CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40261

APPROVAL LETTER

ANDA 40-261

OCT 28 1998

West-ward Pharmaceutical Corp.
Attention: Elizabeth A. Vasquez
435/465 Industrial Way West
Eatontown, NJ 07724

Dear Madam:

This is in reference to your abbreviated new drug application dated July 14, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg.

Reference is also made to your amendments dated February 18, May 1, July 21 and August 28, 1998.

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, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Esgic-Plus Capsules, 50 mg/500 mg/40 mg, of Mikart, Inc.). 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,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40261

DRAFT FINAL PRINTED LABELING

BUTALBITAL*, ACETAMINOPHEN, AND CAFFEINE CAPSULES, USP
*(WARNING: May be habit forming.)
Issued 12/97

0 3001-1297-00 7

DESCRIPTION: Butalbital, acetaminophen and caffeine is supplied in capsule form for oral administration. Each capsule contains:

28

Butalbital, USP.....50 mg
WARNING: May be habit forming.

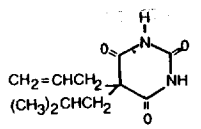
Acetaminophen, USP.....500 mg

Caffeine, USP.....40 mg

In addition, each capsule contains the following inactive ingredients: Colloidal Silicon Dioxide, Magnesium Stearate, Sodium Lauryl Sulfate, and Sodium Starch Glycolate.

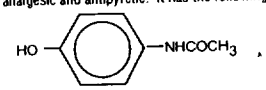
Capsule shell contains: D&C Red #33, D&C Yellow #10, FD&C Red #40, Gelatin and Titanium Dioxide. The imprinting ink contains Titanium Dioxide.

Butalbital (5-allyl-5-isobutylbarbituric acid), a white, odorless, crystalline powder having a slightly bitter taste, is a short to intermediate-acting barbiturate. It has the following structural formula:



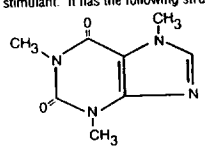
$C_{11}H_{16}N_2O_3$ M.W. 224.26

Acetaminophen (4'-hydroxyacetanilide), a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ M.W. 151.17

Caffeine (1,3,7,-trimethylxanthine), a bitter, white crystalline powder or white-glistening needles, is a central nervous system stimulant. It has the following structural formula:



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

CLINICAL PHARMACOLOGY: This combination drug product is intended as a treatment for tension headache.

It consists of a fixed combination of butalbital, acetaminophen and caffeine. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

Pharmacokinetics: The behavior of the individual components is described below.

Butalbital: Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most 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% to 88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include 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% is conjugated.

The *in vitro* plasma protein binding of butalbital is 45% over the concentration range of 0.5 to 20 mcg/mL. This falls within the range of plasma protein binding (20% to 45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood cells. (See **OVERDOSAGE** for toxicity information.)

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, mostly as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. (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 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 is recovered in the urine, only 3% is unchanged drug. (See **OVERDOSAGE** for toxicity information.)

INDICATIONS AND USAGE: Butalbital, acetaminophen and caffeine capsules are indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

CONTRAINDICATIONS: This product is contraindicated under the following conditions:

* Hypersensitivity or intolerance to any component of this product.

* Patients with porphyria.

WARNINGS: Butalbital is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

PRECAUTIONS: General: Butalbital, acetaminophen and caffeine capsules should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, or acute abdominal conditions.

Information for Patients: This product may impair mental and/or physical abilities required for the 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 combination product, and should be avoided.

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.

Butalbital, acetaminophen and caffeine may enhance the effects of: other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether acetaminophen or butalbital have a potential for carcinogenesis, mutagenesis or impairment of fertility.

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

Nonteratogenic Effects: Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last two 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.

Nursing Mothers: Caffeine, barbiturates and acetaminophen 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 butalbital, acetaminophen and caffeine, 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: Frequently Observed: The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

Infrequently Observed: 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, sluggishness, seizure. Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.

Autonomic Nervous: dry mouth, hyperhidrosis.

Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain, muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.

Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported.

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.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

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

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence: Butalbital: *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 1500 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.

OVERDOSAGE: Following an acute overdosage of butalbital, acetaminophen and caffeine, toxicity may result from the barbiturate or the acetaminophen. Toxicity due to caffeine is less likely, due to the relatively small amounts in this formulation.

Signs and Symptoms: Toxicity from barbiturate poisoning include drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock.

In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necroses, hypoglycemic coma and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Acute caffeine poisoning may cause insomnia, restlessness, tremor, and delirium, tachycardia and extrasystoles.

Treatment: A single or multiple overdose with this combination product is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Pressors should be avoided. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

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

Toxic Doses (for adults):

Butalbital: toxic dose 1 g	(20 capsules)
Acetaminophen: toxic dose 10 g	(20 capsules)
Caffeine: toxic dose 1 g	(25 capsules)

DOSAGE AND ADMINISTRATION: Oral: one capsule every four 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: Butalbital "(WARNING: May be habit forming)", Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg are supplied as salmon/red capsules printed "West-ward 3001" in white ink and are available in:

Bottles of 100 capsules.
Bottles of 500 capsules.
Unit Dose Boxes of 100 capsules.

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

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured By:
West-ward Pharmaceutical Corp.
Eatontown, NJ 07724
Issued December 1997

Butalbital*, Acetaminophen and Caffeine Capsule, USP *(WARNING: May be habit forming) 50 mg/500 mg/40 mg West-ward Pharmaceutical Corp. Eatontown, NJ 07724 Exp. XX/XX C.N. XXXXXX	Butalbital*, Acetaminophen and Caffeine Capsule, USP *(WARNING: May be habit forming) 50 mg/500 mg/40 mg West-ward Pharmaceutical Corp. Eatontown, NJ 07724 Exp. XX/XX C.N. XXXXXX
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NDC 0143-3001-05

Butalbital*, Acetaminophen and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP .... 50 mg
*(WARNING: May be habit forming.)
Acetaminophen, USP .... 500 mg
Caffeine, USP .... 40 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Capsules

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

USUAL ADULT DOSAGE:
One capsule every four hours.
Do not exceed six capsules per day.
See accompanying product literature for complete information.

D-1

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

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

N 3 0143-3001-05 4

Exp. Date:

Control No.:

NDC 0143-3001-05

Butalbital*, Acetaminophen and Caffeine Capsules, USP

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OCT 28 1996

N 3 0143-3001-05

Exp. Date:

Control No.:

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Exp. Date:

Control No.:

NDC 0143-3001-05

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28 1996

N 3 0143-3001-05 4

Exp. Date:

Control No.:

NDC 0143-3001-01

Butalbital*, Acetaminophen and Caffeine Capsules, USP

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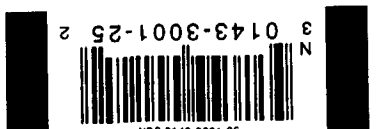
Exp. Date:
Control No.:

BP-1



NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

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West-ward

NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP ..... 50 mg
*(WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE:
One capsule every four hours.
Do not exceed six capsules per day.
See accompanying product literature for complete information.

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

PROTECT FROM LIGHT AND MOISTURE.

THIS UNIT-DOSE PACKAGE IS NOT CHILD-RESISTANT.

100 CAPSULES
UNIT DOSE

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Exp. Date:

Control No.:

BP-1

NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP ..... 50 mg
*(WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

West-ward

NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP ..... 50 mg
*(WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE:
One capsule every four hours.
Do not exceed six capsules per day.
See accompanying product literature for complete information.

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

PROTECT FROM LIGHT AND MOISTURE.

THIS UNIT-DOSE PACKAGE IS NOT CHILD-RESISTANT.

100 CAPSULES
UNIT DOSE

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Exp. Date:

Control No.:

BP-1

NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP ..... 50 mg
*(WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

West-ward

NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP ..... 50 mg
*(WARNING; May be habit forming.)
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE:
One capsule every four hours.
Do not exceed six capsules per day.
See accompanying product literature for complete information.

Store at controlled room temperature 15°-30°C (69°-86°F).

PROTECT FROM LIGHT AND MOISTURE.

THIS UNIT-DOSE PACKAGE IS NOT CHILD-RESISTANT.

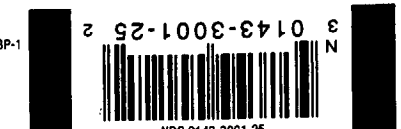
100 CAPSULES
UNIT DOSE

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Exp. Date:

Control No.:

BP-1



NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP ..... 50 mg
*(WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

West-ward

NDC 0143-3001-25

Butalbital*, Acetaminophen, and Caffeine Capsules, USP

*(WARNING: May be habit forming)

50 mg/500 mg/40 mg

Each capsule contains:

Butalbital*, USP ..... 50 mg
*(WARNING: May be habit forming.)
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE:
One capsule every four hours.
Do not exceed six capsules per day.
See accompanying product literature for complete information.

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

PROTECT FROM LIGHT AND MOISTURE.

THIS UNIT-DOSE PACKAGE IS NOT CHILD-RESISTANT.

100 CAPSULES
UNIT DOSE

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Exp. Date:

Control No.:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40261

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA #: 40-261 **DRUG PRODUCT:** **Butalbital, Acetaminophen and Caffeine Capsules, USP 50/500/40 mg**

FIRM: West-Ward Pharmaceuticals Corp.

DOSAGE: Capsules

STRENGTH: 50/500/40 mg

cGMP STATEMENT/EIR UPDATE STATUS:
cGMP: GMP Certification (page # 272) is Adequate
EER: Satisfactory dated 7/6/98

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:
On 7/20/98 the Division of Bioequivalence issued a no comments letter to the firm.

METHODS VALIDATION(Including dosage form description):
Not required because it is a USP drug

STABILITY(Conditions, Containers, methods):
Bio batch

Specifications

Test	Specification
Appearance	Conforms (# 0 Salmon Red capsules printed 'West-ward 3001'
Dissolution	Q % in 60 min for all three actives
Assay	% for all three actives
Impurities (p-amino phenol) (p-chloroacetanilide) Individual impurities Total other Caffeine impurity Total Impurities	 NMT % NMT % NMT % NMT % NMT % NMT %

Stability studies were done on the bio batch. Containers are the same as those listed in the container section. Stability studies are in conformance with the FDA Guidelines. The bio batch was packaged in 100 count, 500 count bottles and blisters.

LABELING REVIEW STATUS: Satisfactory. See review dated 6/18/98.

STERILIZATION VALIDATION(If Applicable): N/A

BATCH SIZES:

BIO BATCH(identity #, DS source)

Batch #: WWCN 5486/01
Batch size: Capsules
NDS sources: Butalbital -
Acetaminophen -
Caffeine -

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)
Stability batch is the same as the bio batch

PROPOSED PRODUCTION BATCH
capsules

Process is the same as the demonstration batch. Scale-up equipment is identified on page 286 of the ANDA.

COMMENTS: Approvable

CHEMISTRY REVIEWER: **DATE:**

Radhika Rajagopalan, Ph.D. September 21, 1998

/S/ 10/1/98

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-261

3. NAME AND ADDRESS OF APPLICANT
West-ward Pharmaceutical Corp.
Attention: Elizabeth A. Vasquez
465 Industrial Way West
Eatontown, NJ 07724

4. BASIS OF SUBMISSION
The reference listed drug is Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg manufactured by Mikart.

Generic Drug Enforcement Act certification and patent and exclusivity certification are provided (p. 4, 7 and 9). In addition, firm states that the active ingredient, dosage form, strength, route of administration and conditions of use are the same as the listed drug.

6. PROPRIETARY NAME
Esgic-Plus™ Capsules

7. NONPROPRIETARY NAME
Butalbital, Acetaminophen and Caffeine Capsules

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

9. AMENDMENTS AND OTHER DATES:
Firm:
7/14/97 - Original application
8/27/97 - Amendment
2/13/98 - Labeling Amendment
2/18/98 - Chemistry Amendment
5/1/98 - Amendment
7/21/98 - Minor amendment response
8/28/98 - Amendment to telephone call

FDA:
9/5/97 - Acknowledgment letter
11/28/98 - Chemistry and labeling deficiency fax out
12/31/97 - Bio letter out
7/20/98 - Chemistry deficiency fax
8/6/98 - Phone call by Chemist

10. PHARMACOLOGICAL CATEGORY
Analgesic/Sedative

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF's:

ANDA: 40-085

13. DOSAGE FORM
Capsules

14. POTENCY
Butalbital/Acetaminophen/Caffeine
(50 mg/500 mg/40 mg)

15. CHEMICAL NAME AND STRUCTURE
Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)

Acetaminophen: N-(4-hydroxyphenyl)-acetamide ($C_3H_9NO_2$)

Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione ($C_3H_{10}N_4O_2$).

17. COMMENTS
A citizen's petition to provide for a change in dosage form from tablets to capsules for the strengths as given above was approved on **10/27/89**.

18. CONCLUSIONS AND RECOMMENDATIONS
Chemistry review is complete and satisfactory.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

DATE COMPLETED:
9/21/98

/S/ 10/15/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40261

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-261 APPLICANT: West-Ward Pharmaceutical Corp.

DRUG PRODUCT: Butalbital, Acetaminophen, and Caffeine Capsules, USP, 50/500/40 mg

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

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

Sincerely yours,

/S/

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

Butalbital, Acetaminophen and Caffeine Capsules USP	West-ward
50 mg/500 mg/40 mg Capsules	Eatontown, NJ
ANDA #40-261	Submission Date: 7/14/97
Reviewer: Moo Park	
Filename: 40261dw.797	

Review of Dissolution Data and a Waiver Request

I. Objective

To review West-ward's waiver request on its Butalbital, Acetaminophen and Caffeine Capsules containing 50 mg of butalbital, 500 mg of acetaminophen and 40 mg of caffeine per capsule. The firm submitted a comparative dissolution data on its test product and the reference product, Mikart's Esgic-Plus^{R} Capsules, 50 mg/500 mg/40 mg strength.

II. Comments

1. The drug product is classified as AB in the Orange Book. However, the Orange Book also lists the product as one which must demonstrate in vivo bioavailability only if product fails to achieve adequate dissolution (p.3-559, 17th edition, 1997).

2. The test formulation contains the same active ingredients as Mikart's Esgic-Plus^{R} Capsules, 50 mg/500 mg/40 mg strength. The test and reference formulations are shown in Table 1.

Table 1. Formulation Comparison

Ingredient	West-ward mg/capsule	Mikart mg/capsule
Butalbital	50	50
Caffeine	40	40
Sodium Lauryl Sulfate		
Acetaminophen	500	500
Colloidal Silicon Dioxide		
Sodium Starch Glycolate		
Magnesium Stearate		
Total fill weight		

3. Assay and content uniformity for the test and reference products are summarized in Table 2.

Table 2. Assay and Content Uniformity Data

Product	Ingredient	Assay, %	Content Uniformity, % (%CV)
West-ward's Test Product, Lot #01	acetaminophen		
	butalbital		
	caffeine		
Mikart's Ref Lot #F960572A; Exp Date=6/98	acetaminophen		
	butalbital		
	caffeine		

4. Comparative dissolution data are summarized in Table 4. The test and reference products met the USP dissolution specifications for Butalbital, Acetaminophen and Caffeine Capsules USP. Dissolution specifications are shown below in Table 3.

Table 3. USP23 Method for Dissolution Testing	
Medium and Volume	water; 900 mL
Apparatus and rpm	I (basket); 100 rpm
Time	60 min
Tolerances	Butalbital: NLT % (Q) in 60 minutes. Acetaminophen: NLT % (Q) in 60 minutes. Caffeine: NLT % (Q) in 60 minutes.
Assay Method	

5. A waiver of *in vivo* bioequivalence study requirements is granted.

III. Recommendations

1. The Division of Bioequivalence agrees that the information submitted by West-ward on its drug product, Butalbital, Acetaminophen and Caffeine Capsules USP containing 50 mg of butalbital, 500 mg of acetaminophen and 40 mg of caffeine per capsule falls under 21 CFR 320.22 (c) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg strength, manufactured by West-ward to be bioequivalent to the reference product, Mikart's Esgic-Plus^{R} Capsules, 50 mg/500 mg/40 mg strength.

2. The dissolution testing conducted by West-ward on its drug product, Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg strength, Lot #01, has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

> Not less than % (Q) of the labeled amount of butalbital, acetaminophen and caffeine is dissolved in 60 minutes.

The firm should be informed of the recommendations.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 12/15/97

Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: /S/ Date: 12/31/97

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

cc: ANDA #40-261 (original, duplicate), Park, Drug File, Division File, HFD-650 (Director)

File history: Draft (10/23/97); Final (12/12/97)

Table 4. *In Vitro* Dissolution Testing Data	
I. General Information	
Drug Product (Generic Name)	Butalbital, Acetaminophen and Caffeine Capsules USP
Strength	50 mg/500 mg/40 mg strength
ANDA Number	40-261
Applicant	West-ward
Reference Drug Product	Mikart's Esgic-Plus® Capsules, 50 mg/500 mg/40 mg strength
II. USP23 Method for Dissolution Testing	
Medium and Volume	water; 900 mL
Apparatus and rpm	I (basket); 100 rpm
Time	60 min
Tolerances	Butalbital: NLT % (Q) in 60 minutes. Acetaminophen: NLT % (Q) in 60 minutes. Caffeine: NLT % (Q) in 60 minutes.
Assay Method	

III-1. Dissolution Data (%) for Butalbital

Time	Test Product Lot No: 01 (54786) Strength: 50 mg/500 mg/40 mg No of Units: 12			Reference Product Lot No:F960572A Strength: 50 mg/500 mg/40 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	90.1		2.3	88.2		5.0
30	95.7		1.5	97.4		2.8
45	96		1.6	100.4		2.6
60	96.2		1.6	101.6		2.4

III-2. Dissolution Data (%) for Acetaminophen						
Time	Test Product Lot No: 01 (54786) Strength: 50 mg/500 mg/40 mg No of Units: 12			Reference Product Lot No:F960572A Strength: 50 mg/500 mg/40 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	92.0		1.5	88.2		5.8
30	94.8		1.4	99.3		2.6
45	95.5		1.0	102.9		1.6
60	96.1		1.1	104.5		1.3

III-3. Dissolution Data (%) for Caffeine						
Time	Test Product Lot No: 01 (54786) Strength: 50 mg/500 mg/40 mg No of Units: 12			Reference Product Lot No:F960572A Strength: 50 mg/500 mg/40 mg No of Units: 12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	93.3		2.2	91.0		5.2
30	97.5		1.5	100		2.7
45	97.6		1.4	102.8		2.4
60	97.9		1.4	103.6		2.5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40261

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 40-261

Date of Submission: July 14, 1997

Applicant's Name: West-ward Pharmaceutical Corp.

Established Name: Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg

Labeling Deficiencies:

1. CONTAINER

   a. 100s and 500s

      i. Front panel

         A). Add an asterisk immediately following "Butalbital*".

         B). Add the statement "*WARNING: May be habit forming" immediately beneath the established name. We refer you to 21 CFR 329.10(c) for further guidance.

         C). Add the strengths in milligrams of each active ingredient, for example:

         Butalbital* Acetaminophen, and Caffeine Capsules, USP

         50 mg/500 mg/40 mg

   b. Unit dose blister

      Please refer to comments 1(a)(i)(A and B).

2. CARTON

   Please refer to comments 1(a)(i)(A, B and C) under CONTAINER.

3. INSERT

a. DESCRIPTION

i. Revise the molecular weight of acetaminophen to be in accord with USP 23, "M.W. 151.17".

ii. Revise the description of caffeine to read, "... white crystalline powder ..."

b. CLINICAL PHARMACOLOGY

i. Pharmacokinetics

A). Butalbital

Revise the last paragraph to read as follows:

The *in vitro* plasma protein binding of butalbital is 45% over the concentration range of 0.5 to 20 mcg/mL. This falls within the range of plasma protein binding (20% to 45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood cells. (See OVERDOSAGE for toxicity information.)

B). Acetaminophen

Revise as follows:

... unchanged drug. (See OVERDOSAGE for toxicity information).

C). Caffeine

Revise as follows:

... unchanged drug. (See OVERDOSAGE for toxicity information).

c. ADVERSE REACTIONS

Delete the bolding for the paragraph, "The

following ... section".

d. HOW SUPPLIED

i. Add the statement "(WARNING: May be habit forming)" immediately following Butalbital. We refer you to 21 CFR 329.10(c) for further guidance.

ii. We encourage you to include "USP" following the established name.

Please revise your labels and labeling, as instructed above, and submit final printed container labels, and final printed, (or draft if you prefer) insert 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.

/S/

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

RECORD OF TELEPHONE CONVERSATION

I initiated a call to the firm and talked to Mike Raya, analytical director regarding the two impurities levels p-aminophenol and p-chloroacetanilide. I requested him to lower the limits on both to what USP is recommending for the drug substance.

He stated that there is no problem with p-aminophenol (to usp's method) but for p-chloroacetanilide they have to use the method with a LOD of %. The USP's method is unsuitable for p-chloroacetanilide since there is interference from other ingredients in the capsule.

I requested him to provide copies of the to pursue development of more sensitive method and to give us a written amendment with new release and stability specifications.

DATE
8/6/98

ANDA NUMBER
40-261

IND NUMBER

TELECON

INITIATED BY **X MADE BY** **APPLICANT/ SPONSOR TELE.**

X FDA **_ IN PERSON**

PRODUCT NAME
Butalbital, Acetaminophen and Caffeine Capsules, USP, 50/500/40 mg

FIRM NAME
West-ward Pharmaceutical Corp.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mike Raya, Analytical R&D

TELEPHONE NUMBER
(908)542-1678

SIGNATURE
/S/

X:\NEW\FIRMSNZ\WESTWARD\TELECONS\40261IMP.WPD

8/6/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75755

CORRESPONDENCE

ANDA 40-261

West-ward Pharmaceutical Corp.
Attention: Elizabeth A. Marro-Jelicks
465 Industrial Way West
Eatontown, NJ 07724

SEP 5 1997

Dear Madam:

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

NAME OF DRUG: Butalbital, Acetaminophen, and Caffeine Capsules USP, 500 mg/50 mg/40 mg

DATE OF APPLICATION: July 14, 1997

DATE OF RECEIPT: July 16, 1997

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:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips 9/4/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Amanda J Middleton 8/19/97 505 (j)

West-ward
PHARMACEUTICAL CORP

465 Industrial Way West, Eatontown, NJ 07724
908-542-1191 FAX 908-542-6150

Copy 1- ARCHIVAL
Copy 2- REVIEW
Copy 3- FIELD

July 14, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Doug Sporn, M.D.
Director, Office of Generic Drugs

UPS NEXT DAY AIR

Re: BUTALBITAL, ACETAMINOPHEN AND CAFFEINE CAPSULES, USP
50/500/40 MG
ORIGINAL ANDA

Dear Dr. Sporn:

In accordance with the statutory provisions governing ANDA requirements outlined in Section 505 (j) of the Federal Food, Drug and Cosmetic Act we submit herewith an Abbreviated New Drug Application for **Butalbital, Acetaminophen and Caffeine Capsules USP, 50/500/40 mg.** This drug product is the generic equivalent of Esgic-Plus™ Capsules manufactured by Mikart, Inc.

The drug product for which the applicant seeks approval will be manufactured, packaged and labeled at West-ward Pharmaceutical Corp. located at 465 Industrial Way West, Eatontown, NJ 07724.

In support of this ANDA submission enclosed please find the following:

- **VOLUMES 1.1 AND 1.2 (2 Red Binders)**

  LABELING, CHEMISTRY AND MANUFACTURING CONTROLS

- **VOLUME 2.1 (1 Orange Binder)**

  IN VIVO BIOEQUIVALENCE WAIVER AND *IN VITRO* DISSOLUTION DATA

- **VOLUMES 1 of 3, 2 of 3, 3 of 3**
  (3 Blue Binders)

  ARCHIVAL COPY

In addition, a Third Copy **(FIELD COPY)** of Volumes 1.1 and 1.2 is being submitted as required under Title 21 CFR Part 314. This third copy is to be used for a Pre-approval Inspection by FDA investigators to audit application commitments and statements against actual manufacturing practices. The applicant certifies that this **FIELD COPY** is a true copy of the original submission and it has been forwarded to the District Office. **(See SECTION XXI- FIELD COPY Certification).**

Pursuant to Title 21 of the United States Code, Section 811 (g) (3) (A) this product has been granted exempt status from the Controlled Substances Act. A copy of the letter received from the Department of Justice immediately proceeds this cover letter.

All correspondence regarding this application should be directed to the undersigned. All telephone communications should be directed to 908-542-1678 or 908-460-0763.

We look forward to your review of this ANDA and await notification of receipt of this submission.

Very truly yours,

Elizabeth A. Marro
Director, Regulatory Affairs

West-ward
PHARMACEUTICAL CORP

465 Industrial Way West, Eatontown, NJ 07724
908-542-1191 FAX 908-542-0940

Copy 1- ARCHIVAL
Copy 2- REVIEW
Copy 3- FIELD

August 27, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Doug Sporn, M.D.
Director, Office of Generic Drugs

NDA ORIG AMENDMENT
AP
40261

UPS NEXT DAY AIR

Re: BUTALBITAL, ACETAMINOPHEN AND CAFFEINE CAPSULES, USP 50/500/40 MG
AMENDMENT TO ORIGINAL ANDA

Dear Dr. Sporn:

Reference is made to the original ANDA dated July 14, 1997 for **Butalbital, Acetaminophen and Caffeine Capsules USP, 50/500/40 mg.**

At this time we submit an amendment to the pending application to include 3 months accelerated stability data for the product packaged in a unit dose blister package. See **ATTACHMENT 1.** In Section XVII, page 1030 it was stated that an amendment would be submitted by August 31, 1997 to include this data.

Information including specifications, blueprints and DMF Referral letters are included in **ATTACHMENT 2.**

Standard Operating Procedures covering the blister pack procedures are included in **ATTACHMENT 3.**

Draft labeling was included in the original ANDA in Section V, pages 21-29.

We appreciate your consideration of this data and information as part of the original ANDA.

Very truly yours,
Elizabeth A. Marro

Elizabeth A. Marro
Director, Regulatory Affairs

RECEIVED
SEP 09 1997
GENERIC DRUGS

West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

MINOR AMENDMENT

May 1, 1998

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

Copy 1 - Archival
Copy 2 - Review
Copy 3 - Field

~~ONC~~ N/AC

UPS NEXT DAY AIR

Re: Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg
ANDA 40-261/**MINOR AMENDMENT TO A PENDING APPLICATION**
PACKAGING SITE CHANGE

Dear Dr. Sporn:

Reference is made to our pending ANDA for Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg. West-ward Pharmaceutical's is submitting this **MINOR AMENDMENT** for a packaging site change from the building located at 465 Industrial Way West to 435 Industrial Way West.

The new packaging site is located at 435 Industrial Way West, Eatontown, New Jersey 07724 within a contiguous campus from the original site located at 465 Industrial Way West, Eatontown, New Jersey 07724. A satisfactory cGMP Inspection was conducted on April 6, 1998.

The operations to be performed at this new site include packaging as well as labeling. The same equipment, Standard Operating Procedures, environmental conditions and controls, and personnel common to both sites will be used and no changes are made to the packaging and labeling records except for administrative information and the location of the facility. In addition, the same container/closure systems will be utilized as included in the original submission on 7/15/97.

In support of this **MINOR AMENDMENT** we provide the following information:

- An acceptable cGMP Inspection was granted by FDA Investigator Amy Josephson on April 6, 1998.

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- The process validation batches of the product packaged at the new site will be placed into the Long Term Room Temperature (25° - 30°C) stability program in the smallest and largest package sizes using the protocol submitted in the February 18, 1998 Major Amendment letter.

- The resulting stability data will be included in the Annual Report.

We look forward to your approval of this original ANDA along with the amended information.

Sincerely,

Elizabeth A. Marro
Director, Regulatory Affairs

West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

February 18, 1998

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Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II

UPS NEXT DAY AIR

Re: Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg
ANDA 40-261/MAJOR AMENDMENT

Dear Dr. Holcombe:

Reference is made to your letter dated November 28, 1997 regarding the above-referenced application. West-ward Pharmaceuticals is submitting this MAJOR AMENDMENT response to address the deficiencies cited in your letter.

Our response follows your highlighted comments below.

Comment:

A. Chemistry Deficiencies

1. **In the Certificates of Analyses of Butalbital USP and Caffeine USP, we notice that the OVI testing is referred to on pages 233 and 241 respectively. However, those pages do not pertain to OVI testing results, methods or exemption letters. Please clarify.**

Response:

On the Certificates of Analyses for all 3 actives (butalbital, acetaminophen, and caffeine) the page referenced under the Test Method Column refers to the page in the USP 23 or applicable supplement where the OVI test requirement is located.

If you refer to pages 139 for acetaminophen and 146 for butalbital, the manufacturer confirms that none of the OVI's listed in the applicable monograph are used in the synthesis process and therefore no potential for any solvent to be present. Hence the test is not required (N/R). For caffeine, the supplier has listed as the only solvent to test for as noted on page 157 of the original submission. This information should clarify West-ward's test record reference.

Comment:

2. **We notice on page 305, that the name of the manufacturer for Butalbital, USP is listed as but the manufacturers of Caffeine and Acetaminophen, USP are left blank. These capsules have three active ingredients, Butalbital, Acetaminophen, and Caffeine and if the manufacturer of any of the active is changed (Acetaminophen, Caffeine or Butalbital), it will require a pre-approval supplement. Hence, please include the approval sources (Acetaminophen – and Caffeine – on your batch record.**

Response:

We concur with your statement that if the manufacturer of any of the active ingredients is changed a prior approval supplement is required. Hence, the approved sources for acetaminophen, caffeine and butalbital appear on the front page of the FMOM, the pharmacy check sheet as well as in the Process Validation Protocol. **SEE ATTACHMENT 1.**

In addition, we have been informed by the supplier of acetaminophen that they have transferred their assets to a newly formed corporate affiliate, A letter describing this merger is included in **ATTACHMENT 2.**

Upon receipt of material labeled by all paperwork will be updated to cross-reference the manufacturer's new name.

Comment:

3. **We could not locate a packaging reconciliation sheet for the ANDA demonstration batch. We notice that units of the 500 count and units of the 100 count are packaged. The unit blisters amount to (page 401). How many capsules do each blister unit contain? Please clarify and provide a packaging reconciliation yield data.**

Response:

ATTACHMENT 3 contains the packing reconciliation sheets for bottles of 100, 500 and unit dose blister packs of 100 capsules. Each blister unit holds 1 capsule and each blister card contains 10 blister units. 10 blister cards are in a blister box for a total of 100 capsules.

Comment:

4. **From the SOP, we notice the weighed material hold time of 30 days, blend hold time of up to 60 days and 30 days for encapsulation and packaging. Please be aware that 21CFR recommends a process time of 30 days from start (blending) to completion of manufacture (packaging).**

Response:

Reference is made to 21 CFR§211.111 "Time Limitations on Production". The following guidance is provided for time limits: *"When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented."*

West-ward has established manufacturing phase time limits (as noted in SOP PR-38; pg. 318 of original submission) to realistically reflect the maximum established time for completion of each phase. Where possible, and in most cases, the time limits necessary to complete each phase of manufacturing are more concise. These time limits are recorded in each batch record on a "Time Limitation of Manufacturing Phases" Sheet which is initiated by the Production Supervisor/Foreman and checked by QA Personnel. This provides assurance that these time limits are adhered to. **SEE ATTACHMENT 4**.

The integrity of the product is verified prior to packaging when Quality Control testing is performed before releasing the finished product.

Expiration dating is assigned from the start of run date of encapsulation in accordance with SOP QC-04 and has been standard practice at West-ward Pharmaceutical Corp. **SEE ATTACHMENT 4** following the Time Limits Sheet.

Comment:

5. **We are unable to locate information in the ANDA regarding bulk density, particle size and moisture for the demonstrated batch, although the SOPs address this. Please comment.**

Response:

Bulk density and moisture data were recorded in the bio waiver submission batch protocol on page 333 of the original application. Particle size was also performed on the blend and the data is included in **ATTACHMENT 5**. A blank QC blend specification sheet is also included in **ATTACHMENT 5** including initial specifications.

In accordance with SOP QA-05, particle size, bulk density, and Karl Fisher moisture testing are performed on the 1st three process validation batches to monitor the manufacturing procedure and the data compared to the submission batch. All data for the 1st three process validation batches will be included in the Annual Report.

Comment:

6. **Please explain if assay preparations are made in duplicate or if duplicate injections are made out of single preparations in method Also, please include the filter make, model descriptions and filter validation study.**

Response:

Duplicate injections are made from duplicate assay preparations for each lot. A special note has been included in as well as the addendum to the method validation report which also addresses the filter make, model descriptions and filter validation study.

SEE ATTACHMENT 6.

Comment:

7. **Please comment about the stability of the standard and sample solutions and if any time limitations are set.**

Response:

Included in (pg. 5 of 13), a note relating to the stability of the sample preparations sets a time limit of NMT 6 days for assay and content uniformity samples. **SEE ATTACHMENT 6.**

Comment:

8. **The method validation report needs to evaluate method robustness. We refer you to USP 23.**

Response:

An addendum to the Validation Report for Assay, ... etc. via has been prepared which addresses and evaluates robustness in accordance with USP 23. **SEE ATTACHMENT 6.**

Comment:

9. **In method under section I (Suitability procedure), we notice a % of % is provided for p-aminophenol. Please also include a % limit for acetaminophen, caffeine and butalbital.**

Response:

As requested, the wording under Section I of' has been updated to include the % limit for butalbital, caffeine and acetaminophen. **SEE ATTACHMENT 6.**

Comment:

10. **Please include a time limit for sample analysis for the dissolution experiment.**

Response:

A study was performed in order to determine the stability of a dissolution sample for Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg. From the data it can be concluded that the standard preparation is stable for 3 days.

SEE ATTACHMENT 7 for the results of the study and the updated test method reflecting the time limit for sample analysis.

Comment:

11. **We are unable to locate the validation for method for the quantitation of impurities such as p-Chloroacetanilide. Please provide.**

Response:

We apologize for the inadvertent omission of the test method validation for and have included a copy in **ATTACHMENT 8.**

Comment:

12. **Based on the stability data obtained, we propose that you limit "Other impurities" to "Single impurity", NMT % during initial release and stability testing.**

Response:

As requested, the related compounds limits have been modified and the update is reflected in as well as the QC Finished Product Release and Stability Report Form. For all timepoints tested after 2/98 the revised specifications will be referenced. **SEE ATTACHMENT 9.**

Comment:

13. **Please clarify if the packaging operations for blister packs will be continued at the West-ward location itself or if any contract facility will be utilized after approval of the ANDA.**

Response:

At this time West-ward will be the only facility performing the packaging operations for blister packs. Should it be our intention to use a contract facility, a prior approval supplement will be submitted.

Comment:

14. **On page 1033, the stability protocol includes organoleptic examination of the product. Please identify in addition to appearance, what other tests are performed and explain.**

Response:

We have included a copy of SOP QC-42 for description and odor testing which is also referenced under the Test Method Section of the Quality Control Finished Product and Stability Test Records. **SEE ATTACHMENTS 9 and 10.**

Finally, the labeling deficiencies were responded to in a separate communication dated February 13, 1998.

We are confident that the enclosed information responds to all the deficiencies and look forward to your prompt approval of this ANDA.

Sincerely,

Elizabeth A. Marro
Director, Regulatory Affairs

West-ward
PHARMACEUTICAL CORP.

465 Industrial Way West, Eatontown, NJ 07724
732-542-1678 FAX 732-542-6150

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February 13, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Jerry Phillips
Director, Division of Labeling and Program Support

Copy 1
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Re: Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg
ANDA 40-261/Amendment to a Pending Application - LABELING

Dear Mr. Phillips:

Reference is made to a facsimile letter dated December 3, 1997 regarding Labeling deficiencies to ANDA 40-261.

In accordance with the recommendations in your letter the container labels and package insert have been revised (Iss. 12/97: 3001-1297-00). Enclosed please find 12 final printed container labels and package inserts and one side-by-side comparison for your review and approval.

Should you have any questions regarding this amendment, please feel free to contact Elizabeth A. Marro or myself at 732-542-1678.

Sincerely,

Colleen M. Hanrahan

Colleen M. Hanrahan
Regulatory Affairs Coordinator

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MINOR AMENDMENT TO A PENDING APPLICATION

August 28, 1998

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Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II

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Re: Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/500 mg/40 mg
ANDA 40-261
Minor Amendment To A Pending Application (Telephone Request)

Dear Dr. Holcombe:

Reference is made to a telephone request for information on July 28, 1998 from Ms. Radhika Rajagopolan (FDA Chemist). It was requested that the limits for impurities in the finished product; specifically p-aminophenol and p-chloroacetanilide, be reduced to the USP limits in the Acetaminophen monograph since they are synthesis impurities.

On August 6, 1998 a Quality Control representative from West-ward (Michael Raya – Senior V.P., Operations) discussed with Ms. Rajagopolan (FDA) the capabilities of using the test method and specifications set forth in the USP. The following summarizes the discussion.

p-aminophenol
West-ward is capable of testing for p-aminophenol (degradent) via the USP (UV) method and will retain the compendial specification of ( )% for release criteria. Analytical Research has retained the USP UV methodology and has deleted the reference to p-aminophenol in the existing test method, 1239. The USP test for p-Aminophenol is a limit test. It is run against an external standard at a relative concentration of %. Sample and standard are read on the UV Spectrophotometer at about 710 nm after color development. The USP procedure was easily adapted to the finished product. An equivalent weight to 5.0 grams of Acetaminophen was used.

All accelerated stability samples and the initial composite sample for ABC Plus Capsules were run by the USP procedure. All sample absorbance were less than the standard absorbance.

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The method was written in West-ward format and assigned a test method number of '_. Test method that was West-ward's method for determining p-Aminophenol, was revised to delete p-Aminophenol. The specification for p-Aminophenol was changed from NMT % to NMT % for the stability samples and NMT % for initial release. ATTACHMENT 1 contains test method and the retest results for the initial and stability samples.

p-chloroacetanilide

The similar situation regarding p-chloroacetanilide (impurity) was discussed. Since this related compound is a synthesis impurity and not a degradent, the FDA requested that the specification be revised to %, which compares to the USP compendial criteria. It was explained that West-ward's limit of detection is % and that the compendial limit of % cannot be attained by West-ward's current procedure.

Conversely, the USP procedure is NOT specific enough and the p-chloroacetanilide spot is exposed to too much interference when testing the finished product. The USP test for p-Chloroacetanilide is a procedure limit test. Any spot in the sample at the same Rf as the standard must be less than the standard spot which is there at a relative concentration of %. Samples of ABC Plus Capsules were analyzed by the USP procedure using an equivalent sample weight to 1.0 grams of Acetaminophen. There was a very large spot in the sample from one of the other ingredients in ABC Plus Capsules at the same Rf (0.4) as the standard (see photo of plates in ATTACHMENT 2). Due to the interference from the other ingredients, the ABC Plus samples cannot be tested by the USP procedure.

The sensitivity of West-ward's test method can be improved by injecting a more concentrated sample solution. The stock solution is 2.5 times more concentrated than the final sample solution. As a comparison, the stock and final sample solution were both analyzed by Neither samples detected any p-Chloroacetanilide but the other related compounds were easier to integrate due to the larger peak sizes from the more concentrated stock solution.

Test Method was revised to inject the stock solution instead of the diluted final solution. The increased sample size improves the accuracy of determining the related compounds and increases our limit of detection for p-Chloroacetanilide. The limit of detection has been improved from '%. See ATTACHMENT 3 for the revised

ATTACHMENT 4 contains the revised stability protocol incorporating the requested and agreed upon limits for p-aminophenol and the improved limits for p-chloroacetanilide and the respective test method references.

Thank you for your consideration of the above information as discussed and we look forward to your prompt approval of this ANDA as amended above.

Sincerely,

Elizabeth A. Vasquez
Director, Regulatory Affairs