CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-283

APPROVAL LETTER

ANDA 40-283

29

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application dated October 27, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg.

Reference is also made to your amendments dated January 1, June 3, and December 5, 1998.

The listed drug referenced in your application is subject to a period of patent protection which expires on August 12, 2002 (patent 4,534,974 [the '974 patent]). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on the '974 patent, and that the '974 patent is invalid and/or unenforceable. Section 505(j)5)B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified FDA that Amide Pharmaceutical, Inc. (Amide) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Amide within the statutory forty-five day period.

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 Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg, respectively, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Soma Compound with Codeine Tablets, 200 mg/325 mg/16 mg, respectively, of Wallace Pharmaceuticals). 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,

D. L. Sporn 12/29/98

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-283

APPROVED DRAFT LABELING

Amide
PHARMACEUTICAL, INC.

NDC 52152-138-02

CARISOPRODOL, ASPIRIN and CODEINE PHOSPHATE TABLETS, USP
200 mg/325 mg/16 mg

C III

Rx only

100 TABLETS

Each Tablet Contains:
Carisoprodol ..... 200 mg
Aspirin ..... 325 mg
Codeine Phosphate ..... 16 mg

Usual Dosage: See package insert for indications, precautions, and dosage.

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

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

N 3 52152-138-02 6

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:
5 98
7916-00

Amide
PHARMACEUTICAL, INC.

NDC 52152-138-04

CARISOPRODOL, ASPIRIN and CODEINE PHOSPHATE TABLETS, USP
200 mg/325 mg/16 mg

C III

Rx only

500 TABLETS

Each Tablet Contains:
Carisoprodol ..... 200 mg
Aspirin ..... 325 mg
Codeine Phosphate ..... 16 mg

Usual Dosage: See package insert for indications, precautions, and dosage.

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

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

N 3 52152-138-04 0

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:
5/98
7917-00

moderate salicylate poisoning. Salicylate poisoning should be considered in children with symptoms of vomiting, hyperpnea, and hyperthermia.

Hyperpnea is an early sign of salicylate poisoning, but dyspnea supervenes at plasma levels above 50mg/dL. These respiratory changes eventually lead to serious acid-base disturbances. Metabolic acidosis is a constant finding in infants but occurs in older children only with severe poisoning; adults usually exhibit respiratory alkalosis initially and acidosis terminally.

Other symptoms of severe salicylate poisoning include hyperthermia, dehydration, delirium, and mental disturbances. Skin eruptions, GI hemorrhage, or pulmonary edema are less common. Early CNS stimulation is replaced by increasing depression, stupor, and coma. Death is usually due to respiratory failure or cardiovascular collapse.

Codeine Phosphate-pinpoint pupils, CNS depression, coma, respiratory depression, and shock.

Treatment: *General*-Provide symptomatic and supportive treatment, as indicated. Any drug remaining in the stomach should be removed using appropriate procedures and caution to protect the airway and prevent aspiration, especially in the stuporous or comatose patient. Incomplete gastric emptying with delayed absorption of carisoprodol has been reported as a cause for relapse. Should respiration or blood pressure become compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously, as indicated.

Carisoprodol-The following have been used successfully in overdosage with the related drug meprobamate: diuretics, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis (see CLINICAL PHARMACOLOGY). Careful monitoring of urinary output is necessary and caution should be taken to avoid overhydration. Carisoprodol can be measured in biological fluid by gas chromatography (Douglas, J.F.,et al:*J Pharm Sci* 58:145,1969).

Aspirin-Since there are no specific antidotes for salicylate poisoning, the aim of treatment is to enhance elimination of salicylate and prevent or reduce further absorption; to correct any fluid electrolyte or metabolic imbalance; and to provide general and cardiorespiratory support. If acidosis is present, intravenous sodium bicarbonate must be given, along with adequate hydration, until salicylate levels decrease to within the therapeutic range. To enhance elimination, forced diuresis and alkalinization of urine may be beneficial. The need for hemoperfusion or hemodialysis is rare and should be used only when other measures have failed.

Codeine Phosphate-Narcotic antagonists, such as nalorphine and levallorphan, may be indicated.

DOSAGE AND ADMINISTRATION

Usual Adult Dosage: 1 or 2 tablets, four times daily.
Not recommended for use in children under age twelve.

HOW SUPPLIED

Carisoprodol, Aspirin and Codeine Phosphate tablets (carisoprodol 200mg, aspirin 325mg, and codeine phosphate, 16mg) are yellow and white color, two- layered round uncored tablets, debossed 'A 138' on one side. The tablets are available in bottles of 100 and 500.

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

Dispense in a tight container.

5/98

MANUFACTURED BY:
AMIDE PHARMACEUTICAL, INC.
LITTLE FALLS, NJ 07424 USA

Rx Only

7930-00

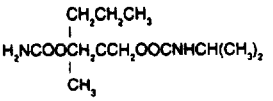
CARISOPRODOL, ASPIRIN AND CODEINE PHOSPHATE TABLETS, USP 200mg/ 325mg/ 16mg

C-III

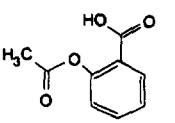
DESCRIPTION

Carisoprodol, Aspirin, and Codeine Phosphate Tablets is a combination product containing carisoprodol, a centrally-acting muscle relaxant, plus aspirin, an analgesic with antipyretic and antiinflammatory properties and codeine phosphate, a centrally-acting narcotic analgesic.

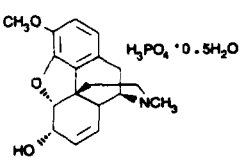
Chemically, carisoprodol is (±)-2-Methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate. Carisoprodol is a white crystalline powder, having a mild, characteristic odor and a bitter taste. It is very slightly soluble in water, freely soluble in alcohol, in chloroform, and in acetone. Its molecular formula is $C_{12}H_{24}N_2O_4$, with a molecular weight of 260.34. The *structural formula* is:



Chemically, aspirin is salicylic acid acetate. It can appear as white crystals, commonly tabular or needle-like, or white crystalline powder. It is odorless or has a faint odor. It is slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether; sparingly soluble in absolute ether. Its molecular formula is $C_9H_8O_4$ with a molecular weight of 180.16. The structural formula is:



Chemically, codeine phosphate appears as fine, odorless, white, needle-shaped crystals, or white, crystalline powder. Is affected by light. Its solutions are acid to litmus. Freely soluble in water; very soluble in hot water at 80°; slightly soluble in alcohol but more so in boiling alcohol. Its molecular formula is $C_{18}H_{21}NO_3H_3PO_4 \cdot 1/2\,H_2O$, with a molecular weight of 406.37. The structural formula is:



Each tablet, for oral administration, contains 200 mg of carisoprodol, 325 mg of aspirin and 16 mg of codeine phosphate. In addition, each tablet contains the following inactive ingredients: D&C Yellow #10 aluminum lake, corn starch, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, silicon dioxide, sodium starch glycolate, stearic acid, and zinc stearate.

CLINICAL PHARMACOLOGY

Carisoprodol: Carisoprodol is a centrally acting muscle relaxant that does not directly relax tense skeletal muscles in man. The mode of action of Carisoprodol in relieving acute muscle spasm of local origin has not been clearly identified, but may be related to its sedative properties. In animals, carisoprodol has been shown to produce muscle relaxation by blocking interneuronal activity and depressing transmission of polysynaptic neurons in the spinal cord and in the descending reticular formation of the brain. The onset of action is rapid and lasts four to six hours.

Carisoprodol is metabolized in the liver and is excreted by the kidneys. It is dialyzable by peritoneal and hemodialysis.

Aspirin: Aspirin is a nonnarcotic analgesic with antiinflammatory and antipyretic activity. Inhibition of prostaglandin biosynthesis appears to account for most of its antiinflammatory and for at least part of its analgesic and antipyretic properties.

Aspirin is rapidly absorbed and almost totally hydrolyzed to salicylic acid following oral administration. Although aspirin has a half- life of only about 15minutes,the apparent biologic half-life of salicylic acid in the therapeutic plasma concentration range is between 6 and 12 hours. Salicylic acid is eliminated by renal excretion and by biotransformation to inactive metabolite. Clearance of salicylic acid in the high-dose range is sensitive to urinary pH (see ***Drug Interactions***) and is reduced by renal dysfunction.

Codeine Phosphate: Codeine phosphate is a centrally acting narcotic-analgesic. Its actions are qualitatively similar to morphine, but its potency is substantially less.

Clinical studies have shown that combining aspirin and codeine produces a significant additive effect in analgesic efficacy.

INDICATIONS AND USAGE

Carisoprodol, Aspirin and Codeine Phosphate Tablets are indicated as an adjunct to rest, physical therapy, and other measures for the relief of pain, muscle spasm, and limited mobility associated with acute, painful musculoskeletal conditions when the additional action of codeine is desired.

CONTRAINDICATIONS

Acute intermittent porphyria; bleeding disorders; allergic or idiosyncratic reactions to carisoprodol, aspirin, codeine, or related compounds.

WARNINGS-On very rare occasions, the first dose of Carisoprodol has been followed by idiosyncratic reactions with symptoms appearing within minutes or hours. These may include extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Although symptoms usually subside over the course of the next several hours, discontinue Carisoprodol, Aspirin and Codeine Phosphate Tablets and initiate appropriate supportive and symptomatic therapy, which may include epinephrine and/or antihistamines. In severe cases, corticosteroids may be necessary. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock.

The effects of carisoprodol with agents such as alcohol, other CNS depressants or psychotropic drugs may be additive. Appropriate caution should be exercised with patients who take one or more of these agents simultaneously with Carisoprodol, Aspirin and Codeine Phosphate tablets.

PRECAUTIONS

General: To avoid excessive accumulation of carisoprodol, aspirin, or their metabolites, use Carisoprodol, Aspirin and Codeine Phosphate tablets with caution in patients with compromised liver or kidney function, or in elderly or debilitated patients (see CLINICAL PHARMACOLOGY).

Use with caution in patients with history of gastritis or peptic ulcer, in patients on anticoagulant therapy, and in addiction-prone individuals.

Information for Patients: Caution patients that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery.

Caution patients with a predisposition for gastrointestinal bleeding that concomitant use of aspirin and alcohol may have an additive effect in this regard.

Caution patients that dosage of medications used for gout, arthritis, or diabetes may have to be adjusted when aspirin is administered or discontinued (see ***Drug Interactions***).

Drug Interactions: Clinically important interactions may occur when certain drugs are administered concomitantly with aspirin or aspirin-containing drugs.

1. *Oral Anticoagulants*-By interfering with platelet function or decreasing plasma prothrombin concentration, aspirin enhances the potential for bleeding in patients on anticoagulants.
2. *Methotrexate*-aspirin enhances the toxic effects of this drug.
3. *Probenicid and Sulfinpyrazone*-large doses of aspirin reduce the uricosuric effect of both drugs. Renal excretion of salicylate may also be reduced.
4. *Oral Antidiabetic Drugs*-enhancement of hypoglycemia may occur.
5. *Antacids*-to the extent that they raise urinary pH, antacids may substantially decrease plasma salicylate concentrations; conversely, their withdrawal can result in a substantial increase.
6. *Ammonium Chloride*-this and other drugs that acidify a relatively alkaline urine can elevate plasma salicylate concentrations.
7. *Ethyl Alcohol*-enhanced aspirin –induced fecal blood loss has been reported.
8. *Corticosteroids*-salicylate plasma levels may be decreased when adrenal corticosteroids are given, and may be increased substantially when they are discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies have been done with Carisoprodol, Aspirin and Codeine Phosphate Tablets.

Pregnancy-Teratogenic Effects: **Pregnancy Category C.** Adequate animal reproduction studies have not been conducted with Carisoprodol, Aspirin and Codeine Phosphate Tablets . It is also not known whether Carisoprodol, Aspirin and Codeine Phosphate Tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Carisoprodol, Aspirin and Codeine Phosphate Tablets should be given to a pregnant woman only if clearly needed.

Studies in rodents have shown salicylates to be teratogenic when given in early gestation, and embryocidal when given in later gestation in doses considerably greater than usual therapeutic doses in humans. Studies in women who took aspirin during pregnancy have not demonstrated an increased incidence of congenital abnormalities in the offspring.

Labor and Delivery: Ingestion of aspirin near term or prior to delivery may prolong delivery or lead to bleeding in mother, fetus, or neonate.

Nursing Mothers: Carisoprodol is excreted in human milk in concentrations two-to-four times that in maternal plasma. Aspirin is excreted in human milk in moderate amounts and can produce a bleeding tendency in nursing infants. Because of the potential for serious adverse reaction in nursing infants, a decision should be made whether to discontinue nursing or 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 twelve have not been established.

ADVERSE REACTIONS

If severe reactions occur, discontinue Carisoprodol, Aspirin and Codeine Phosphate Tablets and initiate appropriate symptomatic and supportive therapy.

The following side effects which have occurred with the administration of the individual ingredients alone may also occur with the combination.

Carisoprodol: Central Nervous System-Drowsiness is the most frequent complaint and along with other CNS effects may require dosage reduction. Observed less frequently are dizziness, vertigo and ataxia. Tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia have been infrequent or rare.

Idiosyncratic-Idiosyncratic reactions are very rare. They are usually seen within the period of the the first to fourth dose in patients having had no previous contact with the drug (see WARNINGS).

Allergic-Skin rash, erythema multiforme, pruritis, eosinophilia, and fixed drug eruptions with cross-reaction to meprobamate have been reported. If allergic reactions occur, discontinue Carisoprodol, Aspirin and Codeine Phosphate Tablets and treat symptomatically. In evaluating possible allergic reactions, also consider allergy to excipients (information on excipients is available to physicians on request).

Cardiovascular-Tachycardia, postural hypotension, and facial flushing.

Gastrointestinal-Nausea, vomiting, epigastric distress, and hiccup.

Hematologic-No serious blood dyscrasias have been attributed to carisoprodol alone. Leukopenia and pancytopenia have been reported, very rarely, in situations in which other drugs or viral infections may have been responsible.

Aspirin: The most common adverse reactions associated with the use of aspirin have been gastrointestinal, including nausea, vomiting, gastritis, occult bleeding, constipation, and diarrhea. Gastric erosion, angioedema, asthma, rash, pruritus and urticaria have been reported less commonly. Tinnitus is a sign of high serum salicylate levels(see OVERDOSAGE).

Aspirin Intolerance-Allergic type reactions in aspirin–sensitive individuals may involve the respiratory tract or the skin. Symptoms of the former range from rhinorrhea and shortness of breath to severe asthma and the latter may consist of urticaria, edema, rash, or angioedema (giant hives). These may occur independently or in combination.

Codeine Phosphate: Nausea, vomiting, constipation, miosis, sedation, and dizziness have been reported.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Schedule CIII (see PRECAUTIONS).

Abuse: In clinical use, has been rare.

Dependence: In clinical use, dependence with Carisoprodol, Aspirin, and Codeine Tablets has been rare and there have been no reports of significant abstinence signs. Nevertheless, the following information on the individual ingredients should be kept in mind.

Carisoprodol- In dogs, no withdrawal symptoms occurred after abrupt cessation of carisoprodol from dosages as high as 1 gm/kg/day. In a study in man, abrupt cessation of 100 mg/kg/day (about five times the recommended daily adult dosage) was followed in some subjects by mild withdrawal symptoms such as abdominal cramps, insomnia, chills, headache, and nausea. Delirium and convulsions did not occur (see PRECAUTIONS).

Codeine Phosphate- Drug dependence of the morphine type may result.

OVERDOSAGE

Signs and symptoms: Any of the following which have been reported with the individual ingredients may occur and may be modified to a varying degree by the effects of the other ingredients present in Carisoprodol, Aspirin and Codeine Phosphate Tablets.

Carisoprodol-Stupor, coma, shock, respiratory depression, and, very rarely, death. Overdosage with carisoprodol in combination with alcohol, other CNS depressants, or psychotropic agents can have additive effects, even when one of the agents has been taken in the usually recommended dosage.

Aspirin - Headache, tinnitus, hearing difficulty, dim vision, dizziness, lassitude, hyperpnea, rapid breathing, thirst, nausea, vomiting, sweating, and occasionally diarrhea are characteristic of mild to

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-283

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-283

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc. (AP)
101 East Main Street
Little Falls, NJ 07424

4. BASIS OF SUBMISSION
Adequately addressed in CR # 1 completed by this reviewer.

Listed drug product: Soma^{R} Compound with Codeine Phosphate by Wallace Laboratories (Division of Carter-Wallace, Inc.) approved in NDA # 12-366 002.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Carisoprodol, Aspirin and Codeine Phosphate Tablets USP

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 10-27-97
NC: 11-21-97
NC: 1-28-98
Major Amendment: 6-3-98 (Response to 5-1-98 letter)
*Fax Amendment: 12-5-98 (Response to 12-2-98 letter)

FDA:
Accepted for filing on: 10-27-97 (Acknowledgment letter date: 12-11-97)
NA letter (Chemistry & Labeling): 5-1-98
NA letter: 12-2-98

10. PHARMACOLOGICAL CATEGORY
Used for relief of painful musculoskeletal conditions.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 40-118 ..approved for Eon (Carisoprodol/Aspirin/Codeine

Phosphate Tablets)
ANDA 40-252.. Approved for Amide Pharmaceutical for Carisoprodol/Aspirin.

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13. DOSAGE FORM
Tablets

14. POTENCY
Carisoprodol 200 mg
Aspirin 325 mg
Codeine Phosphate 16 mg

15. CHEMICAL NAME AND STRUCTURE
Carisoprodol is N-isopropyl-2-methyl-2 propyl-1,3-propanediol dicarbamate

Aspirin is 2-(Acetylase) benzoic Acid.

Codeine Phosphate: 7,8-Didehydro-4,5∝-epoxy-methoxy-17-methylmorphinan-6∝-ol phosphate (1:1) (salt)(hemihydrate)

Structures: See USP 23

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Referenced DMF for carisoprodol drug substance, DMF : or
c)
remains adequate since no new information is submitted by respective DMF holders.
2. EER status is acceptable as of 12-7-98.
3. FPL is approved per T. Watkins reviewed on 6-17-98.
4. Amide submitted acceptable response to 12-2-98 NA letter.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
12-9-98

Page(s) 10

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Rev 3

12/9/98

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-283

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc. (AP)
101 East Main Street
Little Falls, NJ 07424

4. BASIS OF SUBMISSION
Adequately addressed in CR # 1 completed by this reviewer.

Listed drug product: Soma[R] Compound with Codeine Phosphate by Wallace Laboratories (Division of Carter-Wallace, Inc.) approved in NDA # 12-366 002.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Carisoprodol, Aspirin and Codeine Phosphate Tablets USP

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 10-27-97
NC: 11-21-97
NC: 1-28-98
* Major Amendment: 6-3-98 (Response to 5-1-98 letter)

FDA:
Accepted for filing on: 10-27-97 (Acknowledgment letter date: 12-11-97)
NA letter (Chemistry & Labeling): 5-1-98

10. PHARMACOLOGICAL CATEGORY
Used for relief of painful musculoskeletal conditions.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 40-118 ..approved for Eon (Carisoprodol/Aspirin/Codeine Phosphate Tablets)
ANDA 40-252.. Approved for Amide Pharmaceutical for

Carisoprodol/Aspirin.

13. DOSAGE FORM
Tablets

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Carisoprodol 200 mg
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Carisoprodol is N-isopropyl-2-methyl-2 propyl-1,3-propanediol dicarbamate

Aspirin is 2-(Acetylase) benzoic Acid.

Codeine Phosphate: 7,8-Didehydro-4,5∝-epoxy-methoxy-17-methylmorphinan-6∝-ol phosphate (1:1) (salt)(hemihydrate)

Structures: See USP 23

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A. GENERAL COMMENTS:
1.

2. EER status is pending.
3. FPL is approved per T. Watkins reviewed on 6-17-98.

B: COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments listed in section # 20, 23, 29, and 33.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with facsimile amendment is being issued to the applicant citing all the deficiencies listed in this review.

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 10-16-98

Page(s) 10

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Rev 2
10/16/98

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 40-283

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc. (AP)
101 East Main Street
Little Falls, NJ 07424

4. BASIS OF SUBMISSION
The listed drug product is Soma[R] Compound with Codeine Phosphate by Wallace Laboratories (Division of Carter-Wallace, Inc.) approved in NDA # 12-366 002. No exclusivity exists for the drug product according to 17th edition of the Approved Drug Products with Therapeutic Equivalence Evaluation. The proposed drug product contains the same active ingredient and has same strength, dosage form, route of administration, indications and usage as the listed drug.

AP submitted Patent Certification on page 9 to certify that, in their opinion and to the best of knowledge, U.S Patent # 4,534,974, issued on August 1, 1985 assigned to Wallace Laboratories is invalid and/or unenforceable and will not be infringed upon manufacture, use or sale by Amide Pharmaceutical's Carisoprodol/Aspirin/Codeine Phosphate Tablets.

According to NC dated 1-28-98, Amide did notified responsible personnel at Carter Wallace (division of Wallace Laboratories) via certified mail with return receipt requested on 12-1-97. Amide certified that 45 days have passed on 1-15-98 since notification and Amide has not been sued by Carter Wallace.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Carisoprodol, Aspirin and Codeine Phosphate Tablets USP

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 10-27-97
Accepted for filing on: 10-27-97 (Acknowledgment letter date: 12-11-97)
NC: 11-21-97
NC: 1-28-98

10. PHARMACOLOGICAL CATEGORY
Used for relief of painful musculoskeletal conditions.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
ANDA 40-118 ..approved for Eon (Carisoprodol/Aspirin/Codeine Phosphate Tablets)
ANDA 40-252.. Approved for Amide Pharmaceutical for Carisoprodol/Aspirin.

13. DOSAGE FORM
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Codeine Phosphate: 7,8-Didehydro-4,5α-epoxy-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt)(hemihydrate)

Structures: See USP 23

16. RECORDS AND REPORTS
N/A

17. COMMENTS

A. GENERAL COMMENTS:

1. The drug product will be manufactured at AP's facility at Little falls, NJ.
2. DMF for carisoprodol drug substance is adequate per last review dated 11-21-97.
3. DMF for was found adequate per Shing Liu's review dated 2-27-97. Remains adequate per review conducted by this reviewer on 3-12-98.
4. DMF for) is adequate per review completed on 9-18-97 by this reviewer.
5. AP's specifications for Carisoprodol and Codeine Phosphate drug substances are based on USP monograph.
6. AP's intended production batch size is of tablets tablets and tablets.
7. AP's executed batch (lot # 7145A) is of size tablets and is manufactured based on same manufacturing process they will manufacture production size batches.
8. AP's marketplace package size HDPE bottle of 100's and 500's.
9. AP packaged the entire executed batch record into package sizes 100's and 500's.
10. AP's release specification for the finished drug product is based on current USP 23.
11. AP's method for assay carisoprodol, aspirin and free salicylic acid and Codeine Phosphate in the drug product is based on USP method and has been validated as a stability-indicating.
12. Stability data for the executed batch is submitted and AP proposed a expiration dating period of two years.
13. Bio review - acceptable bio review dated 2-17-98.
14. EER has been submitted for the facilities except one facilities for which EER submission is requested by this reviewer.

15. FPL is deficient. All the comments are to be communicated to the firm.

B: COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments listed in section # 20, 23, 25, 28, 29, 32, and 33.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with MAJOR amendment is being issued to the applicant citing all the deficiencies listed in this review.

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 3-25-98

Revised on 4-21-98 to include Mike Smela's comments.

Page(s) 24

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Rev 1

3/25/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-283

ADMINISTRATIVE DOCUMENTS

Verified 12/23/98 per client

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 40283/000**
Stamp: **27-OCT-1997** Regulatory Due:
Applicant: **AMIDE PHARM**
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

Priority: Org Code: **600**
Action Goal: District Goal: **27-DEC-1998**
Brand Name:
Established Name: **CARISOPRODOL; ASPIRIN; CODEINE PHOSPHATE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG/325 MG/16 MG**

FDA Contacts:

ID = 122344			**, Project Manager**
M. SHAIKH	**(HFD-625)**	**301-827-5848**	**, Review Chemist**
M. SMELA JR	**(HFD-625)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 07-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:
AMIDE PHARMACEUTICAL INC
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
FIRM RESPONSE TO DEFIC. ADEQ

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **INTERMEDIATE OTHER TESTER**

Establishment:

MF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: **07-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-APR-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment:

):
No.

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:

DMF N
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-283

FIRM: Amide Pharmaceuticals, Inc.

DOSAGE FORM: Tablets

STRENGTH: 200 mg/325 mg/16 mg

DRUG: Carisoprodol/Aspirin/Codeine Phosphate Tablets

CGMP STATEMENT/EIR UPDATED STATUS:
EER submitted for all the facilities listed in Section # 33 of CR # 3 is acceptable as of 12-7-98 by J.D. Ambrogio.

BIO STUDY:
Acceptable per bio acceptance issued to Amide on 2-17-98.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV is not required as the drug product is a USP material.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Container/closure system used for conducting stability studies are identical to those listed in container section.

Drug product will be marketed in marketplace package of 100's, and 500's.

LABELING:
Satisfactory per T. Watkin's review completed on 6-17-98.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Amide's Bio/stability batch is lot # 7145A and its size is ablets (108 kg).

Source of NDS:
Carisoprodol Drug Substance:
Referenced Labochim's DMF is satisfactory per S. Brown's review dated 11-21-97. No new information is submitted since last review.

Aspirin 10% Starch Granulation:
Referenced Rhone-Poulenc's DMF .s satisfactory per M. Shaikh's review completed on 9-18-97.

Codeine Phosphate: Referenced DMF s adequate per last review conducted by this reviewer dated 3-12-98.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Amide's stability/bio batch 7145A of tablets size.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Amide's intended production batch sizes are tablets (108 kg), lets (288 kg) and tablets (720 kg).

Manufacturing process is identical to that used for the bio/stability batch.

cc:

Endorsements:

12/16/98

M Smelko 12/16/98

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-APR-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment:

MICAL INC

47

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **12-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

CDER Establishment Evaluation Report
for November 18, 1998

Application: **ANDA 40283/000**
Stamp: **27-OCT-1997** Regulatory Due:
Applicant: **AMIDE PHARM**
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

Priority:
Org Code: **600**
Action Goal:
District Goal: **27-DEC-1998**
Brand Name:
Established Name: **CARISOPRODOL; ASPIRIN; CODEINE PHOSPHATE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG/325 MG/16 MG**

FDA Contacts: **M. SHAIKH (HFD-625) 301-827-5848 , Review Chemist**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment:
AMIDE PHARMACEUTICAL INC
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
FIRM RESPONSE TO DEFIC. ADEQ

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
.L LABORA
3901

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **INTERMEDIATE OTHER TESTER**

Establishment:

DMF Nc
A AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **INSPECTION PERFORMED**
Milestone Date: **21-SEP-1998**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

CDER Establishment Evaluation Report for April 29, 1998

Application: ANDA 40283/000
Stamp: 27-OCT-1997 Regulatory Due:
Applicant: AMIDE PHARM
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

Priority:
Action Goal:
Brand Name:
Established Name: CARISOPRODOL; ASPIRIN; CODEINE PHOSPHATE
Generic Name:
Dosage Form: TAB (TABLET)
Strength: 200 MG/325 MG/16 MG

Org Code: 600
District Goal: 27-DEC-1998

FDA Contacts:			
	S. OKEEFE	(HFD-617)	301-827-5848 , Project Manager
	M. SHAIKH	(HFD-625)	301-827-5848 , Review Chemist
	M. SMELA JR	(HFD-625)	301-827-5848 , Team Leader

Overall Recommendation:

Establishment: 2244683
AMIDE PHARMACEUTICAL INC
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: DO RECOMMENDATION
Milestone Date 16-APR-1998
Decision: WITHHOLD
Reason: INSUFFICIENT DEVELOPMENT D

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 11-FEB-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: INTERMEDIATE OTHER TESTER

Establishment:

:
No:

Profile: CSN OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date 03-FEB-1998

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **29-APR-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **18-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment

DMF No
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

CDER Establishment Evaluation Report
for December 11, 1997

Application: **ANDA 40283/000**
Stamp: **27-OCT-1997** Regulatory Due:
Applicant: **AMIDE PHARM**
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

Priority:
Action Goal:
Brand Name:
Established Name: **CARISOPRODOL; ASPIRIN; CODEI**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG/325 MG/16 MG**

Org Code: **600**
District Goal: **27-DEC-1998**

FDA Contacts: **J. WILSON III (HFD-617) 301-827-5848 , Project Manager**
V. SAYEED (HFD-629) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment: **2244683**
AMIDE PHARMACEUTICAL INC
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

DMF No:

AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 11-DEC-1997**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 11-DEC-1997**

Responsibilities:
INTERMEDIATE OTHER TESTER

Establishment:

DMF No:

NTERNA

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 11-DEC-1997**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Establishment.

DMF No

AADA No:

1925021
MALLINCKRODT MEDICAL INC

SAINT LOUIS, MO 63134

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 11-DEC-1997**

Establishment

No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 11-DEC-1997**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

APPROVAL SUMMARY

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

ANDA Number: **40-283** Date of Submission: **JUNE 3, 1998**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 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: June 3, 1998 (100's and 500's)

Professional Package Insert Labeling: June 3, 1998 (Revised 5/98)

Revisions needed post-approval:

a. HOW SUPPLIED

Revise the last sentence to read as follows:

Dispense in a tight, light resistant container.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form:
Soma® Compound with Codeine Tablets

NDA Number: 12-366

NDA Drug Name: Soma® Compound with Codeine Tablets

NDA Firm: Wallace Laboratories

Date of Approval of NDA Insert and supplement #: January 16, 1986/S-021
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: Container labels submitted for side-by-side and container labels in file folders.

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? Aspirin listed first.	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? USAN 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?		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?		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?		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 bioeqivalency values: insert to study. List Cmax, Tmax, 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		

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

1. See comment e.i. under INSERT. Do you concur?

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Soma® Compound with Codeine Tablets; Wallace Laboratories; 12-366/S-021; Approved January 16, 1986, Revised 3/85).

2. Patent/ Exclusivities:

   There is one patent that exists for this drug product. Patent #4534974 for Pharmaceutical compositions with codeine, expires on August 13, 2002. The firm has submitted a paragraph IV certification stating the patent is unenforceable and that they will market as soon as approved.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from moisture. Dispense in a tight container.

   ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from moisture. Dispense in tight, light-resistant container.

   USP: Preserve in well-closed containers.

4. Scoring:

   NDA: Not scored.

   ANDA: Not scored.

5. Product Line:

   The innovator markets their product in bottles of 100.

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

6. The tablet 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 513, Vol. 1.1..

7. 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 097.

8. All manufacturing will be performed by Amide Pharmaceutical, Inc.. All outside firms are utilized for micro and water testing. See pages 258 and 266.

9. Container/Closure:

   This product will be packaged in HDPE bottles with metal screw top closures. See page 482.

Date of Review: December 30, 1997

Date of Submission: October 27, 1997

Reviewer: [signature] **Date:** 6-17-98

Team Leader: John L. Grove **Date:** 6-17-98

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cc:

M E M O R A N D U M

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

DATE : October 30, 1997

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 10/30/97

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Amide Pharmaceutical Inc. has submitted ANDA 40-283 for Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring July 31, 2004 will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence dissolution and waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the dissolution and waiver submitted by Amide Pharmaceutical Inc. on October 30, 1997 for its Carisoprodol, Aspirin and Codeine Phosphate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially

ANDA 40-283 - Carisoprodol, Aspirin and Codeine Phosphate - Amide
Pharmaceutical Inc.

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

__✓__ Dissolution and Waiver meets statutory requirements Vikta Bachhe

_____ Dissolution and Waiver does **NOT** meet statutory requirements

Reason:

/S/

Director, Division of Bioequivalence

11/13/97
Date

complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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

ANDA Number: **40-283** Date of Submission: **October 27, 1997**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg**

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

   Revise to read "Usual Dosage: See package insert...".

2. INSERT

   a. TITLE

      Delete the period following USP in the established name.

   b. DESCRIPTION

      Delete the last sentence of paragraph one. This information is contained in the HOW SUPPLIED section of the insert.

   c. CLINICAL PHARMACOLOGY

      Carisoprodol - Revise the font size of this subsection heading to be consistent with the other subsection headings throughout the text of the insert. Refer to 21 CFR 201.57 for guidance.

   d. PRECAUTIONS

      i. Drug Interactions - See comment c under INSERT.

      ii. Italicize the subsection heading "*Carcinogenesis, Mutagenesis, Impairment of Fertility*" to be consistent with the other

subsection headings throughout the text of the insert.

iii. Pediatric Use - Revise to read "pediatric patients" rather than "children".

e. HOW SUPPLIED

i. Indicate that your tablets are unscored.

ii. We encourage the inclusion of your NDC numbers.

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

Carisoprodol/Aspirin /Codeine Phosphate 200 mg/325 mg/16 mg Tablet
ANDA #40-283
Reviewer: Lin-Whei Chuang

Amide Pharmaceutical, Inc.
Little Falls, NJ

Submission Date:
October 27, 1997

Review of a Waiver Request

The firm is requesting a waiver of *in vivo* bioequivalence requirements for its Carisoprodol/Aspirin/Codeine Phosphate, 200 mg/325 mg/16 mg, in accordance with 21 CFR 320.22 (d)(2). Comparative dissolution data for the test product and the reference listed drug, Wallace Laboratories' Soma^R Compound with Codeine (Carisoprodol/Aspirin/Codeine Phosphate, 200 mg/325 mg/16 mg) were submitted in support of the waiver request and presented below:

Comparative Dissolution Testing

Drug (Generic Name): Carisoprodol/Aspirin/Codeine Phosphate
Dosage Form: Tablet
Dose Strength: 200 mg/325 mg/16 mg
ANDA No.: 40-283
Firm: Amide Pharmaceutical, Inc.
Submission Date: 10/27/97

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 75 No. Units Tested: 12
Medium: Water Volume: 900 mL
Tolerance: NLT of the labeled amount is dissolved in minutes
Reference Drug: Soma^R Compound with Codeine (Wallace Laboratories)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (minute)	Test Product Batch # 7145A Strength (mg): 200/325/16			Reference Product Batch # 41102NA Strength (mg): 200/325/16		
	Mean % of Carisoprodol	Range	%CV	Mean % of Carisoprodol	Range	%CV
20	92.9		1.8	72.0		2.2
30	94.2		2.0	83.8		2.0
45	95.4		2.5	91.8		1.9

	Mean % of Aspirin	Range	%CV	Mean % of Aspirin	Range	%CV
20	97.6		1.6	100.4		1.3
30	98.2		1.4	100.4		1.7
45	97.5		1.2	98.7		1.6
	Mean % of Codeine		%CV	Mean % of Codeine		%CV
20	99.6		0.9	95.7		1.4
30	99.4		0.5	95.1		1.1
45	99.3		1.4	94.7		0.9

The composition of the test product is:

Part A (Yellow Layer) **mg/Tablet**

* Used for

Part B (White Layer)

Comments:

1. The comparative dissolution data are acceptable.

2. Carisoprodol/Aspirin/Codeine tablets are listed in the 17th Edition of the "*Approved Drug Products with Therapeutic Equivalence Evaluations*" at page 3-559 among the drug products for which *in vivo* bioavailability is required only if adequate dissolution is not achieved.

Recommendation:

1. The dissolution testing conducted by Amide Pharmaceutical, Inc. on it Carisoprodol/Aspirin/Codeine Phosphate tablets, 200 mg/325 mg/16 mg, is acceptable.

   The dissolution testing should be incorporated into the firm's's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP XXIII apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

   > Not less than f labeled of carisoprodol, aspirin and codeine in the dosage form is dissolved in minutes.

2. The division Bioequivalence agrees that the information submitted by Amide Pharmaceutical, Inc. demonstrates that its Carisoprodol/Aspirin/Codeine Phosphate tablet, 200 mg/325 mg/16 mg, falls under 21 CFR 320.24(b)(6) of the Bioavailability/Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the test product is granted. The test product is deemed bioequivalent to the currently approved Soma^{R} Compound with Codeine manufactured by Wallace Laboratories.

Lin-Whei Chuang 2/18/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG 2/17/98

Concur /S/ Date: 2/17/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

First Draft, LWC, 02/13/98, X:\NEW\FIRMSAM\AMIDE\LTRS&REV\40-283DW.097
Final Pink, LWC, 02/17/98, X:\NEW\FIRMSAM\AMIDE\LTRS&REV\40-283DW.097

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

ANDA Number: **40-283** Date of Submission: **October 27, 1997**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg**

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

   Revise to read "Usual Dosage: See package insert...".

2. INSERT

   a. TITLE

      Delete the period following USP in the established name.

   b. DESCRIPTION

      Delete the last sentence of paragraph one. This information is contained in the HOW SUPPLIED section of the insert.

   c. CLINICAL PHARMACOLOGY

      Carisoprodol - Revise the font size of this subsection heading to be consistent with the other subsection headings throughout the text of the insert. Refer to 21 CFR 201.57 for guidance.

   d. PRECAUTIONS

      i. Drug Interactions - See comment c under INSERT.

      ii. Italicize the subsection heading "*Carcinogenesis, Mutagenesis, Impairment of Fertility*" to be consistent with the other

subsection headings throughout the text of the insert.

iii. Pediatric Use - Revise to read "pediatric patients" rather than "children".

e. HOW SUPPLIED

i. Indicate that your tablets are unscored.

ii. We encourage the inclusion of your NDC numbers.

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

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

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:
Soma® Compound with Codeine Tablets

NDA Number: 12-366

NDA Drug Name: Soma® Compound with Codeine Tablets

NDA Firm: Wallace Laboratories

Date of Approval of NDA Insert and supplement #: January 16, 1986/S-021
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: Container labels submitted for side-by-side and container labels in file folders.

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? Aspirin listed first.	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? USAN 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?		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?		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?		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 bioeqivalency values: insert to study. List Cmax, Tmax, 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		

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

1. **See comment e.i. under INSERT. Do you concur?** Yes 4/21/98

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Soma® Compound with Codeine Tablets; Wallace Laboratories; 12-366/S-021; Approved January 16, 1986, Revised 3/85).

2. Patent/ Exclusivities:

   There is one patent that exists for this drug product. Patent #4534974, expires on August 13, 2002. The firm has submitted a paragraph IV certification stating the patent is unenforceable and that they will market as soon as approved.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from moisture. Dispense in a tight container.

   ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from moisture. Dispense in tight, light-resistant container.

   USP: Preserve in well-closed containers.

4. Scoring:

   NDA: Not scored.

   ANDA: Not scored.

5. Product Line:

   The innovator markets their product in bottles of 100.

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

6. The tablet 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 513, Vol. 1.1..

7. 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 097.

8. All manufacturing will be performed by Amide Pharmaceutical, Inc.. All outside firms are utilized for micro and water testing. See pages 258 and 266.

9. Container/Closure:

   This product will be packaged in HDPE bottles with metal screw top closures. See page 482.

Date of Review: December 30, 1997

Date of Submission: **October 27, 1997**

Reviewer: C. Halquist **Date:** 12/31/97

Team Leader: **Date:**

John Grace 12/31/97

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cc

M E M O R A N D U M

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

DATE : October 30, 1997

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 10/30/97

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Amide Pharmaceutical Inc. has submitted ANDA 40-283 for Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring July 31, 2004 will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence dissolution and waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the dissolution and waiver submitted by Amide Pharmaceutical Inc. on October 30, 1997 for its Carisoprodol, Aspirin and Codeine Phosphate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially

ANDA 40-283 - ~~Car~~isoprodol, Aspirin and Codeine Phosphate - Amide Pharmaceutical Inc.

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

__L__ Dissolution and Waiver meets statutory requirements Vikta Bude

_____ Dissolution and Waiver does **NOT** meet statutory requirements

Reason:

/S/

Director, Division of Bioequivalence

11/13/97

Date

complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

TELEPHONE MEMO

To: Jasmine Shah, MS, R.Ph. (Amide Pharmaceutical, Inc.)
(973) 890-1440

CC: ANDA 40-283 Carisoprodol, Aspirin, Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg

From: Saundra T. Middleton

Date: November 18, 1997

Subject: Revised Patent IV Certification

Mr. Shah, was asked to revise the Paragraph IV Certification to state "..... patent 4534974 which expires on August 13, 2002". In addition, a statement should be provided along with this certification, that Amide will comply with the notification provisions of sections 21 CFR 314.95(a),(b), and (c) (59 FR 50365-50366) pursuant to 21 CFR 314.94(a)(12)(i)(A)(4), and 314.95.

Mr. Shah, was also informed that he failed to sign the Post Approval Stability Commitment, and that he needed to revised the cover letter to say 505(j) *versus* 505(b).

Amide, will resubmit the above documents by November 19, 1997.

FROM THE DESK OF...

SAUNDRA T. MIDDLETON
CONSUMER SAFETY OFFICER
CDER\FDA\OGD\DLPS
7500 STANDISH PLACE
ROCKVILLE MD 20855

301-827-5862
Fax: 301-594-1174

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-283

CORRESPONDENCE

Amide
PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, New Jersey 07424
Telephone (973) 890-1440
Fax (973) 890-7980

December 5, 1998

NDA ORIG AMENDMENT
FA

Douglas Spom
Director
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD-630
Metropark North II
7500 Standish Place
Rockville, MD 20855

FACSIMILE AMENDMENT

Re: ANDA-40-283
Carisoprodol, Aspirin and Codeine Phosphate Tablets

Dear Mr. Spom:

In response to the facsimile amendment letter dated Dec 2, 1998, for our pending ANDA 40-283, Carisoprodol, Aspirin and Codeine Phosphate Tablets we are submitting our response.

A. Deficiencies:

1. The total weight of one tablet, and total weight for all three batch sizes listed are incorrect in your Composition Statement. Please submit a correct Composition Statement.

Response: The Composition page has been revised. Enclosed in Attachment I is a copy of the revised Composition page.

2. Please clarify if your particle size limits for Carisoprodol drug substance are based on data from the lot used in the exhibit batch. Please provide the data.

Response: The particle size specification for Carisoprodol Drug Substance has been derived from the analysis of four different lots and information from the supplier. Attached in Attachment II is a copy of the particle size specification for Carisoprodol and the test data for the exhibit batch. There was an error in the specification for the particle size in previous submission.

RECEIVED
DEC 07 1998
GENERIC DRUGS

B. In addition to responding to the deficiencies presented above, Amide notes and acknowledges the following in our response:

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

Response: Amide Acknowledges that the cGMP compliance of all facilities listed in our application shall be evaluated by your Office of Compliance and a satisfactory evaluation is required prior to the approval of our application.

2. Please submit the currently available long term stability data for the exhibit batch for both package sizes.

Response: Attached in Attachment III are updated results of the stability studies including the last test station.

Please forward any communication regarding this ANDA to me at the above address. If you need to call or fax me, my telephone number is (973)890-1440 and Fax number is (973)890-7980.

Sincerely
Amide Pharmaceutical, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

DEC 2 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-283 APPLICANT: Amide Pharmaceuticals, Inc.

DRUG PRODUCT: Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg

The deficiencies presented below represent Facsimile deficiencies.

A. Deficiencies:

1. The total weight of one tablet, and total weight for all three batch sizes listed are still incorrect in your Composition Statement. Please submit a correct Composition Statement.

2. Please clarify if your particle size limits for Carisoprodol drug substance are based on data from the lot used in the exhibit batch. Please provide this data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please submit the currently available long term stability data for the exhibit batch for both package sizes.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-283 APPLICANT: Amide Pharmaceuticals, Inc.

DRUG PRODUCT: Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg

The deficiencies presented below represent Facsimile deficiencies.

A. Deficiencies:

1. The total weight of one tablet, and total weight for all three batch sizes listed are still incorrect in your Composition Statement. Please submit a correct Composition Statement.

2. Please clarify if your particle size limits for Carisoprodol drug substance are based on data from the lot used in the exhibit batch. Please provide this data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please submit the currently available long term stability data for the exhibit batch for both package sizes.

Sincerely yours,

/S/

3/26

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

June 3, 1998

ORIG AMENDMENT
w/ AC

Change to Minor denied
See TCon
M Smela 6/12/98

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD-630
Metropark North II
7500 Standish Place
Rockville, MD 20855

CLASSIFICATION CHANGE FOR DEFICIENCY

Re: ANDA-40-283
Carisoprodol, Aspirin and Codeine Phosphate Tablets

Dear Mr. Sporn:

In reference to the deficiency letter dated May 1, 1998, for our pending ANDA 40-283, Carisoprodol, Aspirin and Codeine Phosphate Tablets, Amide is submitting its response.

We are requesting FDA to reclassify the deficiency from a Major to a minor deficiency. The request for reclassification of the deficiency is based on (a) the changes involves are minor changes and (b) the analytical method has remained the same for the testing of impurities.

We would appreciate extremely, if you would review our request.

Please forward any communication regarding this ANDA to me at the above address. If you need to call or fax me, my telephone number is (973)890-1440 and Fax number is (973)890-7980.

Sincerely
Amide Pharmaceutical, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs.

RECEIVED
JUN 0 4 1998
GENERIC DRUGS

MAY 1 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-283 APPLICANT: Amide Pharmaceuticals, Inc.

DRUG PRODUCT: Carisoprodol, Aspirin and Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. The total weight of one tablet, and total weight for all three batch sizes listed are incorrect in your Composition Statement. In addition, _ of Microcrystalline Cellulose s used per tablet according to composition on same page whereas the manufacturing documents for intended production batches for and tablets reflect amount of 55 mg. Please correct and resubmit.

2. You have proposed a hardness range of _ for stability monitoring of the subject drug product. Based on the accelerated stability data submitted in your submission, the exhibit batch fails as packaged in both container/closure systems. Please clarify. You may delete the hardness test for stability purposes, if desired.

3. Please include a particle size specification as an acceptance specification for Carisoprodol drug substance.

4. Please revise your particle size specifications for Aspirin Granulation in order to account for at least 90% of the particles.

5. It is unlikely that the TLC methods used to detect impurities related to the three drug substances are of adequate sensitivity. Your methods must be validated to adequately detect the known impurities ') as well as unidentified impurities at a detection limit of about relative to each drug substance. For example, the standard preparation diluted fold shall exhibit a visible spot. Please either supply photographs and other supporting information to document the sensitivity of the TLC methods, or develop

and validate methods for this purpose. In any case, please supply data for your drug product at the next stability station.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please submit the currently available room temperature stability data for the exhibit batch for both package sizes.

3. Your blend yield and compressed tablet yield reconciliation of 90-102% appears lax. This issue is evaluated by the FDA district investigator during cGMP inspections.

4. You must also address the labeling deficiencies with your response.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date FEB 25 1998

From Consumer Safety Officer
Investigations & Preapproval Compliance Br/DMPQ (HFD-324)

Subject Recommendation to Withhold Approval
Naltrexone Hydrochloride Tablets (ANDA 75-274) Br 6
Oxycodone/Acetaminophen Tablets (ANDA 40-203) Br 6

To Digoxin Tablets (ANDA 40-282) Br 6
Carisoprodol/Aspirin/Codeine Phosphate Tablets (ANDA 40-283) Br 2

Gordon R. Johnston
Office of Generic Drugs (HFD-601)

Applicant/Firm: Amide Pharmaceutical, Inc
101 East Main Street
Little Falls, NJ 07424
CFN #2244683

We have completed our review of the Establishment Inspection Report (EIR) for Amide Pharmaceutical, Inc located at 101 East Main Street, Little Falls, NJ 07424. The facility was inspected by the FDA New Jersey District Office (NWJ-DO) from November 4 to December 1, 1997.

NWJ-DO conducted a CGMP inspection at the request of the NWJ-DO Compliance Branch to determine if the firm's request for relief from the Consent Decree of Permanent Injunction (signed 3-23-92) should be granted.

During the inspection, NWJ-DO observed many significant CGMP violations that affect the firm's entire operation. Following the inspection, NWJ-DO recommended that the firm remain under the Consent Decree, and that approval of ANDA 75-274 be withheld. On December 24, 1997, NWJ-DO also recommended that other pending applications be withheld due to many significant CGMP violations.

The Division of Manufacturing and Product Quality (DMPQ) concurs with the District's recommendation to withhold approval of ANDA 75-274, ANDA 40-203, ANDA 40-282 and ANDA 40-283. Significant CGMP deficiencies noted during the inspection **include but are not limited to** the following:

1. Impurity profile testing has not been conducted/completed for 25 active pharmaceutical ingredients.

2. Storage areas for active pharmaceutical ingredients and excipients are not monitored for temperature and humidity.

3. The quality control laboratory has established a 12 month expiration dating period for all in-house reference standards. However, no stability studies have been conducted to support the expiration dating periods.

4. The quality control laboratory utilizes for data collection. However, the firm cannot assure the integrity of the HPLC data due to the lack of an audit trail.

5. The firm's cleaning validation studies for ANDA drug products only utilized 1 batch of drug product per study. Cleaning validation studies should have been conducted utilizing 3 consecutive batches per study.

6. The firm lacks a written SOP detailing the water sampling procedure for both routine sampling and for use in manufacturing. In addition, the firm lacks data to support the general maintenance and testing requirements for the following areas of the purified water system: two filters, the carbon beds, and the UV light.

A copy of the EIR is attached for your review.

If you have any questions please contact me at (301) 827-0071.

John M. Singer

John M. Singer

Attachment

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (201) 890-1440
Fax (201) 890-7980

NEW CORRESP

January 28, 1998

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

PATENT AMENDMENT

RE: AMENDMENT TO ANDA - 40-283
CARISOPRODOL AND ASPIRIN TABLETS USP 200 mg/325 mg/16 mg

Dear Mr. Sporn:

In reference to our telephone conversation today, enclosed find the amendment to our ANDA 40-283, Carisoprodol, Aspirin and Codeine Tablets USP 200 mg/325 mg/16 mg as follows:

Please note that as required under 21 CFR 314.95(a) Amide has notified responsible personnel at Carte Wallace of which Wallace Laboratories is a division via certified mail with return receipt requested on December 1, 1997. We also certify that 45 days have passed on January 15, 1998, since notification and that Amide has not been sued by Carter Wallace.

If you or your staff have any question, please feel free to contact us.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.P.
Director Regulatory Affairs

RECEIVED
JAN 29 1998
GENERIC DRUGS

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (201) 890-1440
Fax (201) 890-7980

S. Middleton 121-97 pkl
ack 30 5(1)

NEW CORRESP
VC

November 21, 1997

Sandra Middleton
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA - 40-283
CARISOPRODOL, ASPIRIN AND CODEINE PHOSPHATE TABLETS

Dear Ms. Middleton:

Per our telephone conversation of November 19, 1997, enclosed find to corrected documents to our application as follows:

1. Revised Cover letter
2. Signed Post approval Stability Commitment
3. Revised Paragraph 4 Certification.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

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GENERIC DRUGS

BIOEQUIVALENCY COMMENTS

ANDA: 40-283 APPLICANT: Amide Pharmaceutical, Inc.

DRUG PRODUCT: Carisoprodol/Aspirin/Codeine Phosphate

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

BIOEQUIVALENCY COMMENTS

ANDA: 40-283 APPLICANT: Amide Pharmaceutical, Inc.

DRUG PRODUCT: Carisoprodol/Aspirin/Codeine Phosphate

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

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

ANDA 40-283

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah, MS, R.Ph.
101 East Main Street
Little Falls, NJ 07424

DEC 11 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.

NAME OF DRUG: Carisoprodol, Aspirin, Codeine Phosphate Tablets USP, 200 mg/325 mg/16 mg

DATE OF APPLICATION: October 27, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 27, 1997

We also acknowledge your correspondence dated November 21, 1997.

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b),provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

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

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

Should you have questions concerning this application contact:

Jim Wilson
Project Manager
(301) 827-5848

Sincerely yours,

/S/

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

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (201) 890-1440
Fax (201) 890-7980

Alexandra J. Mitchell
505(j) 11-18-97

labeling received
Completed
C. Williams
12/30/97

October 27, 1997

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA - ORIGINAL APPLICATION
CARISOPRODOL, ASPIRIN AND CODEINE PHOSPHATE TABLETS

Dear Dr. Williams:

Enclosed please find Amide Pharmaceutical's original Drug Application for Carisoprodol, Aspirin and Codeine Phosphate Tablets and a transmittal letter (and one copy) describing same.

Kindly, have the copy of the transmittal letter stamped "filed" and return it to our courier who has been instructed to wait.

Thank you for your attention to this matter.

Very truly yours,

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

RECEIVED
OCT 27 1997
GENERIC DRUGS