

FOOD AND DRUG ADMINISTRATION
MS. ANNA MARIE WEIKEL

PLEASE FIND THE FOLLOWING:

- 2 EACH ... REPLACEMENT FOR PAGE 256
- 2 EACH ... REPLACEMENT FOR PAGE 120
- 2 EACH ... REPLACEMENT FOR PAGE 63
- 2 EACH ... REPLACEMENT FOR PAGE 59
- 2 EACH ... EXPLANATION OF "SIDE BY SIDE LABELING"
- 2 EACH ... COPY OF GRINDSTED NAME CHANGE



RONALD STEINLAUF, VICE PRESIDENT
JEROME STEVENS PHARMACEUTICALS, INC.

[314.94(a)(9)] Environmental Impact Analysis Statement

as per FR Vol.39, No.74 - April 16, 1974

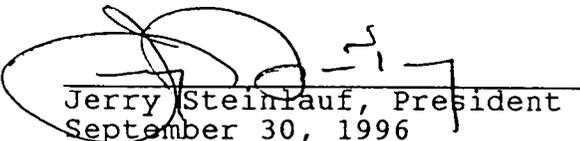
- A. Date: April 6, 1979
B. Address: Jerome Stevens Pharmaceuticals Inc.
60 DaVinci Drive
Bohemia, New York 11716

A Pharmaceutical Manufacturer of compressed and coated tablets and capsules.

1. Described the proposed action.
No probable impact as no emission to outside atmosphere; and no harmful emission into the water waste.
2. No impact on the environment and no primary or secondary consequences thereby.
 - a) 1. No pollution (air, water, soil)
 2. Complies to ordinance of solid and liquid waste.
 3. No toxic substances are emitted.
 4. No effect on humans, animals or plants.
3. No adverse environmental effect can occur due to the nature of our manufacturing pharmaceuticals in dosage forms as all exhausts are connected to internal closed system dust arrestors.
4. Not applicable
5. Short term and long term actions of production and maintenance does not and cannot result in any adverse emissions to the environment.
6. Not applicable
7. No objections have been received by any other agencies.
8. Not applicable
9. Not applicable

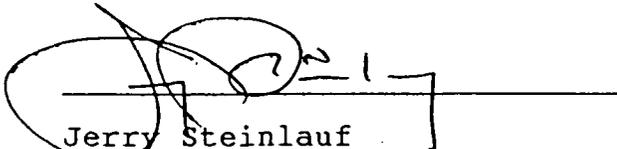
Certification Statement

Jerome Stevens Pharmaceuticals certifies that the manufacture of Aspirin 325mg/Butalbital 50mg/Caffeine 40mg/Codeine Phosphate 30mg Capsule is conducted in full accordance with all State and Federal environmental laws.


Jerry Steinlauf, President
September 30, 1996

CGMP Certification:

At the time of the filing for this application, Jerome Stevens Pharmaceuticals Inc. believes, to the best of it's knowledge that the firm's faciltiy has CGMP certification from FDA's New York Brooklyn District Office.

A handwritten signature in black ink, appearing to read "Jerry Steinlauf", is written over a horizontal line. The signature is somewhat stylized and includes a large loop on the left side.

Jerry Steinlauf
President

September 30, 1996

Caffeine USP is manufactured by

located at

4

Reference is made to DMF
page)

- see authorization letter (next

BUTALBITAL USP, MANUFACTURED BY /
LOCATED AT:

F

K

REFERENCE IS MADE TO DMF

SEE AUTHORIZATION LETTER (NEXT PAGE)


RONALD STEINLAUF, VICE PRESIDENT
JEROME STEVENS PHARMACEUTICALS, INC.
SEPTEMBER 30, 1996

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74-951

CORRESPONDENCE

Jerome Stevens Pharmaceuticals

Inc.
Generic Manufacturers

ANDA DRUG AMENDMENT

August 26, 1998

N/AM

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-951; Butalbital 50mg/Aspirin 325mg/Caffeine
40mg/Codeine Phosphate 30mg Capsule USP

'TELEPHONE AMENDMENT'

Dear Ms. Florence Fang:

As per our telephone conversation on 8/26/98, please find enclosed the analytical method for the noted drug product. This method describes how impurities/degradents are calculated.

As per our discussion, we will continue testing beyond the first three validation batches. Once significant data has been generated, we will submit a supplement to have this testing terminated.

If I can be of further assistance, please contact me at
(516) 567-1113

Sincerely,



William Cardone
Scientific Director

RECEIVED

AUG 28 1998

GENERIC DRUGS



ANDA 74-988

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald Steinlauf
60 DaVinci Drive
Bohemia, NY 11716

|||||

JAN 27 1997

Dear Sir:

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 our "Refuse to File" letter dated January 3, 1997, and your amendment dated January 16, 1997. We also refer to your correspondence dated December 3, and December 12, 1996.

NAME OF DRUG: Orphenadrine Citrate, Aspirin, and Caffeine
Tablets, 25 mg/385 mg/30 mg and 50 mg/770 mg/60 mg

DATE OF APPLICATION: October 21, 1996

DATE OF RECEIPT: October 22, 1996

DATE ACCEPTABLE FOR FILING: January 16, 1997

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

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

Should you have questions concerning this application contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Jerome Stevens Pharmaceuticals

Inc.

Generic Manufacturers

June 4, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-951; Butalbital 50mg/Aspirin 325mg/Caffeine
40mg/Codeine Phosphate 30mg Capsule USP

'MINOR AMENDMENT'

Dear Sir/Madam,

This is a reply to your letter dated May 4, 1998:

1. Response to container/closure system deficiencies:

- a. Please refer to pgs. 2-5. These pages contain results of the Container Permeation Test, USP 23 [671] for the container/closure systems used for the drug product. Page #3 has the data for Lot 015395, 500 count bottle and Lot 007196, 100 & 500 count bottle. Page #5 has the data for Lot 015395, 100 count bottle.
- b. The cap used for the 180cc bottle (100's size) was a 45mm metal screwcap, for lot # 015395 and a 45mm plastic screwcap was used on the 180cc bottle (100's size), for lot # 007196. Both the 45mm metal screwcap and the 45mm plastic screwcap have a _____ liner.

The cap used for the 750cc bottle (500's size) was a 53mm metal screwcap, for lot # 015395 and a 53mm plastic screwcap was used on the 750cc bottle (500's size), for lot #007196. Both the 53mm metal screwcap and the 53mm plastic screwcap have a _____ liner.
- c. The cap liners (_____ liner) are composed of _____ foam with a _____ coating. There is no inner safety seal used in the container/closure system for this drug product.
- d. Please refer to pg. 6 for a concise revised summary of container/closure systems used for this drug product.

RECEIVED

JUN 05 1998



*Labeling review
drafted 7/30/98
A. Vezar*

ANDA ORIG AMENDMENT

*JPL
PC*

Jerome Stevens Pharmaceuticals Inc.

Generic Manufacturers

2. Please refer to pgs. 7-14 for updated stability testing reports, Accelerated and Long-Term, for both 100 and 500 container sizes. These reports now contain tests and specifications for unknown, known and total known & unknown impurities/degradents.
3. As per our telephone conversation with Mr. Tim Ames on May 20, 1998, following approval of the application, we will place the first production batch under accelerated stability conditions for testing at 30, 60 and 90 days. We will perform dissolution testing using the current procedure and using the procedure specified in the 20th IRA to USP 23 published in the Pharmacopeial Forum, Volume 23, #6, Nov. - Dec. 1997. The comparison of this dissolution data will enable us to establish the nature of the pellicule formation observed with this product.
We will submit this data to the Agency for review.
4. Please see pgs. 15-42 for room temperature stability data for Lot: 007196. This data is up to 24 months and includes dissolution data. Room temperature stability data for Lot: 015395 can be found on pgs. 245-253 of our original submission and pgs. 195-204 of our amendment to this application dated 9/29/97.

Labeling Deficiencies:

1. Please refer to pgs. 43-60 which contain three (12) copies of final printed container and insert labeling with the revisions requested. The archival copy (blue) contains twelve (12) copies of final printed container and insert labeling. They can be found on pages 43-114 of the archival copy (blue).

Sincerely,



Ronald Steinlauf
Vice President



38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-951

APPLICANT: Jerome Stevens Pharmaceuticals Inc.

DRUG PRODUCT: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP , 50 mg/325 mg/40 mg/30 mg

The deficiencies presented below represent MAJOR deficiencies.

Chemistry Deficiencies:

1. In regard to the container/closure system, we have the following comments:
 - a. Please submit results of USP 23 <671> Containers-Permeation for both container/closure systems.
 - b. Please describe more clearly the cap used for each bottle. It is unclear as to whether the cap for the 180cc bottle is plastic or metal.
 - c. Please describe more clearly the composition of the cap liners for each bottle and the inner safety seal if used.
 - d. Please submit a concise revised summary of the container/closure systems used for this drug product. This summary should include all applicable information regarding the closure components, materials, manufacturers etc.
2. Please submit a revised stability testing report form which included the tests and specifications for individual and total degradation products (refer to pp. 114 - 115 of your September 29, 1997 amendment).
3. Please perform dissolution testing at accelerated conditions using the procedure specified in the 20th IRA to USP 23 published in the Pharmacopeial Forum, Volume 23, # 6, Nov. - Dec. 1997.

4. Please submit all room temperature stability data for dissolution testing that has been accrued to date for the finished drug product.

Sincerely yours,



Frank O. Holcombe, Jr., Ph.D.

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-951 APPLICANT: Jerome Stevens Pharmaceuticals Inc.

DRUG PRODUCT: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP , 50 mg/325 mg/40 mg/30 mg

The deficiencies presented below represent MAJOR deficiencies.

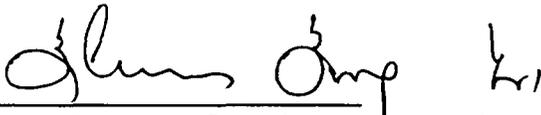
Chemistry Deficiencies:

1. In regard to the container/closure system, we have the following comments:
 - a. Please submit results of USP 23 <671> Containers-Permeation for both container/closure systems.
 - b. Please describe more clearly the cap used for each bottle. It is unclear as to whether the cap for the 180cc bottle is plastic or metal.
 - c. Please describe more clearly the composition of the cap liners for each bottle and the inner safety seal if used.
 - d. Please submit a concise revised summary of the container/closure systems used for this drug product. This summary should include all applicable information regarding the closure components, materials, manufacturers etc.
2. Please submit a revised stability testing report form which included the tests and specifications for individual and total degradation products (refer to pp. 114 - 115 of your September 29, 1997 amendment).
3. Please perform dissolution testing at accelerated conditions using the procedure specified in the 20th IRA to USP 23 published in the Pharmacopeial Forum, Volume 23, # 6, Nov. - Dec. 1997.

54
I

4. Please submit all room temperature stability data for dissolution testing that has been accrued to date for the finished drug product.

Sincerely yours,

 5/1/98

Frank O. Holcombe, Jr., Ph.D.

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

Jerome Stevens Pharmaceuticals

Inc.
Generic Manufacturers

NDA ORIG AMENDMENT

September 29, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AC

RE: ANDA 74-951; Butalbital 50mg/Aspirin 325mg/Caffeine
40mg/Codeine Phosphate 30mg Capsule USP

'MAJOR AMENDMENT'

Dear Sir/Madam,

This is a reply to your letter dated June 9, 1997:

1. Response to active ingredient deficiencies:

Aspirin:

- a. Please refer to pgs 1-2. These COA contain the OVI testing results.
- b. Please refer to pg. 3-4.
- c. Please refer to pg. 5 for the revised Aspirin USP COA.
- d. Please refer to pg. 1. This COA contains results of those tests that are not conducted by JSP. The results from both COA's meet full compendial testing.

Butalbital:

- a. Please refer to pg. 6. This COA contains the results of the OVI testing.
- b. Please refer to pg. 7.

Caffeine:

- a. Please refer to pg. 8.

General comments regarding active ingredients:

- a. Please refer to pgs. 1,2,6,9-12 for the COAs that contain the results for those test not conducted by

RECEIVED

OCT 01 1997

GENERIC DRUGS



Jerome Stevens Pharmaceuticals

Inc.
Generic Manufacturers

JSP. The results from both COA meet full compendial testing for all of the active ingredients.

- b. Firm will establish the reliability of our supplier's analyses through confirmation of our supplier's tests results at appropriate intervals.
- c. Please refer to pgs. 13-15 for the updated COAs for the active ingredients.
- d. Please refer to pg. 16 which will amend pg. 117 of our original submission. Firm has changed our retest period to 18 months.

2. Inactive ingredients:

- a. Please refer to pgs. 17 & 18 for the updated COAs
- b. Please refer to pg. 19 for a composition statement regarding the hard gelatin capsule.
- c. Please refer to pgs. 20-23 which contain a DMF authorization letter from Capsugel for DMF. _____ is the hard gelatin capsule manufacturer. We also included product specifications from the manufacturer of the ink. The manufacturer is _____ and they supply the ink to _____

3. Manufacturing process and controls:

- a. Please refer to pg. 24 which amends pg. 128 of our original submission.
- b. This is an area that the firm has addressed during the post-approval process validation phase of the manufacturing procedures.
- c. Please refer to pg. 25 which revises the ingredient weight sheet.
- d. Please refer to pgs. 26-37 which contain comparative assay and dissolution data from our method and the USP 23 method.
- e. Please refer to pgs. 38-54 which contains the Method Validation report and data for our method.
- f. Due to storage considerations and cost, we packaged



Jerome Stevens Pharmaceuticals

Inc.

Generic Manufacturers

only those 100 count bottles needed to conduct our stability studies.

- g. Please refer to pg. 55 which amends pg. 126 of our original submission.

4. Stability testing protocol and procedures:

- a. Please refer to pgs. 59-113 which contains data from a study which includes forced degradation data which demonstrates that our method is suitability for stability testing purposes.
- b. Please refer to pg. 56 which amends pg. 218 of our original submission.
- c. Please refer to pg. 56.
- d. Please refer to pgs. 57-58 which revises our accelerated stability protocol to include dissolution testing.
- e. Firm has a temperature/humidity recorder monitoring the long term stability samples. Firm stores the long term stability samples under ambient humidity conditions. Review of the charts show a range of 30-80% relative humidity over a 12 month period. The mean relative humidity is about 60%.
- f. Firm has conducted accelerated dissolution testing on lot #015395, please see pgs. 125-138
- g. Firm conducted a study to evaluate this drug product for degradation products other than free
Please see pgs. 59-113. Results of this study show that our method used for the assay of this drug product is stability indicating and can be used to monitor for degradation products. Analysis of long term stability sample (2 years) and accelerated stability sample show no degradation products other than free
Firm proposes a limit of for both individual known and unknown degradation products and a limit of for total known and unknown degradation products, excluding free salicylic acid.
- h. Firm has revised its limit for free on long term stability testing to Please refer to pgs. 114-115.



Jerome Stevens Pharmaceuticals

Inc.
Generic Manufacturers

- i. Please refer to pgs. 116-138 for comparative dissolution data at accelerated conditions for our drug product and Fiorinal with Codeine.

5. Container/closure:

- a. Please refer to pgs. 139-143 for testing conducted on the 180cc container from Container. Please refer to pgs. 144-150 for testing conducted on the 750cc container from Plastics.

- b. Please refer to pgs 151-153 for COA and a letter of authorization to DMF from

- c. The colorant used for the 180cc bottle was White.

- d. Please refer to pgs. 154-155 for letter of authorization for DMF and technical data from the manufacturer of the cap liner supplied to

Please refer to pg 156 for the letter of authorization for DMF from the manufacturer of the plastic caps. Please refer to pgs. 157-158 for the letter of authorization for DMF and a product data sheet from the

~~manufacturer of the cap liner supplied to~~
The liner used in not an inner tamper resistant seal.

TEKNIKA
MANUFACTURES
THE PS 22

- e. Please refer to pgs. 159 & 160 for letter of authorization for DMF from the manufacturer's of resins, respectively.

- f. Please refer to pgs. 161-166 for the engineering drawings for the bottles and caps.

- g. The closures are not two piece Child Resistant Closures. The description refers to a cap made of either plastic or metal. ?? WHICH IS USED ?

- h. The cap manufacturers used were

WHICH ONE MAKES
WHICH CAP ??

- i. Please refer to pgs. 167-168.



Jerome Stevens Pharmaceuticals

Inc.
Generic Manufacturers

- j. There is a Drug Master File authorization letter for DMF on pg. 167 of our original submission.
- k. Please refer to pg. 169.
- 6. Please refer to pg. 170 which amends pg. 256 of our original submission.

Labeling Deficiencies:

- 1. Please refer to pgs 171-194 which contain four (4) copies of draft container and insert labeling with the revisions requested.

Supplemental Data:

- 1. Firm is submitting Long-Term Stability Data (18 & 24 months) for Lot # 015395 as was stated on pg 219 of our original submission. Please refer to pgs. 195-204 for this data.

If I can be of further assistance, please contact me at (516) 567-1113

Sincerely,



Ronald Steinlauf
Vice President



1/1
Shoote, D

ANDA 74-951

MAY 2 1997

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald Steinlauf
60 DaVinci Drive
Bohemia NY 11716
|||||

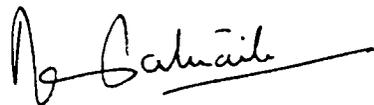
Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Aspirin, Butalbital, Caffeine, Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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,


for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Jerome Stevens Pharmaceuticals Inc.

Generic Manufacturers

NEW CORRESP

BIOAVAILABILITY

for me B
NC/ASD

April 2, 1997

Office of Generic Drugs, CDER, FDA
Attn: Ms. Sandra Middleton
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-951; Butalbital 50mg/Aspirin 325mg/Caffeine
40mg/Codeine Phosphate 30mg Capsule USP

Dear Ms. Middleton:

Here is the information you requested as per our telephone conversation on 4/2/97:

- The label claim for the Reference Listed Drug and Submitted Drug Product is Butalbital 50mg/Aspirin 325mg/Caffeine 40mg/Codeine Phosphate 30mg Capsule. This information can also be found in Bioavailability/Bio-equivalence part of the application in SECTION 6, volume 1, the Summary section (pg 2).

-The batch size for drug product used bioequivalence study is capsules (Lot #: 015395).

If I can be of further assistance, please contact me at (516) 567-1113

Sincerely,



Ronald Steinlauf
Vice President

RECEIVED

APR 05 1997

PHARMACEUTICALS



Jerome Stevens Pharmaceuticals

Inc.
Generic Manufacturers

NEW CORRESP
4/8/97
AVAILABILITY

April 10, 1997

Office of Generic Drugs, CDER, FDA
Attn: Ms. Sandra Middleton
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC/EO

RE: ANDA 74-951; Butalbital 50mg/Aspirin 325mg/Caffeine
40mg/Codeine Phosphate 30mg Capsule USP

Dear Ms. Middleton:

Here is the information you requested as per our telephone conversation on 4/8/97:

- Enclosed please find a certificate of analysis of the reference lot for the above application.

If I can be of further assistance, please contact me at
(516) 567-1113

Sincerely,

William Cardone

William Cardone
Scientific Director

RECEIVED

APR 11 1997

GENERIC DRUGS



ANDA 74-951

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-951

APPLICANT: Jerome Stevens

DRUG PRODUCT: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP

The deficiencies presented below represent MAJOR deficiencies.

Chemistry Deficiencies:

1. In regard to the active ingredients, we have the following comments:

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

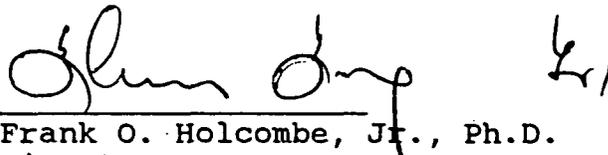
releasable.

Chem. Comments

2 / 9 / 97

6. Your environmental impact statement should include a claim for a categorical exclusion per 21 CFR 25.24 (c) (1).

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Frank O. Holcombe, Jr.", with a horizontal line underneath. To the right of the signature is a small handwritten mark that looks like "Lr".

Frank O. Holcombe, Jr., Ph.D.

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-951

APPLICANT: Jerome Stevens

DRUG PRODUCT: Butalbital, Aspirin, Caffeine and Codeine Phosphate
Capsules USP

The deficiencies presented below represent MAJOR deficiencies.

Chemistry Deficiencies:

1. In regard to the active ingredients, we have the following comments:

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem. Comments.

6/5/97

6. Your environmental impact statement should include a claim for a categorical exclusion per 21 CFR 25.24 (c)(1).

Sincerely yours,



Frank O. Holcombe, Jr., Ph.D.

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

6/5/97

ANDA 74-951

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald Steinlauf
Sixty DaVinci Drive
Bohemia, NY 11716

|||||

DEC 27 1996

Dear Sir:

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 our "Refuse to File" letter dated November 20, 1996, and to your amendment dated November 26, 1996.

NAME OF DRUG: Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg.

DATE OF APPLICATION: August 29, 1996

DATE OF RECEIPT: August 30, 1996

DATE ACCEPTABLE FOR FILING: November 27, 1996

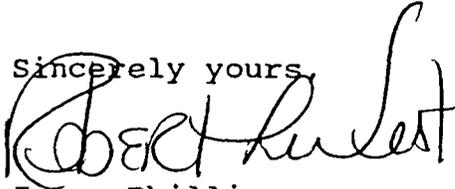
We will correspond with you further after we have had the opportunity to review the application.

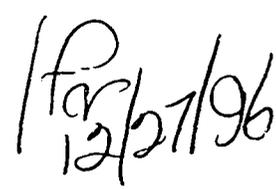
Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,


Jeffrey Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



ANDA 74-951

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald Steinlauf
Sixty DaVinci Drive
Bohemia, NY 11716

NOV 20 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated August 29, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg.

We also acknowledge receipt of your correspondence dated September 30 and October 16, 1996.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

You have failed to provide a certification that the third (field copy) of the application has been submitted to the appropriate district office and a statement that it is a "true copy" of the technical sections contained in the application.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

For future reference, all submissions to the ANDA must be accompanied by a cover letter and a Form FDA 356h.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3) If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Anna Marie H. Weikel
Project Manager
(301) 594-0315

Sincerely yours,

Jerry Phillips 11/20/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

771

Jerome Stevens Pharmaceuticals

Inc.
Generic Manufacturers

OCTOBER 16, 1996

MS. CECELIA PARISE
OFFICE OF GENERIC DRUG, CDER, FDA
DOCUMENT CONTROL ROOM
METRO PARK NORTH II
7500 STANDISH PLACE, ROOM 150
ROCKVILLE, MD 20855-2773

NEW CORRESP
NC

RE: ANDA - 74-951

NAI
10/28/96
CPW

DEAR MS. PARISE:

ENCLOSED PLEASE FIND AS PER YOUR REQUEST CGMP CERTIFICATION FOR
ASPIRIN 325MG/BUTALBITAL 50MG/ CAFFEINE 40MG/ CODEINE PHOSPHATE 30MG
CAPSULE USP.

THANK YOU FOR YOUR ATTENTION GIVEN THIS MATTER.

SINCERELY,



RONALD STEINLAUF, VICE PRESIDENT
JEROME STEVENS PHARMACEUTICALS, INC.

RECEIVED

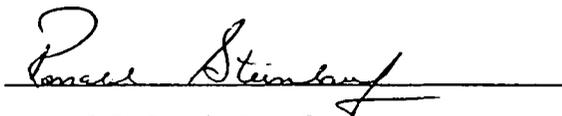
OCT 17 1996

GENERIC DRUGS



CGMP Certification:

The drug product, Aspirin 325mg/Butalbital 50mg/Caffeine 40mg/
Codeine Phosphate 30mg Capsule USP was manufactured by Jerome
Stevens Pharmaceuticals Inc. under compliance with all current
Good Manufacturing Practices listed in 21 CFR Parts 210 and 211.

A handwritten signature in cursive script, reading "Ronald Steinlauf", is written over a solid horizontal line.

Ronald Steinlauf
Vice President

October 16, 1996

505(j)(2)(a) (pk)
C. Marie Hill
Jerome Stevens Pharmaceuticals

12/16/96

Inc.

Generic Manufacturers

NE

NDA ORIG AMENDMENT

N/AC

November 26, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Forward to
C. Marie Hill
12/4/96

RE: ANDA 74-951; Butalbital 50mg/Aspirin 325mg/Caffeine
40mg/Codeine Phosphate 30mg Capsule USP

Dear Sir/Madam,

This is a reply to your letter dated November 20, 1996. Jerome Stevens Pharmaceuticals Inc. certifies that the third (field copy) of the noted application was sent to FDA's Brooklyn, NY District Office and that it is a "true copy" of the technical sections contained in the application.

Sincerely,

Ronald Steinlauf

Ronald Steinlauf
Vice President

RECEIVED

NOV 27 1996

GENERAL INVESTIGATIVE DIVISION

Maclean
12.3.96

