ANDA 40-203

MAR 15 1999

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

Dear Sir:

This is in reference to your abbreviated new drug application dated July 22, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg.

Reference is also made to your amendment dated January 11, 1999.

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 Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Percocet® Tablets, 5 mg/325 mg, of Endo Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

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

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

Sincerely yours,

/S/ 3/15/99

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40203

DRAFT FINAL PRINTED LABELING

7830-00

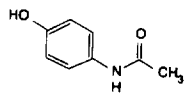
OXYCODONE AND ACETAMINOPHEN TABLETS, USP ©

DESCRIPTION

Each tablet for oral administration contains:
Oxycodone hydrochloride 5 mg*
WARNING: May be habit forming
Acetaminophen, USP 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

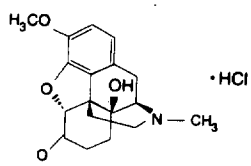
Each Tablet also contains: crospovidone, magnesium stearate, microcrystalline cellulose, pregelatinized starch, povidone, colloidal silicon dioxide, sodium starch glycolate and stearic acid.

Acetaminophen is 4'hydroxyacetanilide, a white, odorless, crystalline powder, possessing a slightly bitter taste. It may be represented by the following structural formula:



$C_8H_9NO_2$ M.W. 151.17

The oxycodone component is 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinone-6-one hydrochloride, a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



$C_{18}H_{21}NO_4 \cdot HCl$ M.W. 351.83

CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in oxycodone and acetaminophen tablets are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

Oxycodone and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Oxycodone and acetaminophen tablets should not be administered to patients who are hypersensitive to oxycodone or acetaminophen.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore,

has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of oxycodone and acetaminophen tablets, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, oxycodone and acetaminophen tablets is subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of oxycodone and acetaminophen tablets or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: Oxycodone and acetaminophen tablets should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using oxycodone and acetaminophen tablets should be cautioned accordingly.

Drug Interactions

Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone and acetaminophen tablets may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with narcotics may produce paralytic ileus.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C: Animal reproductive studies have not been conducted with oxycodone and acetaminophen tablets. It is also not known whether oxycodone and acetaminophen tablets can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone and acetaminophen tablets should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of narcotics during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all narcotics, administration of oxycodone and acetaminophen tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers:

It is not known whether oxycodone and acetaminophen is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxycodone and acetaminophen tablets are administered to a nursing woman.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash, and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

Oxycodone and acetaminophen tablets are a Schedule II controlled substance. Oxycodone can

produce drug dependence and has the potential for being abused. (See WARNIN

OVERDOSAGE

Acetaminophen

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, po... ...al hepa... necrosis is the most serious adverse effect. Renal tubular necrosis, hypog... ...yma a... thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less tha... ...ams a... fatalities with less than 15 grams. Importantly, young children seem to be more resis... ...adults ... the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outli... ...w shou... be initiated in any adult or child suspected of having ingested an acetaminophen overd...

Early symptoms following a potentially hepatotoxic overdose may include: na... ...vomitin... diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxi... ...y not apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup ipecac. Patient's estimates of the quantity of a drug ingested are notoriously unreliable. ...efore, if acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early possible, but no sooner than four hours following ingestion. Liver function studies should be obtai... initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably ...than 16 h of the overdose ingestion for optimal results, but in any case, within 24 hours. Followin... ...covery, I are no residual, structural, or functional hepatic abnormalities.

Oxycodone

Signs and Symptoms: Serious overdosage with oxycodone is characterized by respiratory depre... (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cy...osis), ex... somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and c...my slow sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, c... arrest and death may occur.

Treatment: Primary attention should be given to the re-establishment of adequate re... ...atory ex... through provision of a patent airway and the institution of assisted or controlled ventila...on. The r... antagonist naloxone hydrochloride is a specific antidote against respiratory depressio... which ma... from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an app... dose of naloxone hydrochloride (usual initial adult dose 0.4 mg to 2 mg) shou... be admi... preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitati... package insert). Since the duration of action of oxycodone may exceed that of the antagonist th... should be kept under continued surveillance and repeated doses of the antagonist st... administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant resp... cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive ... should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response ...pati... occasionally be necessary to exceed the usual dosage recommended below in c... ...of m... pain or in those patients who have become tolerant to the analgesic effect of narcot... ...ly acetaminophen tablets are given orally. The usual adult dosage is one tablet ever... ...n for pain.

HOW SUPPLIED

Oxycodone hydrochloride 5 mg and Acetaminophen 325 mg Tablets are supplied a... ...ved 4/97 one face scored and inscribed "A75" and are available in:

Bottles of 100	NDC 52152-075-02
Bottles of 1000	NDC 52152-075-05

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

CAUTION: Federal law prohibits dispensing without a prescription. DEA Orde... ...orm

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

MAR 15 1999

Amide
PHARMACEUTICAL, INC.

NDC 52152-075-05

OXYCODONE & ACETAMINOPHEN TABLETS, USP
5 mg/325 mg

CII

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Each Tablet Contains:
Oxycodone hydrochloride ..... 5 mg*
Warning: May be habit forming.
Acetaminophen ..... 325 mg
* 5 mg Oxycodone hydrochloride is equivalent to 4.4815 mg oxycodone.

USUAL DOSAGE: For dosage and full prescribing information, read accompanying product information.

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

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

DEA ORDER FORM REQUIRED.

N 3 52152-075-05 5

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

Control No.:
Exp. Date:
7829-00

Amide
PHARMACEUTICAL, INC.

NDC 52152-075-02

OXYCODONE & ACETAMINOPHEN TABLETS, USP
5 mg/325 mg

C II

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Oxycodone hydrochloride ..... 5 mg*
Warning: May be habit forming.
Acetaminophen ..... 325 mg
* 5 mg Oxycodone hydrochloride is equivalent to 4.4815 mg oxycodone.

USUAL DOSAGE: For dosage and full prescribing information, read accompanying product information.

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

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

DEA ORDER FORM REQUIRED.

MAR 15 1999

N 3 52152-075-02 4

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

Control No.:

Exp. Date:

7828-00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40203

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 40-203

DRUG PRODUCT:Oxycodone and Acetaminophen Tablets USP, 3 mg/325 mg

FIRM: Amide Pharmaceutical, Inc. DOSAGE FORM: Tablet

STRENGTH: 5 mg/325 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP statement for Amide Pharmaceuticals are in conformity with the current GMP regulations. Section X on page 241. Satisfactory/ ~~BER pending~~ Acceptable 3/12/99 JWS

BIO STUDY:
Bioequivalence Waiver has been granted by the Division of Bioequivalence (See bio.rev. on 2-19-1997)

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required, USP product.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

24 month expiration dating period requested. Containers used are same as described. (100's and 1000's of plastic with metal screw cap).

LABELING:
Satisfactory per A. Vezza (5-15-1998).
Dispense in tight and light resistant containers.

STERILIZATION VALIDATION (IF APPLICABLE):
Solid oral dosage form.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
Bio. Batch lot#6079 A, lot size tablets.

Source of NDS DMF found satisfactory by N. Gregory on 1-22-98. Source of NDS for Oxycodone HCL DMF found satisfactory by G. Smith on 8-27-97.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?).
Lot# 6079A, Batch size tablets kg).

Same production process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Intended production batch size: kg) tablets.
kg) tablets
kg)

CHEMIST: S. Basaran Date: 1-19-99
TEAM LEADER: U. Venkataram Date: 1-19-99

X:\NEW\FIRMSAM\AMIDE\LTRS&REV\40203SUM.fin

/S/ 2/3/99
/S/ 2/4/99

1. CHEMISTRY REVIEW NO. 4

2. ANDA 40-203

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

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies, that to the best of its knowledge the patent on this product has expired and there is no exclusivity for this product and the applicant is not requesting exclusivity for this product.

Innovator: Dupont Pharma - Percocet®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Oxycodone and Acetaminophen

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

9. AMENDMENTS AND OTHER DATES:

Firm:
- 7/22/96 - Original
- 8/22/96 - Response to refuse to file.
- 2/5/97 - Response to phone memo (not in jacket), Bio. information.
- 11/26/97 - Response to 1st def. letter (Chem. & labeling). Subject of this review.
- June/3/98- Response to facsimile letter
- January 11, 1999: Minor Amendment

FDA:
- 8/19/96 - Refuse to file.
- 1/17/97 - Acknowledgment.
- 1/17/97 - Phone memo, explaining time delay.
- 2/24/97 - 1st Bio. review, acceptable.
- 2/26/97 - Bio. letter, no further questions at this time.
- 2/28/97 - 1st def. letter (Chem.& labeling).
- 6/3/98- Facsimile deficiency letter
- 9/10/98- Minor deficiency letter

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesics

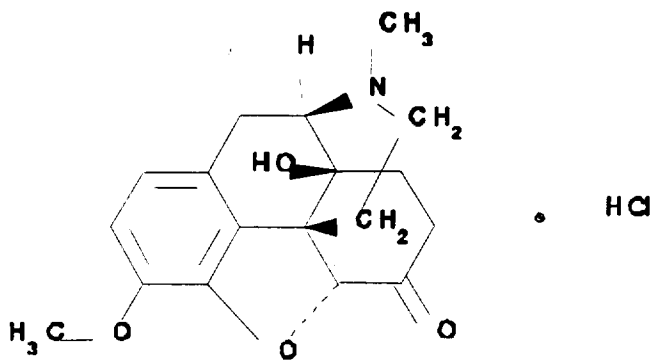
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF (Facility, Amide, LoA not needed); **DMF** (Facility, LoA); **DMF** (Active <Oxycodone Hydrochloride>, LoA); **DMF** (Active <Acetaminophen %>, LoA); **DMF** (Container, LoA); **DMF** (LoA); **DMF** (Inner Seal, LoA).

13. DOSAGE FORM
Tablet

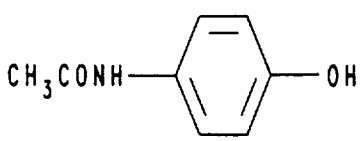
14. POTENCY
5 mg/325 mg

15. CHEMICAL NAME AND STRUCTURE
Oxycodone Hydrochloride USP
$C_{18}H_{21}NO_4.HCl$; M.W. = 351.83



4,5 -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. CAS [124-90-3]

Acetaminophen USP
$C_8H_9NO_2$; M.W. = 151.17



4'-Hydroxyacetanilide. CAS [103-90-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application can be approved. The approval letter is pending acceptable EER. EER acceptable 3/12/99

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable (see item 17)

19. REVIEWER: Sema Basaran

DATE COMPLETED: 1-19-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40203

BIOEQUIVALENCY REVIEW(S)

Office of Generic Drugs

DIVISION OF BIOEQUIVALENCE

ANDA 40-203 Sponsor: Amide Pharmaceuticals
Drug and Dosage form: Oxycodone Hydrochloride/Acetaminophen Tablets USP
Strengths: 5 mg/325 mg
Type of Study: SD: SDF: MULT: OTHER: X

Study Summary Drug is classified AA
Dissolution Data Acceptable
Waiver is granted as per 21 CFR 320.22 (c)

Primary Reviewer: Man M. Kochar Branch: III

Initial: /S/ Date: 2/9/99

Team Leader: Barbara M. Davit Branch: III

for Initial: /S/ Date: 2/9/1999

Director, Division of Bioequivalence

Initial: /S/ Date: 2/9/99

Director, Office of Generic Drugs

Initial: Date:

FEB 2 4 1997

Oxycodone Hydrochloride:
Acetaminophen, USP
5 mg: 325 mg Tablet
ANDA # 40-203
Reviewer: Man M. Kochhar
40203DW.796

Amide Pharmaceuticals, Inc.
Little Falls, NJ
Submission Date:
July 23, 1996

Review of Dissolution Data and a Waiver Request

Oxycodone is a semisynthetic narcotic analgesic and acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic agent.

The firm has submitted comparative dissolution data in support of a request for a bioequivalence study waiver on its test product as provided for under 21 CFR 320.22. The listed drug product is Percocet (acetaminophen:oxycodone, 325 mg:5 mg) manufactured by DuPont Pharmaceuticals, Inc.

Comments:

1. The test drug product contains active ingredients in the same strength and dosage form as the currently approved reference product, Percocet Tablets, manufactured by DuPont Pharmaceuticals.

2. Dosage, strength, labeling and the indications for use for the test product are identical to those of the reference product Percocet.

3. The USP dissolution method was used. The dissolution testing data demonstrate that the test and reference products meet the dissolution specifications (Table 1).

4. The reference product, Percocet (acetaminophen:Oxycodone, 325 mg:5 mg) is classified AA in "Approved Drug Products with Therapeutic Equivalence Evaluations". The dissolution testing is acceptable and the waiver of in vivo bioequivalence study should be granted based upon 21 CFR 320.22.

5.The batch size is tablets.

6. The formulation of the test product is given in Table 2.

Recommendations:

1. The Division of Bioequivalence agrees that the information submitted by Amide Pharmaceuticals, Inc. On its drug product, Oxycodone Hydrochloride:Acetaminophen, 5 mg:325 mg tablet falls under 21 CFR 320.22(c) of the Bioavailability/Bioequivalence

Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Oxycodone Hydrochloride:Acetaminophen tablets, USP, 5 mg:325 mg to be bioequivalent to the reference product, Percocet tablets 5 mg:325 mg manufactured by DuPont Pharmaceuticals.

2. The dissolution testing conducted by Amide Pharmaceuticals on its drug product, Oxycodones Hydrochloride:Acetaminophen, 5 mg:325 mg (lot # 6079A) has been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCL at 37° C using USP XXIII apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % (Q) of the labeled amount of acetaminophen and oxycodone hydrochloride in the dosage form is dissolved in 45 minutes.

The firm should be informed of the recommendations.

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

RD RMHATRE
FT RMHATRE /S/ Date: 2/19/97
Ramakant M. Mhatre, Ph.D.
Chief, Review Branch III

Concur: /S/ Date: 2/19/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMK/mmk/2-12-97; 2-18-97; 40-203

cc: ANDA # 40-203 original, HFD-650, HFD-600 (Hare), HFD-658 (Mhatre, Kochhar), Drug File, Division File

TABLE 1

IN VITRO DISSOLUTION TESTING

Drug: Oxycodone Hydrochloride:Acetaminophen
Dose Strength: 5 mg:325 mg
ANDA # 40-203
Firm: Amide Pharmaceuticals, Inc.
Submission Date: July 23, 1996

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 0.1N HCL
Specifications: %(Q)in 45 minutes
Assay Methodology:

Results:

Sampling Time	Test Product Lot # 6079A			Reference Product Lot # EJK266A		
Minutes	**Oxycodone HCL**			**Oxycodone HCL**		
	Mean	Range	St Dev	Mean	Range	St Dev
20	96.0		1.5	95.6		5.5
30	94.5		1.4	99.3		1.3
45	94.4		1.7	97.8		2.1
	Acetaminophen			**Acetaminophen**		
20	97.4		0.9	76.7		0.9
30	99.2		1.3	89.5		1.2
45	101.1		1.4	99.9		0.3

POTENCY:
Oxycodone HCL 96.6%
Acetaminophen 98.9%

CONTENT UNIFORMITY:
Oxycodone HCL 95.4%
Acetaminophen 99.8%

TABLE 2

FORMULATION

Ingredients	Mg/Tablet
Oxycodone Hydrochloride, USP*	
Acetaminophen 90%	
Microcrystalline Cellulose 101, NF	
Starch Pregelatinized, NF	
Sodium Starch Glycolate, NF	
Colloidal Silicon Dioxide, NF	
Stearic Acid, NF	
Magnesium Stearate, NF	
TOTAL WEIGHT	

* % added to compensate for moisture

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40203

CORRESPONDENCE

ANDA 40-203

Amide Pharmaceuticals, Inc.
Attention: Jasmine Shah, M.S., R.Ph.
101 E. Main St.
Little Falls, NJ 07424

JAN 17 1997

Dear Sir:

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

Reference is also made to our "Refuse to File" letter dated August 19, 1996, and your amendment dated August 22, 1996.

NAME OF DRUG: Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg

DATE OF APPLICATION: July 22, 1996

DATE OF RECEIPT: July 23, 1996

DATE ACCEPTABLE FOR FILING: August 23, 1996

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

/S/

for 1/17/97

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

ANDA 40-203

FEB 26 1997

Amide Pharmaceuticals, Inc.
Attention: Jasmine Shah, M.S., R.Ph.
101 E. Main Street
Little Falls NJ 07424

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg.

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

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-203

Amide Pharmaceuticals, Inc.
Attention: Jasmine Shah, M.S., R.Ph.
101 E. Main St.
Little Falls, NJ 07424

AUG 19 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated July 22, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg.

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

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

> You have failed to request a waiver of evidence of *in vivo* bioavailability or bioequivalence [21 CFR 320.22(c)].
>
> You have failed to submit comparative *in vitro* dissolution profiles comparing dissolution data between your proposed drug product and the reference listed drug. Comparative dissolution data profiles should include individual tablet data as well as the mean, range, and standard deviation at each point for twelve tablets. Please provide this comparative profile.

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

In addition, your cover letter cites Section 505(b) of the Federal Food, Drug, and Cosmetic (Act). Whereas, abbreviated new drug applications must be filed under Section 505(j)of the Act. Please revise your cover letter accordingly.

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

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

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

Sincerely yours,

/S/ 8/19/96

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

ANDA 40-203
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief /S/ 8/19/96 date
HFD-615/AMWeikel,CSO /S/ 8/19/96 date
HFD-647/JSimmons/Chem Branch_____date
X:\new\firmsam\Amide\ltrs&rev\40203rtf.f
F/T File hrw 8-16-96
ANDA Refuse to File!

Amide Pharmaceutical, Inc.

101 E. Main Street, Little Falls, NJ 07424 • Ph:(201) 890-1440 • Fax:(201) 890-7980

February 5, 1997

Sandra Lizziesanchez
Division of Bioequivalence
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place
Rockville, MD 20855

NC BE
NAC 4/24/98
B.V. ltr

RE: ANDA - 40-203 AMENDMENT
OXYCODONE & ACETAMINOPHEN TABLETS, USP

Dear Ms. Lizziesanchez:

In response to our telephone conversation, enclosed please find the following:

1. comparative *in vitro* dissolution profile

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

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

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

Enc.

Amide Pharmaceutical, Inc.

101 E. Main Street, Little Falls, NJ 07424 • Ph:(201) 890-1440 • Fax:(201) 890-7980

Release to File
5/9/96
Anne H. Weikel

July 22, 1996

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

RE: ANDA - ORIGINAL APPLICATION
OXYCODONE & ACETAMINOPHEN TABLETS, USP

Dear Mr. Sporn:

Pursuant to section 505 (b) of the Food, Drug and Cosmetic Act and amendments thereto, we are submitting herewith, in duplicate, and Original Abbreviated New Drug Application for the drug, Oxycodone and Acetaminophen Tablets USP.

Included in the file are:

1. All information required by Form 356-H including:

   a) Form 356-H
   b) Archival Copy (blue folder) - 2 Volumes
   c) Review Copy - CMC (red folder) - 2 Volume
   e) Three copies of Analytical Method and Validation Report

2. A copy of CMC Section of the ANDA; the third copy is being to the FDA's Newark District Office, Attn: Regina Brown as required under FDA guidelines.

If you or your staff have any question, please feel free to contact us. Your review of this Abbreviated New Drug Application would be greatly appreciated.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

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

cc: Regina Brown
FDA, Newark District Office (w/CMC section of ANDA only)

Amide Pharmaceutical, Inc.

101 E. Main Street, Little Falls, NJ 07424 • Ph:(201) 890-1440 • Fax:(201) 890-7980

505(j)(2)(A)(vi)
1/16/97
Carie Marie H. Weidel

RECEIVED

AUG 23 1996

GENERIC DRUGS

BIOAVAILABILITY

August 22, 1996

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
CDER, FDA
Metropark North II
Document Room, HFD 630, Room 150
7500 Standish Place
Rockville, MD 20855

RE: ANDA - 40-203
OXYCODONE & ACETAMINOPHEN TABLETS, USP

MINOR AMENDMENT

ORIG AMENDMENT
N/AC

Dear Mr. Phillips:

In response to your letter dated Aug 19, 1996, enclosed please find the following:

1. request for *in vivo* bioavailability or bioequivalence waiver
2. comparative *in vitro* dissolution profile
3. revised cover letter citing section 505(j) of the FD&C Act.

If you or your staff have any question, please feel free to contact us. Your review of this Abbreviated New Drug Application would be greatly appreciated.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

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

Āmide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

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

November 26, 1997

ORIG AMENDMENT

N/AC

MAJOR AMENDMENT

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD 630
Metropark North II
7500 Standish Place,
Rockville, MD 20855

RE: Oxycodone & Acetaminophen Tablets 5 mg/325 mg
ANDA 40-203

Dear Dr. Holcombe:

In reference to the facsimile deficiency letter dated February 28, 1997, regarding our ANDA 40-203, Oxycodone & Acetaminophen Tablets 5 mg/325 mg, please find our response to each observation as follows:

A. Chemistry Deficiencies:

1. Regarding Composition:

a. Please revise and resubmit your composition statement so you are formulating to % of Oxycodone Hydrochloride (5 mg), not %. You may add a footnote to indicate you are adjusting the active ingredient, due to moisture content, and the inactive ingredients, keeping the tablet weight the same.

RESPONSE: The Component and Composition statement has been revised to include the recommended change. Enclosed find revised copy of the Component and Composition Statement. (Attachment I)

b. Please revise and resubmit your composition statement and indicate that the Acetaminophen % is

RESPONSE: The Component and Composition statement has been revised to include the recommended change. Enclosed find revised copy of the Component ad Composition Statement. (Attachment I)

RECEIVED
NOV 28 1997
GENERIC DRUGS

2. **Regarding Active ingredient;**

a. **DMF has been found to be deficient. A letter has been sent to the holder identifying these issues. It is necessary that all deficiencies be corrected before this application can be approved.**

RESPONSE: The supplier has been contacted regarding the deficiency letter. According to the supplier the deficiency has been addressed and responded to FDA.

b. **Please revise and resubmit your Analytical Methods, Raw Material Specification Sheet and Certificate of Analysis (COA) (pages 121 to 126) for Acetaminophen % and include specifications for Microbial Limits**

(Manufacturer's specification) and Residue on ignition (Manufacturer's specification).

RESPONSE: Enclosed find a copy of the revised copies of the Analytical Method, Raw Material Specification sheet and Certificate of Analysis for Acetaminophen %. The next incoming lot of Acetaminophen % will be tested as per the new specifications (Attachment II).

3. **Regarding Inactive Ingredients:**

Please revise and resubmit your COA for Magnesium Stearate and include numerical results for specifications with numerical values.

RESPONSE: Enclosed find a copy of revise COA for Magnesium Stearate with recommended changes. (Attachment III).

4. **Regarding Manufacturing and Processing:**

a. **Please revise and resubmit your batch record and include the manufacturer of the active ingredient and the manufacturing site of the finished product.**

RESPONSE: The batch record has been revised and the formulation page now includes the manufacturer of the active ingredient. Enclosed find a copy of the formulation page of the batch record with name of manufacturer for the active manufacturer. (Attachment IV).

Currently Amide has only one location at this time. Therefore, the address for the manufacturing site does not change and we feel that this information is not needed at this time. When in the future Amide has a second manufacturing location we will include the address for the manufacturing site in the batch record.

b. Your packaging and labeling records should be part of your batch record. In the future please include this information with the batch record. Please comment.

RESPONSE: The packaging and labeling batch record are separate part of the batch record. Amide's products are currently sold in the market under private label and there may be numerous sub-lots from the batch. Controlling these sub-lots under one batch record would be confusing. Therefore, the packaging and labeling batch records are issued and maintained separately from the production batch record.

C. Please revise your practice of assuming that the moisture content of Oxycodone Hydrochloride is always % and formulating to %. You should determine the moisture content of the Oxycodone Hydrochloride for each batch and adjust the Oxycodone Hydrochloride and one of the inactive ingredients (i.e., microcrystalline cellulose), keeping the tablet weight the same.

Please revise and resubmit your blank batch records (units of tablets) incorporating this change. Because the assay value of the finished product is within the specifications, we are not requiring you to manufacture pre-approval batches incorporating this change, but production batches should be manufactured incorporating this change.

RESPONSE: The master batch record for Oxycodone and Acetaminophen Tablets have been revised as follows: The formulation has been designed with Oxycodone HCl of 5 mg. The quantity of Oxycodone Hydrochloride to be added will be based on the amount of moisture content in the raw material and the increase in amount of Oxycodone HCl will be adjusted with Microcrystalline Cellulose 101, NF keeping the tablet weight constant. Copies of revised batch record are attached. (Attachment IV).

5. **Regarding Container/Closure:**

Please submit data for USP <671> testing for your container/Closure systems.

RESPONSE: Enclosed find USP test data for the container closure system attached in (Attachment V).

6. **Regarding Laboratory Controls (Finished Dosage Form).**

Please revise and resubmit your finished product specifications and finished product COA to include the specifications and results for Related Substances and Impurities.

RESPONSE: Enclosed find revise copy of the finished product specifications and finished product COA as recommended to include Related Substances and Impurities in (Attachment VI).

7. **Regarding Stability:**

a. **Your stability reports lack some required information (e.g., the manufacturer of the active ingredient, the manufacturing site of the finished product, the manufacture date, container/closure information...). Please refer to The Office Of Generic Drugs Policy and Procedure Guide #33-92 and the Guidance to Industry: Format and Content For The CMC Section of an Annual Report. Your stability reports should also include the formulation, this may be an attachment. Please revise and resubmit your stability reports and include -this information.**

RESPONSE: Enclosed find revised copies of the Stability Protocol as recommended. (Attachment VII).

b. **Please revise and resubmit your stability reports and include the specifications and results for Related Substances and Impurities and Description.**

RESPONSE: Enclosed find revised copies of the Stability Repots with changes as recommended in (Attachment VII).

LABELING DEFICIENCIES:

1. CONTAINER

RESPONSE: Container labels have been revised as recommended. Enclosed find twelve (12) copies of final printed labels.

2. INSERTS

RESPONSE: Insert labeling has been revised as recommended. Enclosed find twelve (12) copies of final printed inserts.

Also, enclosed is a side by side comparison of our proposed labeling with the last submission with all differences annotated and explained. (Attachment VIII).

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

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

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

Enc.

Amide PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

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

June 3, 1998

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD 630
Metropark North II
7500 Standish Place,
Rockville, MD 20855

FACSIMILE AMENDMENT

RE: Oxycodone & Acetaminophen Tablets 5 mg/325 mg
ANDA 40-203

Dear Dr. Holcombe:

In reference to the facsimile deficiency letter dated June 3, 1998, regarding our ANDA 40-203, Oxycodone & Acetaminophen Tablets 5 mg/325 mg, please find our response to each observation as follows:

Chemistry Deficiencies:

1. Regarding Laboratory Controls (Finished Dosage Form):

   Your data does not support your specifications for related substances and impurities. Please revise and resubmit your finished product specifications and finished product COA and change your specification for *p*-Aminophenol to NMT % and for 7,8, Dihydro-14-hydroxy-codeine to NMT %.

Response: **Enclosed in Attachment I, find revised copy for finished product specification (for *p*-Aminophenol to NMT % and for 7,8, Dihydro-14-hydroxy-codeine to NMT %) and Certificate of Analysis for the submission batch (Control #6079A)**

2. Regarding Stability:

a. Please revise and resubmit your stability reports and include the manufacturers of the active ingredients and the formulation, the formulation may be an attachment.

Response: Attached in Attachment II are the stability report which includes as an attachment the manufacturers of the active ingredients and the formulation of the finished product.

b. Your data does not support your specifications for related substances and impurities. Please revise and resubmit your stability reports specification and change your specification for *p*-Aminophenol to NMT % and for 7,8, Dihydro-14-hydroxy-codeine to NMT %.

Response: Attached in Attachment II are the updated revised stability reports (changed specification for *p*-Aminophenol to NMT % and for 7,8, Dihydro-14-hydroxy-codeine to NMT %).

c. Please revise and resubmit your stability reports and include the specifications and results for the Description.

Response: Attached in Attachment II are the updated revised stability reports which includes description.

If you or your staff have any question, please feel free to contact us at the above address or call me at (973)890-1440.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

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

Enc.

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

1/20/99 All related - Reviewer Requested. To Chemistry Reviewer for review. New EER

ORIG AMENDMENT
N/A

January 11, 1999

Timothy Ames
Project Manager
Division of Chemistry II
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD 630
Metropark North II
7500 Standish Place,
Rockville, MD 20855

MINOR AMENDMENT

RE: Oxycodone & Acetaminophen Tablets 5 mg/325 mg
ANDA 40-203

Dear Mr. Ames:

In reference to our telephone conversation on January 8, 1999 and the Minor Deficiency letter dated September 10, 1999, please note our response as follows:

Regarding the CGMP issues during the November 4, 1997 inspection, Amide has resolved all issues with the district FDA Office regarding the inspectional observation on the FDA Form 483 issued during that inspection. Also during the pre-approval inspections for this product FDA District Office has recommended approval for our products.

Amide has had three FDA inspections since the inspection of November 1997 and no major deficiencies were observed. Two inspections were Pre-Approval inspections for pending ANDA and both these products were recommended for approval. During December 1998 to January 1999, Amide had a comprehensive CGMP inspection and no major issues were cited on the FDA Form 483.

As per our meetings with the district office there are no outstanding issues at this time.

1-19-99

In response to changes in other Applications, we are withdrawing for the testing of Raw materials form our ANDA application.

All tests performed by
tests will be performed by
as follows:

- Microbial testing on inactive raw materials.

- Organic Volatile Impurity, Lead, Arsenic and Conductivity on inactive raw materials.

Also, enclosed is a CGMP Certification and DMF referral letter from

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

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

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

Enc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40203

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 40-203 Dates of Submission: July 22, 1996
August 22, 1996

Applicant's Name: Amide Pharmaceutical, Inc.

Established Name: Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg.

Labeling Deficiencies:

1. CONTAINER (100's and 1000's)

   a. Please note that the controlled substance symbol must be at least twice as large as the largest type otherwise printed on the label. Alternatively, the symbol may be overprinted on the label, in which case the symbol must be printed at least one-half the height of the label and in a contrasting color providing clear visibility against the background color of the label. Please revise to be in accord with 21 CFR 1302.04.

   b. Associate the strengths corresponding to the active ingredients of your drug product with the established name on the main display panel.

   c. Revise to read, **USUAL DOSAGE:** For dosage...

2. INSERT

   a. GENERAL COMMENT

      You may revise, "oxycodone and acetaminophen tablets" to appear in lower case letters throughout the package insert labeling.

   b. DESCRIPTION

      i. Each tablet for oral administration contains:

      ii. In the listing of inactive ingredients, revise "silicon dioxide" to read "colloidal silicon dioxide" as specified in your statement of components and composition.

iii. Revise the chemical name of acetaminophen to be in accord with the second name appearing in the monograph for acetaminophen in USP 23, 4'-hydroxyacetanilide.

iv. Revise the chemical name of oxycodone to correspond with the second name appearing in the monograph for oxycodone hydrochloride in USP 23.

c. PRECAUTIONS

i. Drug Interactions

Delete the second paragraph in this subsection. This paragraph is no longer considered a supportable statement.

ii. **Pregnancy:**

Teratogenic Effects: Pregnancy Category C:

Revise this subsection heading as above.

iii. Pediatric Use

...in pediatric patients have...

d. OVERDOSAGE (Oxycodone, Treatment)

Let the penultimate sentence, "An antagonist...", begin a new paragraph.

e. DOSAGE AND ADMINISTRATION

Make the following revision in the penultimate sentence, "...tablets are given...", (plural).

f. HOW SUPPLIED

i. Include the strength of your product in this section.

ii. You reference a product, bottles of 500, for which you have not submitted container labels. Also, you have submitted container labels (1000's) which are not referenced in this section. Please revise and/or comment.

iii. We encourage the inclusion of the, "Caution: Federal law..." statement in this section.

iv. Include the revision date for the package insert in this section.

Please prepare and submit final printed container labels and package insert labeling.

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.

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

/S/

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

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: January 17, 1997

FROM: Anna Marie H. Weikel
Consumer Safety Officer, HFD-615

/S/ 1/17/97

SUBJECT: Delayed Response to "Refuse to File" Letter

TO: The File 40-203

The filing of this application was delayed because the response to the "Refuse to File" letter was mistakenly not forwarded to the Regulatory Support Branch from the document control room. In addition, the firm, Amide Pharmaceuticals never inquired about the status of this application.

However, despite this unfortunated occurrence, the actual file date of the application is not effected by this since per Office procedure, we are using the OGD receipt date of the amendment as the filing date.