

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**75-295**

***Generic Name:*** Morphine Sulfate Extended-release  
Tablets, 15 mg, 30 mg, and 60 mg

***Sponsor:*** Endo Pharmaceuticals Inc.

***Approval Date:*** October 28, 1998

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**75-295**

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RESEARCH**

**APPLICATION NUMBER:**

**75-295**

**APPROVAL LETTER**

ANDA 75-295

OCT 28 1998

Endo Pharmaceuticals Inc.  
Attention: Andrew G. Clair, Ph.D.  
500 Endo Boulevard  
Garden City, NY 11530  
|||||

Dear Sir:

This is in reference to your abbreviated new drug application dated December 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg and 60 mg.

Reference is also made to your amendments dated June 15, June 23, July 30, August 24, September 1, September 24, and October 5, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg and 60 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (MS<sup>®</sup> Contin Tablets, 15 mg, 30 mg, and 60 mg, respectively, of Purdue Frederick Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution test and tolerances are:

The dissolution testing should be conducted in 500 mL of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:

1 hr	NLT	—	and	NMT	—
2 hr	NLT	—	and	NMT	—
4 hr	NLT	—	and	NMT	—
8 hr	NLT	—			

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70 (c)(1) when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under 21 CFR 314.70 (b)(2)(ii).

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

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

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

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

Sincerely yours,

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

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**75-295**

**Final Printed Labeling**

ENDO  
ENDO GENERIC PRODUCTS

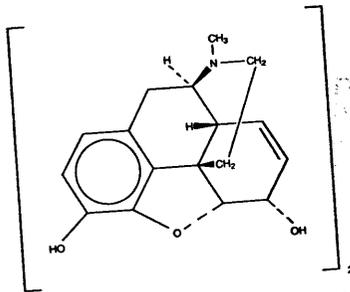
# MORPHINE SULFATE EXTENDED-RELEASE TABLETS

R<sub>X</sub> only



## DESCRIPTION

Chemically, morphine sulfate is 7,8-didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate (2:1) (salt) pentahydrate. The molecular formula is (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>·5H<sub>2</sub>O; and the molecular weight is 758.85. The structural formula is as follows:



001 28

Each morphine sulfate extended-release tablet, for oral administration, contains 15 mg, 30 mg, or 60 mg of morphine sulfate. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, and stearic acid. The 15 mg and 30 mg strengths contain FD&C Blue No. 1 Lake; and the 30 mg and 60 mg strengths contain FD&C Yellow No. 6 Lake.

## CLINICAL PHARMACOLOGY

### Metabolism and Pharmacokinetics

Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is morphine sulfate extended-release tablets or a conventional formulation. Morphine is released from this product somewhat more slowly than from conventional oral preparations. Because of pre-systemic elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment.

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Morphine also crosses the placental membranes and has been found in breast milk.

Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites; among these, morphine-3-glucuronide is present in the highest plasma concentration following oral administration.

The glucuronide system has a very high capacity and is not easily saturated even in disease. Therefore, rate of delivery of morphine to the gut and liver should not influence the total and, probably, the relative quantities of the various metabolites formed. Moreover, even if rate affected the relative amounts of each metabolite formed, it should be unimportant clinically because morphine's metabolites are ordinarily inactive.

The following pharmacokinetic parameters show considerable inter-subject variation but are representative of average values reported in the literature. The volume of distribution (V<sub>d</sub>) for morphine is 4 liters per kilogram, and its terminal elimination half-life is normally 2 to 4 hours.

Following the administration of conventional oral morphine products, approximately fifty percent of the morphine that will reach the central compartment intact reaches it within 30 minutes. Following the administration of an equal amount of morphine sulfate extended-release tablets to normal volunteers, however, this extent of absorption occurs, on average, after 1.5 hours.

The possible effect of food upon the systemic bioavailability of morphine sulfate extended-release tablets has not been systematically evaluated for all strengths. Data from at least one study suggests that concurrent administration of morphine sulfate extended-release tablets with a fatty meal may cause a slight decrease in peak plasma concentration.

Variation in the physical/mechanical properties of a formulation of an oral morphine drug product can affect both its absolute bioavailability and its absorption rate constant (k<sub>a</sub>). The formulation employed in morphine sulfate extended-release tablets has not been shown to affect morphine's oral bioavailability, but does decrease its apparent k<sub>a</sub>. Other basic pharmacokinetic parameters (e.g., volume of distribution [V<sub>d</sub>], elimination rate constant [k<sub>e</sub>], clearance [Cl]) are unchanged as they are fundamental properties of morphine in the organism. However, in chronic use, the possibility that shifts in metabolite to parent drug ratios may occur cannot be excluded.

When immediate-release oral morphine or extended-release morphine sulfate is given on a fixed dosing regimen, steady state is achieved in about a day.

For a given dose and dosing interval, the AUC and average blood concentration of morphine at steady state (C<sub>ss</sub>) will be independent of the specific type of oral formulation administered so long as the formulations have the same absolute bioavailability. The absorption rate of a formulation will, however, affect the maximum (C<sub>max</sub>) and minimum (C<sub>min</sub>) blood levels and the times of their occurrence.

### Pharmacodynamics

The effects described below are common to all morphine-containing products.

#### Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis). The precise mechanism of the analgesic action is unknown. However, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia.

#### Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of sphincter of Oddi.

#### Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

### Plasma Level- Analgesia Relationships

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose. In non-tolerant individuals, plasma morphine concentration-efficacy relationships have been demonstrated and suggest that opiate receptors occupy effector compartments, leading to a lag-time, or hysteresis, between rapid changes in plasma morphine concentrations and the effects of such changes. The most direct and predictable concentration-effect relationships can, therefore, be expected at distribution equilibrium and/or steady state conditions. In general, the minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately 5 to 20 ng/mL.

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10-50 times as great (or greater) than the appropriate dose for opioid-naïve individuals. Dosages of morphine should be chosen and must be titrated on the bases of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

For any fixed dose and dosing interval, morphine sulfate extended-release tablets will have at steady state, a lower  $C_{max}$  and a higher  $C_{min}$  than conventional morphine. This is a potential advantage; a reduced fluctuation in morphine concentration during the dosing interval should keep morphine blood levels more centered within the theoretical "therapeutic window." (Fluctuation for a dosing interval is defined as  $[C_{max}-C_{min}]/[C_{ss} \text{ average}]$ .) On the other hand, the degree of fluctuation in serum morphine concentration might conceivably affect other phenomena. For example, reduced fluctuations in blood morphine concentrations might influence the rate of tolerance induction.

The elimination of morphine occurs primarily as renal excretion of 3-morphine glucuronide. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling. Because morphine is primarily metabolized to inactive metabolites, the effects of renal disease on morphine's elimination are not likely to be pronounced. However, as with any drug, caution should be taken to guard against unanticipated accumulation if renal and/or hepatic function is seriously impaired.

### INDICATIONS AND USAGE

Morphine sulfate extended-release tablets are indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.

### CONTRAINDICATIONS

Morphine sulfate extended-release tablets are contraindicated in patients with known hypersensitivity to morphine, or any other component of this product, in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

Morphine sulfate extended-release tablets are contraindicated in any patient who has or is suspected of having a paralytic ileus.

### WARNINGS (See also: CLINICAL PHARMACOLOGY)

#### Impaired Respiration

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in the elderly and debilitated patients, as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of morphine may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

#### Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries.

#### Hypotensive Effect

Morphine sulfate extended-release tablets, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (See also: PRECAUTIONS; Drug Interactions.) Morphine sulfate extended-release tablets may produce orthostatic hypotension in ambulatory patients.

Morphine sulfate extended-release tablets, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

#### Interactions with other CNS Depressants

Morphine sulfate extended-release tablets, like all opioid analgesics, should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol because respiratory depression, hypotension and profound sedation or coma may result.

#### Interactions with Mixed Agonist/Antagonist Opioid Analgesics

From a theoretical perspective, agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

#### Drug Dependence

Morphine can produce drug dependence and has a potential for being abused. Tolerance as well as psychological and physical dependence may develop upon repeated administration. Physical dependence, however, is not of paramount importance in the management of terminally ill patients or any patients in severe pain. Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. After prolonged exposure to opioid analgesics, if withdrawal is necessary, it must be undertaken gradually. (See DRUG ABUSE AND DEPENDENCE.)

Infants born to mothers physically dependent on opioid analgesics may also be physically dependent and exhibit respiratory depression and withdrawal symptoms. (See DRUG ABUSE AND DEPENDENCE.)

### PRECAUTIONS (See also: CLINICAL PHARMACOLOGY)

#### General

Morphine sulfate extended-release tablets are intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The extended-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY: "Metabolism and Pharmacokinetics".) However, morphine sulfate extended-release tablets do not release morphine continuously over the course of a dosing interval. The administration of single doses of morphine sulfate extended-release tablets on a q12 hour dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater fluctuations in morphine plasma level has not been systematically evaluated. (See DOSAGE AND ADMINISTRATION.)

As with any potent opioid, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose and dosing interval of morphine sulfate extended-release tablets, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (e.g., whether it is pure agonist or mixed agonist/antagonist), 2) the reliability of the relative potency estimate used to calculate the dose of morphine needed [N.B. potency estimates may vary with the route of administration], 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient.

Selection of patients for treatment with morphine sulfate extended-release tablets should be governed by the same principles that apply to the use of morphine or other potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis; or inability to swallow.

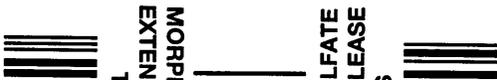
The administration of morphine, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Morphine may aggravate preexisting convulsions in patients with convulsive disorders. Morphine should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi. Similarly, morphine should be used with caution in patients with acute pancreatitis secondary to biliary tract disease.

#### Information for Patients

If clinically advisable, patients receiving morphine sulfate extended-release tablets should be given the following instructions by the physician:

1. Appropriate pain management requires changes in the dose to maintain best pain control. Patients should be advised of the need to contact their physician if pain control is inadequate, but not to change the dose of morphine sulfate extended-release tablets without consulting their physician.
2. Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on morphine sulfate extended-release tablets or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
3. Morphine should not be taken with alcohol or other CNS depressants (sleep aids, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other prescription medications are currently being used or are prescribed for future use.
4. For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted regarding analgesics and other drug use.
5. Upon completion of therapy, it may be appropriate to taper the morphine dose, rather than abruptly discontinue it.
6. While psychological dependence ("addiction") to morphine used in the treatment of pain is very rare, morphine is one of a class of drugs known to be



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  4. For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted regarding analgesics and other drug use.
  5. Upon completion of therapy, it may be appropriate to taper the morphine dose, rather than abruptly discontinue it.
  6. While psychological dependence ("addiction") to morphine used in the treatment of pain is very rare, morphine is one of a class of drugs known to be



abused and should be handled accordingly.

7. Special care must be taken to avoid accidental ingestion or the use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.

#### Drug Interactions (See WARNINGS)

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including morphine sulfate extended-release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

#### Carcinogenicity/Mutagenicity/Impairment of Fertility

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

#### Pregnancy

**Teratogenic effects - Category C:** Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus.

Morphine sulfate extended-release tablets should be used in pregnant women only when clearly needed. (See also: PRECAUTIONS: Labor and Delivery, and DRUG ABUSE AND DEPENDENCE.)

**Nonteratogenic effects:** Infants born of mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

#### Labor and Delivery

Morphine sulfate extended-release tablets are not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, naloxone, should be available for reversal of opioid-induced respiratory depression in the neonate.

#### Nursing Mothers

Low levels of morphine have been detected in the breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving morphine sulfate extended-release tablets since morphine may be excreted in the milk.

#### Pediatric Use

Use of morphine sulfate extended-release tablets has not been evaluated systematically in pediatric patients.

#### ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

#### Most Frequently Observed

Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoria.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

#### Less Frequently Observed Reactions

**Central Nervous System:** Weakness, headache, agitation, tremor, uncoordinated muscle movements, seizure, alterations of mood (nervousness, apprehension, depression, floating feelings), dreams, muscle rigidity, transient hallucinations and disorientation, visual disturbances, insomnia and increased intracranial pressure.

**Gastrointestinal:** Dry mouth, constipation, biliary tract spasm, laryngospasm, anorexia, diarrhea, cramps and taste alterations.

**Cardiovascular:** Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension.

**Genitourinary:** Urine retention or hesitance, reduced libido and/or potency.

**Dermatologic:** Pruritus, urticaria, other skin rashes, edema and diaphoresis.

**Other:** Antidiuretic effect, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis.

#### DRUG ABUSE AND DEPENDENCE

Opioid analgesics may cause psychological and physical dependence (see WARNINGS). Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, etc.; See also OVERDOSAGE). Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect and, subsequently, by decreases in the intensity of analgesia.

In chronic-pain patients, and in opioid-tolerant cancer patients, the administration of morphine sulfate extended-release tablets should be guided by the degree of tolerance manifested. Physical dependence, per se, is not ordinarily a concern when one is dealing with opioid-tolerant patients whose pain and suffering is associated with an irreversible illness.

If morphine sulfate extended-release tablets are abruptly discontinued, a moderate to severe abstinence syndrome may occur. The opioid antagonist abstinence syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep or "y'en" and mydriasis during the first 24 hours. These symptoms often increase in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, twitching and spasms of muscles; kicking movements; severe backache, abdominal and leg pains; abdominal and muscle cramps; hot and cold flashes, insomnia; nausea, anorexia, vomiting, intestinal spasm, diarrhea; coryza and repetitive sneezing; increase in body temperature, blood pressure, respiratory rate and heart rate. Because of excessive loss of fluids through sweating, vomiting and diarrhea, there is usually marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse can occur. Without treatment most observable symptoms disappear in 5-14 days; however, there appears to be a phase of secondary or chronic abstinence which may last for 2-6 months characterized by insomnia, irritability, and muscular aches.

If treatment of physical dependence of patients on morphine sulfate extended-release tablets is necessary, the patient may be detoxified by gradual reduction of the dosage. Gastrointestinal disturbances or dehydration should be treated accordingly.

#### OVERDOSAGE

Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, bradycardia and hypotension.

In the treatment of overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonist, naloxone, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2.0 mg) should be administered intravenously; however, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. If the response to naloxone is suboptimal or not sustained, additional naloxone may be re-administered, as needed, or given by continuous infusion to maintain alertness and respiratory function; however, there is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on morphine sulfate extended-release tablets. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

**Note:** In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with care and by titration with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

**DOSAGE AND ADMINISTRATION** (See also: CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections)

MORPHINE SULFATE EXTENDED-RELEASE TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED.

TAKING BROKEN, CHEWED OR CRUSHED MORPHINE SULFATE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

Morphine sulfate extended-release tablets are intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The extended-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY: "Metabolism and Pharmacokinetics.") However, morphine sulfate extended-release tablets do not release morphine continuously over the course of a dosing interval. The administration of single doses of morphine sulfate extended-release tablets on a q2h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater fluctuations in morphine plasma level has not been systematically evaluated.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of initial dose and dosing interval of morphine sulfate extended-release tablets, attention should be given to 1) the daily dose, potency and precise characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist/antagonist), 2) the reliability of the relative potency estimate used to calculate the dose of morphine needed [N.B. potency estimates may vary with the route of administration], 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient.

#### Conversion from Conventional Oral Morphine to Morphine Sulfate Extended-Release Tablets

A patient's daily morphine requirement is established using immediate-release oral morphine (dosing every 4 to 6 hours). The patient is then converted to morphine sulfate extended-release tablets in either of two ways: 1) by administering one-half of the patient's 24-hour requirement as morphine sulfate extended-release tablets on an every 12-hour schedule; or, 2) by administering one-third of the patient's daily requirement as morphine sulfate extended-release tablets on an every eight hour schedule. With either method, dose and dosing interval is then adjusted as needed (see discussion below). The 15 mg extended-release morphine sulfate tablet should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. Morphine sulfate extended-release tablets of 30 mg strength are recommended for patients with a daily morphine requirement of 60 to 120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

#### Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets

Morphine sulfate extended-release tablets can be administered as the initial oral morphine drug product; in this case, however, particular care must be exercised in the conversion process. Because of uncertainty about, and intersubject variation in, relative estimates of opioid potency and cross tolerance, initial dosing regimens should be conservative; that is, an underestimation of the 24-hour oral morphine requirement is preferred to an overestimate. To this end, initial individual doses of morphine sulfate extended-release tablets should be estimated conservatively. In patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day, morphine sulfate extended-release tablets of 30 mg strength are recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted to the 60 mg or 100 mg tablet strength, or appropriate combination of tablet strengths, if desired.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and possibly, by an individual's medical condition. Consequently, it is difficult to recommend any fixed rule for converting a patient to morphine sulfate extended-release tablets directly. The following general points should be considered, however.

**1. Parenteral to oral morphine ratio:** Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

**2. Other parenteral or oral opioids to oral morphine:** Because there is lack of systemic evidence bearing on these type of analgesic substitutions, specific recommendations are not possible.

Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safer to underestimate the daily dose of morphine sulfate extended-release tablets required and rely upon ad hoc supplementation to deal with inadequate analgesia. (See discussion which follows.)

#### Use of morphine sulfate extended-release tablets as the first opioid analgesic

There has been no systematic evaluation of morphine sulfate extended-release tablets as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using an extended-release morphine, it is ordinarily advisable to begin treatment using an immediate-release formulation.

#### Considerations in the Adjustment of Dosing Regimens

Whatever the approach, if signs of excessive opioid effects are observed early in a dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, "breakthrough" pain occurs late in the dosing interval, the dosing interval may be shortened. Alternatively, a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief, opioid side effects, and the convenience of the dosing schedule.

In adjusting dosing requirements, it is recommended that the dosing interval never be extended beyond 12 hours because the administration of very large single doses may lead to acute overdose. (N.B. This product is an extended-release formulation; it does not release morphine continuously over the dosing interval.)

For patients with low daily morphine requirements, morphine sulfate extended-release tablets of 15 mg strength should be used.

#### Conversion from morphine sulfate extended-release tablets to parenteral opioids:

When converting a patient from morphine sulfate extended-release tablets to parenteral opioids, it is best to assume that the parenteral to oral potency is high. NOTE THAT THIS IS THE CONVERSE OF THE STRATEGY USED WHEN THE DIRECTION OF CONVERSION IS FROM THE PARENTERAL TO ORAL FORMULATIONS. IN BOTH CASES, HOWEVER, THE AIM IS TO ESTIMATE THE NEW DOSE CONSERVATIVELY. For example, to estimate the required 24-hour dose of morphine for IM use, one could employ a conversion of 1 mg of morphine IM for every 6 mg of morphine as morphine sulfate extended-release tablets. Of course, the IM 24-hour dose would have to be divided by six and administered on a q4h regimen. This approach is recommended because it is least likely to cause overdose.

#### Safety and Handling

MORPHINE SULFATE EXTENDED-RELEASE TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED MORPHINE SULFATE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

#### HOW SUPPLIED

Morphine Sulfate Extended-Release Tablets are supplied as follows:

15 mg	Bottles of 100	NDC 60951-652-70
Blue, round tablets,	Bottles of 500	NDC 60951-652-85
embossed "E652" on	Unit dose package	NDC 60951-652-75
one side, and "15"	of 100	
on the other side.		
30 mg	Bottles of 100	NDC 60951-653-70
Green, round tablets,	Bottles of 500	NDC 60951-653-85
embossed "E653" on	Unit dose package	NDC 60951-653-75
one side, and "30"	of 100	
on the other side.		
60 mg	Bottles of 100	NDC 60951-655-70
Orange, capsule-	Bottles of 500	NDC 60951-655-85
shaped tablets,	Unit dose package	NDC 60951-655-75
embossed "E655" on	of 100	
one side, and "60"		
on the other side.		

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured for:  
Endo Pharmaceuticals Inc.  
Chadds Ford, Pennsylvania 19317

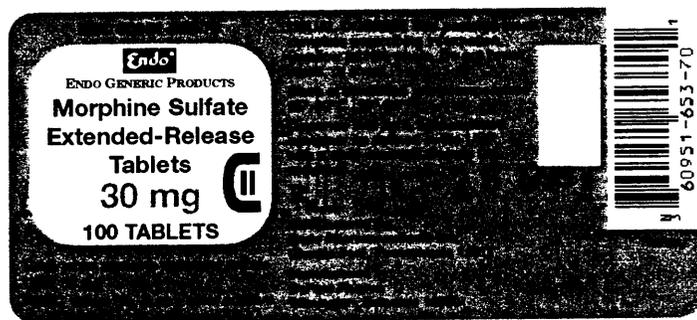


Manufactured by:  
DuPont Pharma  
Wilmington, Delaware 19880

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Printed in U.S.A.

6507-00/August, 1998



**Endo**  
ENDO GENERIC PRODUCTS  
**Morphine Sulfate  
Extended-Release  
Tablets**  
**30 mg**  
**100 TABLETS**

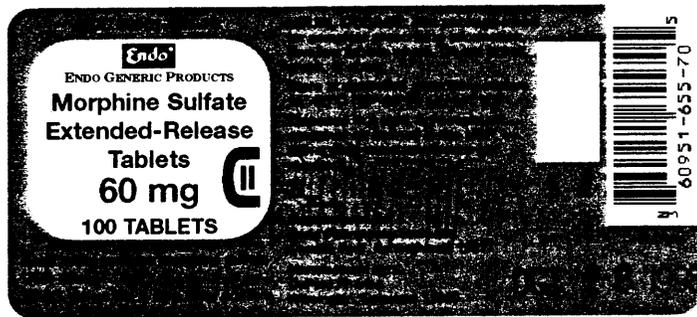
60951-653-70



**Endo**  
ENDO GENERIC PRODUCTS  
**Morphine Sulfate**  
**Extended-Release**  
**Tablets**  
**30 mg**  
**500 TABLETS**



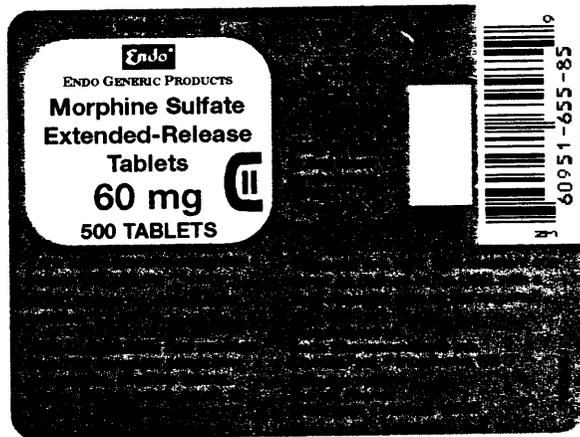
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**Endo**  
ENDO GENERIC PRODUCTS  
**Morphine Sulfate**  
**Extended-Release**  
Tablets  
**60 mg**   
**100 TABLETS**

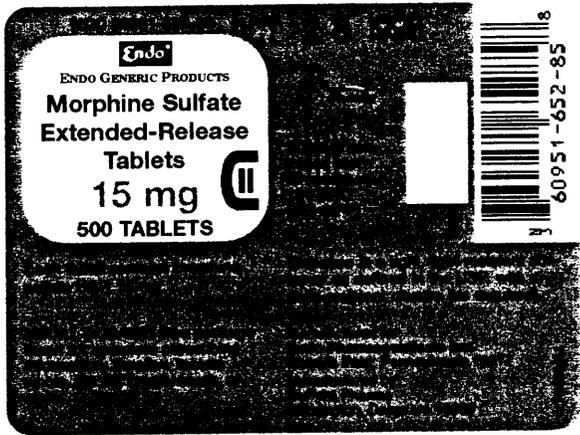


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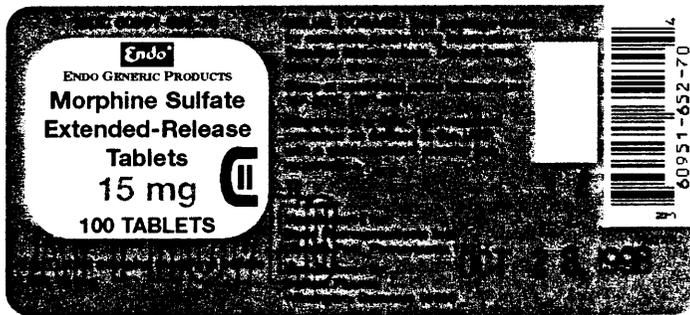
**Endo**  
ENDO GENERIC PRODUCTS  
**Morphine Sulfate**  
**Extended-Release**  
**Tablets**   
**60 mg**  
**500 TABLETS**

  
60951-655-85



**Endo**  
ENDO GENERIC PRODUCTS  
**Morphine Sulfate  
Extended-Release  
Tablets**  
**15 mg**   
**500 TABLETS**

60951-652-85



**Endo**

ENDO GENERIC PRODUCTS

**Morphine Sulfate  
Extended-Release  
Tablets  
15 mg  
100 TABLETS**



60951-652-70

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**75-295**

**CHEMISTRY REVIEW(S)**

**THERE IS NO CHEMISTRY REVIEW #1.**

✓ 1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-295

3. NAME AND ADDRESS OF APPLICANT

Endo Pharmaceuticals, Inc.  
Attention: Andrew G. Clair, Ph.D.  
500 Endo Boulevard  
Garden City, NY 11530

4. LEGAL BASIS FOR SUBMISSION

The listed drug is MS Contin® (Morphine Sulfate Controlled Release Tablets) 15 mg. 30 mg and 60 mg of The Purdue Frederick Co. The applicant certifies that to the best of their knowledge patents for MS Contin® Tablets have expired and no exclusivity exists.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Morphine Sulfate

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

9. AMENDMENTS AND OTHER DATES:

Firm:

Submitted: December 30, 1997  
Bio. Amendment: June 15, 1998  
Bio. Amendment: June 23, 1998  
Telephone amendment: July 30, 1998  
Labeling amendment: August 24, 1998

FDA:

Acknowledgement: February 6, 1998  
Bio. letter: July 1, 1998  
Telephone amendment: July 27, 1998

10. PHARMACOLOGICAL CATEGORY  
Narcotic analgesic

11. Rx or OTC  
Rx

12. RELATED IND/NDA/DMF(s)

DMF \_\_\_\_\_  
DMF \_\_\_\_\_  
DMF \_\_\_\_\_  
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13. DOSAGE FORM

Tablet (Extended-release)

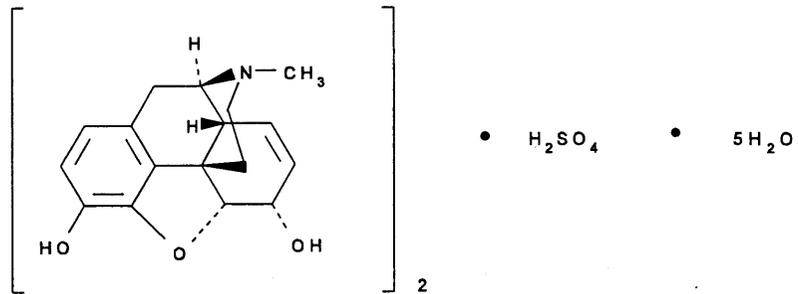
14. POTENCIES

15 mg, 30 mg, 60 mg

15. CHEMICAL NAME AND STRUCTURE

Morphine Sulfate USP

(C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>·5H<sub>2</sub>O; M.W. = 758.85



7,8-Didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate. CAS [6211-15-0]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

[ ]



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**commercial**

**information**

ANDA 75-295

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-295

3. NAME AND ADDRESS OF APPLICANT

Endo Pharmaceuticals, Inc.  
Attention: Andrew G. Clair, Ph.D.  
500 Endo Boulevard  
Garden City, NY 11530

4. LEGAL BASIS FOR SUBMISSION

The listed drug is MS Contin® (Morphine Sulfate Controlled Release Tablets) 15 mg. 30 mg and 60 mg of The Purdue Frederick Co. The applicant certifies that to the best of their knowledge patents for MS Contin® Tablets have expired and no exclusivity exists.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Morphine Sulfate

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

9. AMENDMENTS AND OTHER DATES:

Firm:

Submitted: December 30, 1997  
Bio. Amendment: June 15, 1998  
Bio. Amendment: June 23, 1998  
Telephone amendment: July 30, 1998  
Labeling amendment: August 24, 1998  
Labeling amendment: September 1, 1998  
Chemistry amendment: September 24, 1998  
Chemistry amendment: October 5, 1998

FDA:

Acknowledgement: February 6, 1998  
Bio. letter: July 1, 1998  
Telephone amendment: July 27, 1998  
Facsimile deficiency letter: September 22, 1998

10. PHARMACOLOGICAL CATEGORY

Narcotic analgesic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF \_\_\_\_\_  
DMF \_\_\_\_\_  
DMF \_\_\_\_\_

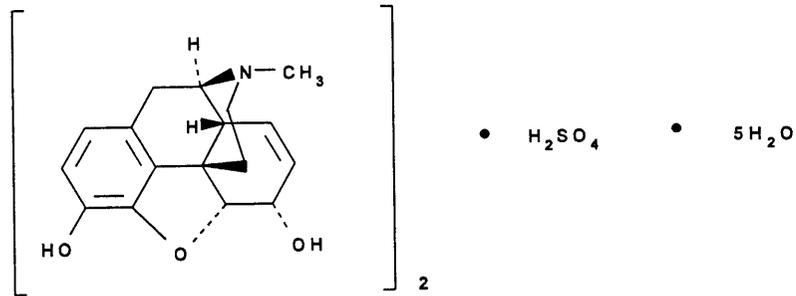
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 DMF# \_\_\_\_\_

13. DOSAGE FORM  
 Tablet (Extended-release)

14. POTENCIES  
 15 mg, 30 mg, 60 mg

15. CHEMICAL NAME AND STRUCTURE

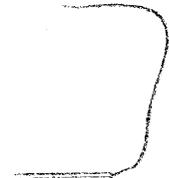
Morphine Sulfate USP  
 $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ ; M.W. = 758.85



7,8-Didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate  
 (2:1) (salt) pentahydrate. CAS [6211-15-0]

16. RECORDS AND REPORTS: N/A

17. COMMENTS



18. CONCLUSIONS AND RECOMMENDATIONS

The ANDA can be aproved ~~when~~ <sup>pending</sup> MV is found ~~satisfactory~~. 

19. REVIEWER:

Sema Basaran, Ph.D.

DATE COMPLETED:

10/9/98

**APPEARS THIS WAY  
ON ORIGINAL**

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**information**

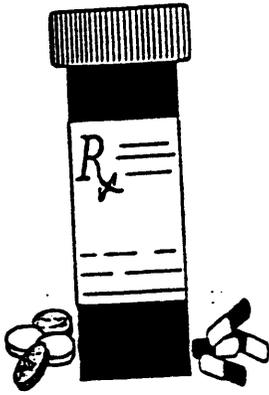
**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**75-295**

**BIOEQUIVALENCE REVIEW**

# Fax Cover Sheet



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Generic Drugs  
Rockville, Maryland

Date: July 1, 1998

To: Endo Pharmaceuticals / Carol Patterson

Phone: \_\_\_\_\_ Fax: 516-832-2291

From: Pat Bein Block, Review Support Branch Chief

Phone: (301) 827-5849

Fax: (301) 443-3839

Number of pages: 2  
(Including Cover Sheet)

Comments: Bioequivalency comments - Pls.  
note the dissolution testing  
requirements. ANDA # 75-295

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JUL 1 1998

BIOEQUIVALENCY DEFICIENCIES

AND# 75-295

APPLICANT: Endo Pharmaceuticals, Inc.

DRUG PRODUCT: Morphine Sulfate ER Tablets, 15 mg, 30 mg and 60 mg

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

You should incorporate the dissolution testing into your manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37° C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specification:

1 hr NLT  and NMT   
2 hr NLT  and NMT   
4 hr NLT  and NMT   
8 hr NLT

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,

JSF

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

BIOEQUIVALENCY DEFICIENCIES

AND: 75-295

APPLICANT: Endo Pharmaceuticals, Inc.

DRUG PRODUCT: Morphine Sulfate ER Tablets, 15 mg, 30 mg and 60 mg

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2 hr NLT — and NMT —  
4 hr NLT — and NMT —  
8 hr NLT —

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Sincerely yours,



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

CC: AND  
AND DUPLICATE  
DIVISION FILE  
FIELD COPY  
HFD-651/ Bio Secretary - Bio Drug File  
HFD-650/ Reviewer

Endorsements: (Final with Dates)

HFD-652/ S. Pradhar 1/31/98  
HFD-650/ Y. Huang 1/25/98  
HFD-617/ L. Sanchez 1/25/98  
HFD-650/ D. Conner 7/9/98

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Printed in final on 06/24/98

BIOEQUIVALENCY STUDIES

submission date: 12/31/97

- |    |  |  |
|----|--|--|
| 1. | <b>FASTING STUDY (STF)</b><br>Clinical: <u>AC</u><br>Analytical: <u>AC</u> | Strengths: <u>15 mg, 30 mg &amp; 60 mg</u><br>Outcome: <b>AC</b> |
| 2. | <b>FOOD STUDY (STP)</b><br>Clinical: <u>AC</u><br>Analytical: <u>AC</u>    | Strength: <u>60 mg</u><br>Outcome: <b>AC</b>                     |
| 3. | <b>Multiple Dose Study</b><br>Clinical: <u>AC</u><br>Analytical: <u>AC</u> | Strength: <u>60 mg</u><br>Outcome: <b>AC</b>                     |

**WinBio:** Dissolution AC - Acceptable  
OUTCOME DECISIONS: AC - Acceptable

**Morphine Sulfate ER Tablets**  
15 mg, 30 mg & 60 mg  
AND #75-295  
Reviewer: Sikta Pradhan  
XWP# 75295S5D.D97

**Endo Pharmaceuticals, Inc.**  
Garden City, N.Y.  
Submission Date:  
December 31, 1997  
June 15, 1998  
June 23, 1998

**REVIEW OF FIVE BIOEQUIVALENCE STUDIES ( THREE SINGLE DOSE  
FASTING, ONE SINGLE DOSE FED, ONE MULTIPLE DOSE FASTING)**

Morphine is a phenanthrene-derivative opiate agonist. It is a strong analgesic used to relieve severe, acute pain or moderate to severe, chronic pain (in terminally ill patients). After its oral administration, morphine is mainly converted to glucuronide metabolites, among these, morphine-3-glucuronide which is considered to be inactive, formed in the highest concentration in plasma. Morphine-6-glucuronide has been reported to be active. Morphine sulfate from oral administration is variably absorbed from the GI tract due to first-pass metabolism in the liver, with the bioavailability of about 30-40%, and peak plasma concentrations occurring between 30 minutes to 1.5 hours. The volume of distribution (Vd) for morphine is 4 liters per kilogram, and its terminal elimination half-life is normally 2 to 4 hours.

Although morphine sulfate is often administered parenterally (SC, IM or IV), oral tablets are available in either immediate or extended-release formulation. In addition, there are also oral solutions and rectal suppository formulations. Morphine sulfate controlled-release tablets are usually administered initially at an oral dosage of 15 or 30 mg every 12 hours, depending on the patient's requirement. Morphine sulfate controlled-release oral tablets, 15 mg, 30 mg, 60 mg, 100 mg and 200 mg are marketed as MS Contin<sup>R</sup> manufactured by Purdue Frederick. The 200 mg tablet is only for use in opioid tolerant patients.

The most serious adverse effect of morphine is respiratory depression, respiratory arrest, circulatory depression including orthostatic hypotension, shock and cardiac arrest.

Endo Pharmaceuticals, Inc. has submitted the results of the following (five) bioequivalence studies comparing its test product Morphine Sulfate ER Tablets, 15 mg, 30 mg and 60 mg with the

reference product MS Contin<sup>R</sup> CC, 15 mg, 30 mg and 60 mg Tablets (Purdue Frederick), respectively:

1. Single dose fasting study on 15 mg tablet,  
Protocol #EN3174-006
2. Single dose fasting study on 30 mg tablet,  
Protocol #EN3174-003
3. Single dose fasting study on 60 mg tablet,  
Protocol #EN3174-004
4. Single dose food study 60 mg tablets,  
Protocol #EN3174-005
5. Multiple dose steady-state study on 60 mg tablets,  
Protocol #EN3174-007

**I. SINGLE DOSE FASTING STUDY (15 mg tablets)**

**Objective:**

The objective of the study is to compare the relative bioavailability of Morphine Sulfate ER Tablets, 15 mg, manufactured by The Dupont Merck Pharmaceutical Company for Endo Pharmaceuticals, Inc., with that of MS Contin<sup>R</sup> 15 mg, Tablets, manufactured by Purdue Frederick, in healthy, male and female volunteers dosed under fasting condition.

**Study Sites:** \_\_\_\_\_ (both clinical & analytical); \_\_\_\_\_ Project #19862)

**Principal Investigator:** \_\_\_\_\_

**Protocol #EN3174-006**

**Study Dates (Clinical):** The study was conducted in the period of August 7, 1997 - August 16, 1997.

**Dosing Dates:**

Period I: August 8, 1997  
Period II: August 15, 1997

## Study Design

This was a randomized, single dose, two-way crossover design in comparing the test product, Morphine Sulfate ER tablets, 15 mg, with the reference product, MS Contin<sup>R</sup> 15 mg tablets, in forty (40) normal, healthy, non-smoking male and female volunteers of any race between 19 and 50 years of age under fasting conditions with a seven-day washout between treatments.

## Subject Selection

Forty (40) subjects were selected for this study after signing informed consent according to the following criteria:

### 1. Inclusion Criteria:

- Non-smoking males, 18-45 years old
- Within 15% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983)
- Good health as determined by interview, physical examination, hematology, serum chemistry, ECG, and urinalysis
- Laboratory values not to exceed 10% of normal limits (with the exception of parameters that are not clinically relevant)
- Normal findings in the physical examination, vital signs and ECG (blood pressure  $\geq$  100/60 mm/Hg, pulse rate  $\geq$  50 beats per minute)

### 2. Exclusion Criteria:

- Known history of hypersensitivity to morphine (MS Contin<sup>R</sup>), or related drugs.
- History or presence of alcohol or drug of abuse, use of psychotropic agents, cardiac arrhythmias, adverse reactions or allergy to any methylxanthine
- Presence of significant systemic or organ disease, or acute illness or surgery in the four weeks prior to study start
- Exposure to an investigational drug in the four weeks prior to study start
- Use of tobacco products
- Use of any medication within two weeks of study start
- Ingestion of alcohol or xanthine-containing beverages within 48 hours of study start
- If female, a positive serum pregnancy test at screening or throughout the study

Treatments:

- A. 15 mg x 1 Morphine Sulfate ER tablet (Endo), Lot #LF301A, Lot size         , Potency 99.3%
- B. 15 mg x 1 MS Contin<sup>R</sup> tablet (Purdue Frederick), Lot #J021, Potency 99.1%, Exp. Date: February 1, 2001.

Dose Administration:

A single dose of 15 mg Morphine Sulfate ER tablet (test or reference) was administered with 240 mL of water.

Vital signs (resting blood pressure, pulse rate, etc.) were recorded at 0.0 (pre-dose), 4.0 and 24.0 hours post-dose.

Urine samples of all subjects were analyzed to get additional information.

Drug Washout Period: 7 days

Meal and Food Restrictions:

All volunteers fasted for 10 hours prior to and 4 hours after drug administration. No fluids were allowed from 1 hour before dosing until 1 hour after each dose. Water was given ad lib after 1 hour of dosing. Standard meal was served after 4 hours of dosing. No caffeine-containing food or beverages were served during the first 24 hours. All subjects were confined from 10 hours pre-dose to 24 hours post-dose.

Blood Samples Collection

[ ]

Assay Methodology

[ ]

[Redacted]

Dates of Samples Received: August 11, 1997 - August 16, 1997.  
Dates of Sample Extraction: August 18, 1997 - August 25, 1997.  
Dates of Sample Analysis: August 19, 1997 - August 26, 1997

[Redacted]

**A. Pre-study validation:**

[Redacted]

**B. Within-study validation:**

**Redacted** 2

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**information**

**Results:**

Forty (40) subjects were selected for the study and all forty subjects completed both periods of the study. Thirty-two (32) adverse events, including mild episodes of headache, nausea, lightheadedness, vomiting, euphoria, elevated temperature, loose stool, vision blacked out, and pallor, were experienced by 16 subjects during this study. All of the events were mild or moderate in severity. No serious adverse events occurred during the study and no medication was required for any clinical complaint. There were few protocol deviations (minor) reported during the study. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

All forty (40) volunteers' plasma samples were analyzed. The mean plasma morphine and morphine-6-glucuronide levels for the test and the reference drugs are presented in Table 1 (and in Figure 1 attached) and in Table 3 (and in Figure 2 attached), respectively. Nine samples of subject #4 (period 2, from 3 hr. to 16 hr.) were subjected to repeat analysis, and the reason for repeat analysis was given as "sample out of order". Some differences between the original values and repeat values are very high as shown below:

Original morphine data and Repeat data

747.23,	210.52
23.84	201.44
19.89	155.73
27.91	100.60
52.38	69.91
73.51	49.55

111.35	25.45
158.77	<20
210.05	21.29

The firm was asked to provide further explanation for this repeat analysis, and the amendment submitted on June 15, 1998 contains acceptable justifications.

The mean pharmacokinetic parameters derived from the plasma morphine levels and morphine-6-glucuronide levels are presented in Table 2 and Table 4, respectively.

Table 1  
Mean Plasma Morphine Levels (ng/mL)

Time (hour)	TEST (A) (Endo) Lot #LF301A	Reference (B) (MS Contin) Lot #J021
Pre-dose	0	0
0.5	1.69 (41)	1.87 (53)
1.0	2.69 (47)	3.15 (42)
1.5	3.46 (44)	4.00 (41)
2.0	3.65 (45)	4.05 (38)
2.5	3.63 (40)	3.83 (40)
3.0	3.71 (42)	3.58 (37)
3.5	3.49 (39)	3.30 (35)
4.0	3.22 (36)	3.23 (33)
5.0	3.55 (37)	3.43 (35)
6.0	2.45 (38)	2.60 (33)
7.0	1.78 (42)	2.06 (40)
8.0	1.33 (46)	1.63 (39)
10.0	0.77 (70)	1.06 (43)
12.0	0.54 (93)	0.69 (74)
16.0	0.53 (84)	0.60 (76)
24.0	0.52 (82)	0.49 (83)

Number of Subjects 40  
\* Coefficient of Variation

Table 2  
Mean Pharmacokinetic Parameters for Plasma Morphine

Parameters	Test (A)	Ref. (B)	A/B	90% C.I.
AUC <sub>0-T</sub> (ng.hr/mL)	31.27 (41)*	34.05 (37)	0.93	
LnAUC <sub>0-T</sub> Geometric Mean	3.351** 28.53	3.458 31.75	0.90	84; 96
AUC <sub>0-inf</sub> (ng.hr/mL)	49.21 (73)	47.13 (45)	1.04	
LnAUC <sub>0-inf</sub> Geometric Mean	3.755** 42.73	3.774 (LSM) 43.55	0.98	84; 115
C <sub>MAX</sub> (ng/mL)	4.523 (36)	4.60 (36)	1.00	
LnC <sub>MAX</sub> Geometric Mean	1.441** 4.22	1.464 4.32	0.98	93; 103
T <sub>max</sub> (hour)	3.11 (44)	2.70 (52)	1.38	
t <sub>1/2</sub> (hour)	17.96 (113)	13.16 (76)	1.53	
KE (1/hour)	0.127 (115)	0.102 (98)	1.37	

Number of Subjects 40

\* Coefficient of Variation

\*\* Based on Least Squares Means (LSM)

Intra-subject variability(%) for: LnAUC(0-t)=16.94

LnAUC(0-inf)=27.35

LnCmax=14.02

Table 3

Mean Plasma Morphine-6-Glucuronide levels (ng/mL)

Time (hour)	TEST (A) (Endo) Lot #LF301A	Reference (B) (MS Contin) Lot #J021
Pre-dose	0	0
0.5	3.73 (58)	4.00 (58)
1.0	14.19 (28)	15.28 (35)
1.5	23.96 (28)	25.67 (25)
2.0	31.12 (25)	31.95 (21)
2.5	34.19 (24)	33.21 (21)
3.0	35.25 (23)	33.01 (18)
3.5	35.28 (25)	31.03 (17)
4.0	34.25 (27)	29.15 (19)
5.0	29.87 (23)	25.04 (22)
6.0	22.92 (26)	20.06 (26)
7.0	15.84 (26)	15.49 (14)
8.0	11.18 (28)	11.17 (30)
10.0	6.26 (37)	7.24 (29)
12.0	4.55 (39)	5.41 (36)
16.0	4.31 (32)	4.45 (34)
24.0	3.26 (37)	3.26 (37)

Number of Subjects 40

\* Coefficient of Variation

Table 4  
Mean Pharmacokinetic Parameters for Plasma Morphine-6-Glucuronide

<u>Parameters</u>	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B</u>	<u>90% C.I.</u>
AUC <sub>0-T</sub> (ng.hr/mL)	265.10 (17)*	257.50 (17)		
LnAUC <sub>0-T</sub> Geometric Mean	5.567** 261.65	5.537 253.91	1.03	99; 107
AUC <sub>0-inf</sub> (ng.hr/mL)	356.0 (32)	348.00 (26)		
LnAUC <sub>0-inf</sub> Geometric Mean	5.829** 340.02	5.816 335.63	1.01	92; 112
C <sub>MAX</sub> (ng/mL)	39.14 (20)	35.62 (18)		
LnC <sub>MAX</sub> Geometric Mean	3.649** 38.44	3.558 35.09	1.10	105; 115
T <sub>max</sub> (hour)	3.25 (26)	2.86 (26)		
t <sub>1/2</sub> (hour)	19.12 (70)	19.29 (83)		
KE (1/hour)	0.051 (51)	0.052		

Number of Subjects 40

\* Coefficient of Variation

\*\* Based on Least Squares Means (LSM)

Intra-subject variability(%) for: LnAUC(0-t)=9.87

LnAUC(0-inf)=21.20

LnCmax=11.77

This is a balanced study, and therefore, the arithmetic means and the least squares means (LSM) should be same for all parameters. However, the Kel values for morphine and morphine-6-Glucuronide could not be estimated for several subjects due to the fluctuations in terminal concentrations, and as a result, data for LnAUC(0-inf) were unbalanced.

The differences between the test and reference products in LnAUC<sub>0-T</sub>, LnAUC<sub>0-inf</sub> and LnC<sub>MAX</sub> for both morphine and morphine-6-glucuronide were not more than 10%. The 90% confidence intervals for LnAUC<sub>0-T</sub>, LnAUC<sub>0-inf</sub> and LnC<sub>MAX</sub> for morphine and morphine-6-glucuronide of the

test product remained within the 80% to 125% limit of the corresponding reference values.

## II. SINGLE DOSE FASTING STUDY (30 mg tablets)

### Objective:

The objective of the study is to compare the relative bioavailability of Morphine Sulfate ER Tablets, 30 mg, manufactured by The Dupont Merck Pharmaceutical Company for Endo Pharmaceuticals, Inc., with that of MS Contin<sup>R</sup> 30 mg, Tablets, manufactured by Purdue Frederick, in healthy, male volunteers dosed under fasting condition.

Study Sites: \_\_\_\_\_ (both clinical & analytical); \_\_\_\_\_ Project #19861)

Principal Investigator: \_\_\_\_\_

**Protocol #EN3174-003**

Study Dates (Clinical): The study was conducted in the period of June 28, 1997 - July 6, 1997.

Study Dates (analytical): July 8, 1997 - July 17, 1997

### Study Design

This was a randomized, single dose, two-way crossover design in comparing the test product, Morphine Sulfate ER tablets, 30 mg, with the reference product, MS Contin<sup>R</sup> 30 mg tablets, in normal, healthy, non-smoking male and female volunteers of any race between 20 and 46 years of age under fasting conditions with a seven-day washout between treatments.

### Subject Selection

Forty-six (46) subjects were selected for this study after signing informed consent according to the Inclusion Criteria/Exclusion Criteria mentioned in the previous study of 15 mg tablets. Thirty-six (36) subjects entered the study.

Treatments:

- A. 30 mg x 1 Morphine Sulfate ER tablet (Endo), Lot #LB085A, Lot size  Potency 97.2%
- B. 30 mg x 1 MS Contin<sup>R</sup> tablet (Purdue Frederick), Lot #F05, Potency 99.0%, Exp. Date: September, 2000.

All subjects received a single oral dose of one 50 mg ReVia<sup>R</sup> (naltrexone HCl) tablet of DuPont (Lot#LD158A) followed by 240 mL water at the minus fifteen hour and the minus three hour for a total of two doses per period.

Naltrexone HCl is a pure opiate antagonist with no opioid agonist properties. It has been suggested in the literatures that the use of ReVia<sup>R</sup> prior to administration of a morphine product in subjects may decrease incidents of serious adverse reactions.

Dose Administration:

A single dose of 30 mg Morphine Sulfate ER tablet (test or reference) was administered with 240 mL of water.

Vital signs (resting blood pressure, pulse rate, etc.) were recorded at 0.0 (pre-dose), 4.0 and 24.0 hours post-dose.

Urine samples of all subjects were collected for analysis.

Drug Washout Period: 7 days

Meal and Food Restrictions: As mentioned in the previous study of 15 mg tablets.

Blood Samples Collection



Assay Methodology

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Stability:



Results:

Thirty-six (36) subjects entered the study and 33 subjects completed both periods of the study. Twenty-six (26) adverse events, including mild episodes of headache, nausea, lightheadedness, vomiting, euphoria, elevated temperature, loose stool, vision blacked out, and pallor, were experienced by 6 subjects during this study. All of the events were mild or moderate in severity. No serious adverse events occurred during the study and no medication was required for any clinical complaint. Fifteen (15) of the adverse events were experienced by Subject #23 following the initial <sup>Raver</sup> dose in Period 2. This subject was withdrawn from the study. Subject #8 could not tolerate the adverse event. Subject #34 did not return for Period 2 study due to personal reasons.

There were few protocol deviations (minor) reported during the study. Subject #9 was 5 pounds overweight according to the protocol. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

For morphine analysis, six samples of subject #32 (period 2, from 7 hr. to 24 hr.) were subjected to repeat analysis, and the reason

for repeat analysis was given as "processing error". The differences between the original values and repeat values in most of the cases are 50% or more. For morphine-6-glucuronide analysis, seven samples of subject #16 (period 1, 8 hr. and period 2, from 3.5 hr. to 7 hr.) were subjected to repeat analysis, and the reason for repeat analysis was given as "sample out of order". The firm was asked to provide further explanation for this repeat analysis, and the amendment submitted on June 15, 1998 contains acceptable justifications.

Furthermore, the firm has reported that for morphine, 15 analytical runs were required to process the clinical samples from this study. Of these 15 analytical runs, 11 runs were acceptable. The firm has provided acceptable reasons for the selection or rejection of these analytical runs in the amendment dated June 15, 1998.

All thirty-three (33) volunteers' plasma samples were analyzed. The mean plasma morphine and morphine-6-glucuronide levels for the test and the reference drugs are presented in Table 5 (and in Figure 3 attached) and in Table 7 (and in Figure 4 attached), respectively.

The mean pharmacokinetic parameters derived from the plasma morphine levels and morphine-6-glucuronide levels are presented in Table 6 and Table 8, respectively.

Table 5

Mean Plasma Morphine Levels (ng/mL)

Time (hour)	TEST (A) 30 mg Tab. (Endo) Lot #LB085A	Reference (B) 30 mg Tab. (MS Contin) Lot #F05
Pre-dose	0	0
0.5	5.06 (61)	4.98 (57)
1.0	7.63 (54)	7.24 (49)
1.5	8.55 (51)	7.74 (46)
2.0	10.19 (44)	9.89 (40)
2.5	10.27 (44)	10.37 (38)
3.0	10.37 (48)	10.10 (40)
3.5	9.42 (46)	9.12 (39)
4.0	8.54 (49)	8.00 (34)
5.0	7.28 (36)	8.16 (42)
6.0	5.73 (38)	6.12 (33)
7.0	4.84 (34)	5.08 (39)
8.0	4.06 (30)	4.15 (37)
10.0	2.87 (33)	3.11 (34)
12.0	2.24 (41)	2.36 (42)
16.0	1.50 (38)	1.54 (46)
24.0	1.23 (68)	1.16 (45)

Number of Subjects 33

\* Coefficient of Variation

Table 6  
Mean Pharmacokinetic Parameters for Plasma Morphine

<u>Parameters</u>	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B</u>	<u>90% C.I.</u>
AUC <sub>0-T</sub> (ng.hr/mL)	86.92 (27)*	88.17 (24)		
LnAUC <sub>0-T</sub> Geometric Mean	4.4271** 83.69	4.4554 86.09	0.97	93; 102
AUC <sub>0-inf</sub> (ng.hr/mL)	99.48 (27)	111.10 (26)		
LnAUC <sub>0-inf</sub> Geometric Mean	4.5988** 99.36	4.6768 107.42	0.92	88; 97
C <sub>MAX</sub> (ng/mL)	12.14 (41)	12.06 (34)		
LnC <sub>MAX</sub> Geometric Mean	2.4228** 11.28	2.4378 11.45	0.98	93; 104
T <sub>max</sub> (hour)	2.67 (37)	2.81 (47)		
t <sub>1/2</sub> (hour)	9.84 (39)	10.98 (51)		
KE (1/hour)	0.083 (49)	0.084 (71)		

Number of Subjects 33

\* Coefficient of Variation

\*\* Based on Least Squares Means (LSM)

Intra-subject variability(%) for: LnAUC(0-t)=11.41  
LnAUC(0-inf)=9.04  
LnCmax=13.63

Table 7

Mean Plasma Morphine-6-Glucuronide levels (ng/mL)

Time (hour)	TEST (A) 30 mg Tab. (Endo) Lot #LB085A	Reference (B) 30 mg Tab. (MS Contin) Lot #F05
Pre-dose	0	0
0.5	7.28 (68)	7.22 (81)
1.0	35.38 (40)	33.16 (55)
1.5	50.01 (30)	47.72 (44)
2.0	61.23 (27)	58.34 (36)
2.5	68.26 (23)	63.87 (31)
3.0	67.76 (26)	67.11 (28)
3.5	66.30 (21)	64.72 (29)
4.0	57.94 (22)	60.52 (29)
5.0	44.28 (26)	50.39 (30)
6.0	32.81 (27)	34.81 (34)
7.0	25.06 (27)	28.02 (33)
8.0	20.98 (30)	22.19 (30)
10.0	15.54 (34)	16.27 (31)
12.0	12.71 (34)	13.13 (33)
16.0	9.26 (30)	9.40 (27)
24.0	6.20 (42)	5.84 (29)

Number of Subjects 33

\* Coefficient of Variation

Table 8

Mean Pharmacokinetic Parameters for Plasma Morphine-6-Glucuronide

<u>Parameters</u>	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B</u>	<u>90% C.I.**</u>
AUC <sub>0-T</sub> (ng.hr/mL)	504.70 (18)*	514.50 (20)		
LnAUC <sub>0-T</sub> Geometric Mean	6.2071** 496.26	6.2255 505.48	0.98	96;100
AUC <sub>0-inf</sub> (ng.hr/mL)	590.90 (20)	608.90 (20)		
LnAUC <sub>0-inf</sub> Geometric Mean	6.3731** 585.87	6.3883 594.84	0.98	96; 101
C <sub>MAX</sub> (ng/mL)	76.29 (19)	75.65 (24)		
LnC <sub>MAX</sub> Geometric Mean	4.3129** 74.66	4.3025 73.88	1.01	97; 105
T <sub>max</sub> (hour)	2.85 (24)	3.15 (29)		
t <sub>1/2</sub> (hour)	10.28 (28)	10.61 (33)		
KE (1/hour)	0.073 (28)	0.071 (26)		

Number of Subjects 33

\* Coefficient of Variation

\*\* Based on Least Squares Means (LSM)

Intra-subject variability(%) for: LnAUC(0-t)=4.8  
 LnAUC(0-inf)=6.6  
 LnCmax=10.0

The differences between the test and reference products in LnAUC<sub>0-T</sub>, LnAUC<sub>0-inf</sub> and LnC<sub>MAX</sub> for both morphine and morphine-6-glucuronide were not more than 3%. The 90% confidence intervals for LnAUC<sub>0-T</sub>, LnAUC<sub>0-inf</sub> and LnC<sub>MAX</sub> for morphine and morphine-6-glucuronide of the test product remained within the 80% to 125% limit of the corresponding reference values.

### III. SINGLE DOSE FASTING STUDY (60 mg tablets)

#### Objective:

The objective of the study is to compare the relative bioavailability of Morphine Sulfate ER Tablets, 60 mg, manufactured by The Dupont Merck Pharmaceutical Company for Endo Pharmaceuticals, Inc., with that of MS Contin<sup>R</sup> 60 mg, Tablets, manufactured by Purdue Frederick, in healthy, male and female volunteers (19 to 46 years of age) dosed under fasting condition.

Study Sites: \_\_\_\_\_ (both clinical & analytical); \_\_\_\_\_ project #19858)

Principal Investigator: \_\_\_\_\_

**Protocol #EN3174-004**

Study Dates (Clinical): Study Dates (Clinical): The study was conducted in the period of July 19, 1997 - July 27, 1997.

Study Dates (analytical): July 28, 1997 - July 30, 1997

#### Study Design

This was a randomized, single dose, two-way crossover design in comparing the test product, Morphine Sulfate ER tablets, 60 mg, with the reference product, MS Contin<sup>R</sup> 60 mg tablets, in normal, healthy, non-smoking volunteers under fasting conditions with a seven-day washout between treatments.

#### Subject Selection

Forty-five (45) subjects were selected for this study after signing informed consent according to the Inclusion Criteria/Exclusion Criteria mentioned in the previous study of 15 mg or 30 mg tablets. All forty-five (45) subjects received an initial 50 mg dose of naltrexone hydrochloride on Day 0 at 15 hours predose. ReVia<sup>R</sup> (naltrexone HCl) is a pure opiate antagonist with no opioid agonist properties. It has been suggested in the literatures that the use of ReVia<sup>R</sup> prior to administration of a morphine product in

subjects may decrease incidents of serious adverse reactions. This initial ReVia<sup>®</sup> dose was administered as part of the screening assessment to determine subjects' tolerability for ReVia<sup>®</sup>. Subjects unable to tolerate this dose were not enrolled in the study. Thirty-nine (39) subjects were enrolled in the study. All these subjects received a second 50 mg dose of ReVia<sup>®</sup> on Day 1 at three hours predose of morphine sulfate. The purpose of the second dose of ReVia<sup>®</sup> was to block the effects of the morphine dose. Thirty-five (35) subjects completed the study. At the zero hour on Day 1 of each study period, the subjects received one of two treatments.

Treatments:

- A. 60 mg x 1 Morphine Sulfate ER tablet (Endo), Lot #LE249, Lot size          Potency 98.3%
- B. 60 mg x 1 MS Contin<sup>®</sup> tablet (Purdue Frederick), Lot #J051, Potency 99.5%, Exp. Date: March, 2002.

Dose Administration:

A single dose of 60 mg Morphine Sulfate ER tablet (test or reference) was administered with 240 mL of water.

Vital signs (resting blood pressure and pulse rate) were recorded at 0.0 (pre-dose), 4.0 and 24.0 hours post-dose.

Urine samples of all subjects were collected for analysis.

Drug Washout Period: 7 days

Meal and Food Restrictions: As mentioned in the previous study of 15 mg tablets.

Blood Samples Collection

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stool, vision blacked out, and pallor, were experienced by 18 subjects during this study. All of the events were mild or moderate in severity. No serious adverse events occurred during the study and no medication was required for any clinical complaint. Subject #9 was withdrawn from the study due to positive urine drug screen. Subjects #10, #24 and #35 could not tolerate the adverse events due to the second dose of <sup>Raver</sup>.

There were few protocol deviations (minor) reported during the study. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

All thirty-five (35) volunteers' plasma samples were analyzed. The mean plasma morphine and morphine-6-glucuronide levels for the test and the reference drugs are presented in Table 9 (and in Figure 5 attached) and in Table 11 (and in Figure 6 attached), respectively.

The mean pharmacokinetic parameters derived from the plasma morphine levels and morphine-6-glucuronide levels are presented in Table 10 and Table 12, respectively.

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Table 9  
Mean Plasma Morphine Levels (ng/mL)

Time (hour)	TEST (A) 60 mg Tab. (Endo) Lot #LE249	Reference (B) 60 mg Tab. (MS Contin) Lot #J051
Pre-dose	0	0
0.5	6.47 (48)*	7.51 (50)
1.0	10.07 (34)	11.32 (50)
1.5	13.11 (36)	12.73 (51)
2.0	14.81 (40)	14.11 (38)
2.5	15.84 (37)	14.16 (38)
3.0	16.50 (35)	14.04 (37)
3.5	16.88 (39)	14.02 (38)
4.0	16.46 (35)	14.40 (42)
5.0	15.49 (38)	16.14 (53)
6.0	12.03 (38)	12.75 (44)
7.0	9.53 (35)	10.53 (47)
8.0	7.84 (32)	8.92 (38)
10.0	5.63 (37)	6.58 (38)
12.0	4.30 (35)	5.28 (37)
16.0	3.48 (41)	3.72 (34)
24.0	3.01 (59)	2.88 (33)

Number of Subjects 35

\* Coefficient of Variation

Table 10  
Mean Pharmacokinetic Parameters for Plasma Morphine

<u>Parameters</u>	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B</u>	<u>90% C.I.</u>
AUC <sub>0-T</sub> (ng.hr/mL)	165 (28)	170.40 (28)		
LnAUC <sub>0-T</sub> Geometric Mean	5.0711 (LSM) ** 159.35	5.1045 (LSM) 164.76	0.97	93; 100
AUC <sub>0-inf</sub> (ng.hr/mL)	247.80 (46)	245.10 (29)		
LnAUC <sub>0-inf</sub> Geometric Mean	5.4481 (LSM) ** 232.32	5.4671 (LSM) 236.77	0.98	89; 108
C <sub>MAX</sub> (ng/mL)	19.23 (32)	19.28 (44)		
LnC <sub>MAX</sub> Geometric Mean	2.9046 (LSM) ** 18.26	2.8872 (LSM) 17.94	1.02	95; 109
T <sub>max</sub> (hour)	3.41 (31)	3.26 (52)		
t <sub>1/2</sub> (hour)	19.41 (62)	18.43 (52)		
KE (1/hour)	0.0443 (39)	0.0486 (50)		

Number of Subjects 35

\* Coefficient of Variation

\*\* Based on Least Squares Means (LSM)

Intra-subject variability(%) for: LnAUC(0-t)=7.93  
LnAUC(0-inf)=11.71  
LnCmax=14.83

Table 11

Mean Plasma Morphine-6-Glucuronide levels (ng/mL)

Time (hour)	TEST (A) 60 mg Tab. (Endo) Lot #LE249	Reference (B) 60 mg Tab. (MS Contin) Lot #J051
Pre-dose	0.05 (592)	0
0.5	10.25 (72)	9.67 (84)
1.0	51.03 (41)	51.28 (46)
1.5	81.14 (33)	81.24 (35)
2.0	96.79 (22)	95.14 (30)
2.5	112.70 (25)	105.0 (37)
3.0	115.10 (22)	106.1 (29)
3.5	117.60 (24)	103.3 (27)
4.0	116.80 (23)	100.8 (21)
5.0	101.20 (26)	97.82 (30)
6.0	76.98 (29)	78.39 (28)
7.0	57.81 (29)	62.34 (32)
8.0	45.63 (30)	51.18 (36)
10.0	32.06 (30)	40.34 (37)
12.0	26.41 (33)	31.57 (34)
16.0	20.56 (32)	22.54 (32)
24.0	13.17 (26)	14.20 (25)

Number of Subjects 35

\* Coefficient of Variation

Table 12  
Mean Pharmacokinetic Parameters for Plasma Morphine-6-Glucuronide

<u>Parameters</u>	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B</u>	<u>90% C.I.**</u>
AUC <sub>0-T</sub> (ng.hr/mL)	1004 (19)*	1034 (18)		
LnAUC <sub>0-T</sub> Geometric Mean	6.8916** 983.97	6.9236 1015.97	0.97	94; 100
AUC <sub>0-inf</sub> (ng.hr/mL)	1263 (19)	1300 (16)		
LnAUC <sub>0-inf</sub> Geometric Mean	7.1271** 1245.26	7.1584 1284.85	0.97	92; 102
C <sub>MAX</sub> (ng/mL)	128.6 (22)	123.0 (20)		
LnC <sub>MAX</sub> Geometric Mean	4.8260** 124.71	4.7882 120.08	1.04	98; 110
T <sub>max</sub> (hour)	3.29 (21)	3.20 (36)		
t <sub>1/2</sub> (hour)	12.80 (53)	12.10 (40)		
KE (1/hour)	0.0644 (37)	0.0656 (37)		

Number of Subjects 35

\* Coefficient of Variation

\*\* Based on Least Squares Means (LSM)

Intra-subject variability(%) for: LnAUC(0-t)=7.97  
LnAUC(0-inf)=11.13  
LnCmax=13.51

The differences between the test and reference products in LnAUC<sub>0-T</sub>, LnAUC<sub>0-inf</sub> and LnC<sub>max</sub> for both morphine and morphine-6-glucuronide were not more than 4%. The 90% confidence intervals for LnAUC<sub>0-T</sub>, LnAUC<sub>0-inf</sub> and LnC<sub>max</sub> for morphine and morphine-6-glucuronide of the test product remained within the 80% to 125% limit of the corresponding reference values.

#### IV. LIMITED FOOD STUDY:

Protocol #EN3174-005' \_\_\_\_\_ Project 19859)

The firm has submitted the results of a single oral 60 mg dose three-way crossover post-prandial bioequivalence study conducted on the test product, Morphine Sulfate ER Tablets, 60 mg, manufactured by The Dupont Merck Pharmaceutical Company for Endo Pharmaceuticals, Inc., and the reference product, MS Contin<sup>R</sup> 60 mg, Tablets, manufactured by Purdue Frederick. The study was conducted in healthy, male and female volunteers (19 to 46 years of age) dosed under fed and fasting conditions in order to determine the effect of food on the bioavailability of those products.

The study was conducted at \_\_\_\_\_ beginning on August 29, 1997 and ending on October 11, 1997.

#### Dosing Schedule:

Thirty-two (32) healthy volunteers received an initial 50 mg dose of Raver on Day 0, 15 hours predose after completing a physical examination and laboratory screening tests. Subjects unable to tolerate this dose were not enrolled in the study. Thirty (30) volunteers entered into the study and received a second 50 mg dose of Raver on Day 1, 3 hours predose. At the zero hour on Day 1 of each study period, the subjects received one of three treatments:

- A. 1x60 mg Morphine Sulfate ER Tablet, manufactured by The Dupont Merck Pharmaceutical Company for Endo Pharmaceuticals, Inc. (test product); Lot #LE249, after an overnight fast for at least 10 hours.
- B. 1x60 mg Morphine Sulfate ER Tablet, manufactured by The Dupont Merck Pharmaceutical Company for Endo Pharmaceuticals, Inc. (test product); Lot #LE249, immediately after a standard breakfast.
- C. 1x60 mg MS Contin<sup>R</sup> Tablets, manufactured by Purdue Frederick. (Reference product); Lot #J051, immediately after a standard breakfast.

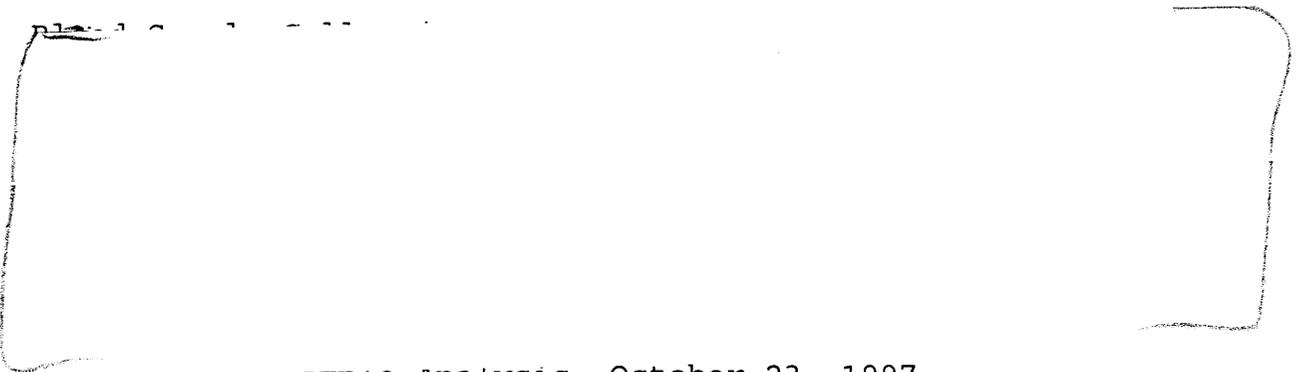
Following dosing, subjects remained ambulatory for 4 hours and were not allowed to engaged in any strenuous activity at any time during

the study. For safety, sitting blood pressure and heart rate were measured predose and at different time intervals after dosing.

Vital sign information for all subjects was collected. No clinically significant trends were observed with respect to the different treatment regimens regarding vital signs.

Drug Washout Period: One week

Meal and Food Restrictions: Water was given ad lib until one hour pre-drug and after one hour post-drug. A standard meal was served after 4.5 hours post-dose. No alcohol, caffeine and xanthine-containing beverages was served during the study. Subjects remained at the clinic through the 48 hour post-drug blood draw.



Date of Last Sample Analysis: October 23, 1997

Assay Methodology:



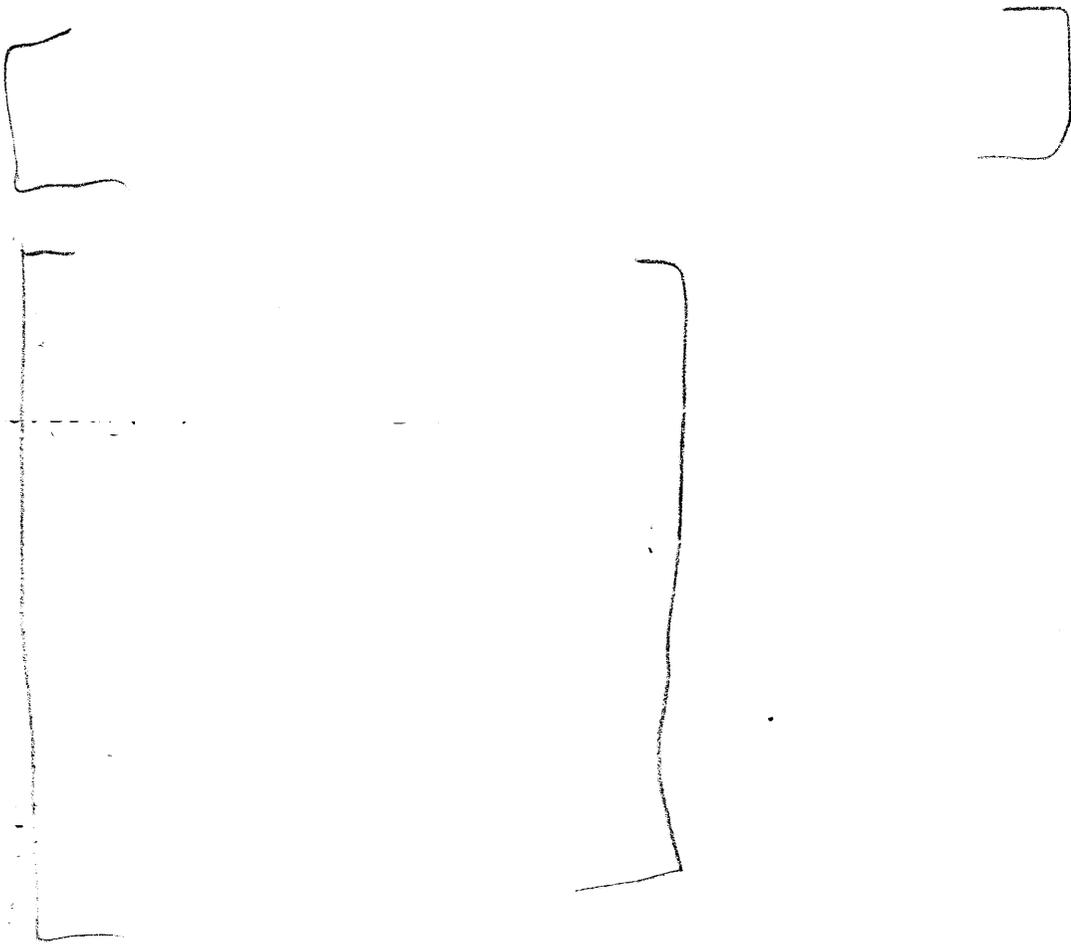
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**Results:**

Thirty (30) subjects entered the study and 27 subjects completed all three periods of the study. Thirty-two (32) adverse events, including mild episodes of headache, nausea, lightheadedness, vomiting, euphoria, elevated temperature, loose stool, vision blacked out, and pallor, were experienced by 11 subjects during this study. All of the events were mild or moderate in severity. No serious adverse events occurred during the study and no medication was required for any clinical complaint. Subjects #15, #28 and #30 could not tolerate the adverse events due to the second dose of ReVia<sup>R</sup>, were withdrawn from the study.

This study was conducted in two groups as the initial group did not have a sufficient number of participants enrolled to meet the protocol requirement of 24 participants. The first group (subjects # 1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, and 16) started the study on August 29, 1997 and completed on September 15, 1997. The second

group (subjects # 2, 10, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30) started the study on September 26, 1997 and finished on October 13, 1997.

There were few protocol deviations (minor) reported during the study. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

All thirty-five (35) volunteers' plasma samples were analyzed. The mean plasma morphine and morphine-6-glucuronide levels for the test and the reference drugs are presented in Table 13 (and in Figure 7 attached) and in Table 15 (and in Figure 8 attached), respectively.

The mean pharmacokinetic parameters derived from the plasma morphine levels and morphine-6-glucuronide levels are presented in Table 14 and Table 16, respectively.

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Table 13  
Mean Plasma Morphine Levels (ng/mL)

Time (hour)	TEST (A) 60 mg Tab. (Endo) Lot #LE249 <u>Fasted</u>	Test (B) 60 mg Tab. (Endo) Lot #LE249 <u>Fed</u>	Reference © 60 mg Tab. (MS Contin) Lot #J051 <u>Fed</u>
Pre-dose	0	0	
0.5	7.39 (52) *	2.97 (119)	2.28 (166)
1.0	10.62 (46)	7.81 (97)	6.21 (102)
1.5	12.77 (39)	11.04 (69)	10.13 (78)
2.0	15.81 (36)	16.45 (51)	15.18 (61)
2.5	17.47 (32)	23.92 (65)	21.16 (56)
3.0	17.24 (30)	25.97 (55)	22.92 (52)
3.5	15.70 (31)	24.01 (45)	23.72 (46)
4.0	15.64 (32)	22.72 (40)	22.97 (36)
5.0	14.64 (38)	23.54 (40)	23.55 (24)
6.0	11.47 (32)	16.20 (37)	17.02 (29)
7.0	9.44 (32)	11.94 (37)	12.72 (35)
8.0	7.95 (30)	9.60 (43)	10.27 (35)
10.0	6.32 (34)	6.84 (41)	7.69 (42)
12.0	4.93 (37)	5.06 (36)	5.48 (38)
16.0	3.53 (43)	3.42 (29)	3.77 (34)
24.0	2.78 (29)	2.73 (27)	2.74 (32)
30.0	1.53 (43)	1.47 (34)	1.48 (38)
36.0	0.70 (78)	0.81 (42)	0.75 (52)
48.0	0.45 (97)	0.35 (118)	0.41 (96)

Number of Subjects 27

\* Coefficient of Variation

Table 14  
Mean Pharmacokinetic Parameters for Plasma Morphine

<u>Parameters</u> (Arithmetic Means)	<u>Test (A)</u> <u>Fasted</u>	<u>Test (B)</u> <u>Fed</u>	<u>Ref. (C)</u> <u>FED</u>	<u>B/C</u>	<u>B/A</u>
AUC <sub>0-T</sub> (ng.hr/mL)	192.40 (28) *	223.70 (23)	226.50 (24)		
AUC <sub>0-inf</sub> (ng.hr/mL)	205.80 (28)	235.60 (24)	236.90 (24)		
C <sub>MAX</sub> (ng/mL)	19.92 (28)	33.33 (44)	30.50 (33)		
T <sub>max</sub> (hour)	2.85 (38)	3.80 (31)	3.69 (31)		
t <sub>1/2</sub> (hour)	9.86 (42)	9.66 (43)	10.47 (35)		
KE (1/hour)	0.09 (53)	0.08 (38)	0.07 (38)		
<u>Parameters</u> (Least Squares Means)	<u>Test (A)</u> <u>Fasted</u>	<u>Test (B)</u> <u>Fed</u>	<u>Ref. (C)</u> <u>FED</u>	<u>B/C</u>	<u>B/A</u>
AUC <sub>0-T</sub> (ng.hr/mL)	194.37	224.66	227.36	0.99	1.16
AUC <sub>0-inf</sub> (ng.hr/mL)	206.39	237.78	240.28	0.99	1.15
C <sub>MAX</sub> (ng/mL)	20.05	33.12	30.22	1.10	1.65

Number of Subjects 27

\* Coefficient of Variation

Table 15  
Mean Plasma Morphine-6-Glucuronide Levels (ng/mL)

Time (hour)	TEST (A) 60 mg Tab. (Endo) Lot #LE249 <u>Fasted</u>	Test (B) 60 mg Tab. (Endo) Lot #LE249 <u>Fed</u>	Reference © 60 mg Tab. (MS Contin) Lot #J051 <u>Fed</u>
Pre-dose	0	0	0
0.5	12.79 (69)*	2.88 (159)	1.14 (232)
1.0	52.60 (40)	18.23 (106)	13.13 (138)
1.5	80.99 (27)	38.04 (81)	33.15 (95)
2.0	102.60 (24)	61.53 (60)	56.35 (69)
2.5	121.30 (20)	90.52 (44)	77.61 (57)
3.0	129.00 (18)	120.20 (45)	108.7 (46)
3.5	125.90 (19)	133.70 (41)	128.40 (39)
4.0	121.60 (25)	134.10 (32)	140.80 (31)
5.0	100.80 (32)	131.4 (34)	142.20 (20)
6.0	78.85 (26)	102.90 (40)	111.60 (21)
7.0	61.47 (23)	75.01 (42)	85.77 (28)
8.0	50.70 (24)	57.76 (41)	67.22 (35)
10.0	39.19 (25)	39.63 (40)	47.43 (42)
12.0	33.11 (32)	30.77 (30)	36.13 (38)
16.0	23.11 (24)	22.67 (23)	25.17 (22)
24.0	13.71 (28)	13.36 (23)	13.65 (27)
30.0	8.59 (38)	8.40 (33)	8.72 (32)
36.0	5.45 (43)	5.49 (36)	5.60 (37)
48.0	2.88 (52)	2.99 (52)	2.83 (53)

Number of Subjects 27

\* Coefficient of Variation

Table 16  
Mean Pharmacokinetic Parameters for Plasma Morphine-6-Glucuronide

<u>Parameters</u> <u>Arithmetic Means</u>	<u>Test (A)</u> <u>Fasted</u>	<u>Test (B)</u> <u>Fed</u>	<u>Ref. (C)</u> <u>FED</u>	<u>B/C</u>	<u>B/A</u>
AUC <sub>0-T</sub> (ng.hr/mL)	1250.0 (17)*	1247.0 (17)	1324.0 (17)		
AUC <sub>0-inf</sub> (ng.hr/mL)	1300.0 (17)	1303 (17)	1377.0 (17)		
C <sub>MAX</sub> (ng/mL)	138.2 (16)	163.8 (33)	161.9 (22)		
T <sub>max</sub> (hour)	3.46 (22)	4.06 (20)	4.13 (22)		
t <sub>1/2</sub> (hour)	11.03 (27)	11.29 (28)	11.19 (28)		
KE (1/hour)	0.07 (35)	0.07 (37)	0.07 (36)		
<u>Parameters</u> <u>Least Squares</u> <u>Means</u>	<u>Test (A)</u> <u>Fasted</u>	<u>Test (B)</u> <u>Fed</u>	<u>Ref. (C)</u> <u>FED</u>	<u>B/C</u>	<u>B/A</u>
AUC <sub>0-T</sub> (ng.hr/mL)	1248.25	1244.74	1322.33	<u>0.98</u>	<u>1.00</u>
AUC <sub>0-inf</sub> (ng.hr/mL)	1297.29	1298.26	1373.57	<u>0.94</u>	<u>1.00</u>
C <sub>MAX</sub> (ng/mL)	137.79	161.99	160.27	<u>1.01</u>	<u>1.18</u>

Number of Subjects 27

\* Coefficient of Variation

The mean value of each of the parameters AUC<sub>0-T</sub>, AUC<sub>0-inf</sub> and C<sub>MAX</sub> for morphine and M-6-G following the administration of the test formulation with food were less than 7% different from those resulting from the administration of the reference formulation under same condition. The ANOVA model included sequence, subject within sequence, period, and treatment. An additional ANOVA analysis was performed to test if the makeup group was significantly different from the first group with respect to the pharmacokinetic parameters of morphine and M-6-G. The analysis indicated that there was no statistically significant differences between the first group and the makeup group for the parent compound and its metabolite, M-6-G.

## V. MULTIPLE DOSE, STEADY-STATE STUDY

### Objective:

The objective of this study was to compare the steady-state bioavailability of the test and reference (MS Contin<sup>R</sup> CC) 60 mg Morphine Sulfate Extended-Release Tablets under fasted conditions.

Study Design: Protocol #EN3174-007

This was a randomized, open-label, multiple-dose, steady-state, two-way crossover design comparing the test product morphine sulfate 60 mg extended-release tablets with the reference product MS Contin<sup>R</sup> CC 60 mg tablets under fasting conditions in 44 healthy male and female volunteers (36 completing) with an seven day washout between the last dose of Period 1 and the first dose of Period 2. Plasma was analyzed for the parent drug, morphine and its metabolite, morphine-6-glucuronide (M-6-G) concentrations.

Study Sites and PI : Same as mentioned in single dose fasting study.

Study Dates: Study (dosing date of each period, I & II) began on September 3, 1997 and ended on September 24, 1997.

### Subject Selection:

Forty-eight (44) healthy volunteers received an initial 50 mg dose of ReVia<sup>R</sup> on Day 0, 15 hours predose after completing a physical examination and laboratory screening tests. Subjects unable to tolerate this dose were not enrolled in the study.

### Study Procedures

Volunteers entered into the study and received a second 50 mg dose of ReVia<sup>R</sup> on Day 1, 3 hours predose. At the zero hour on Day 1 of each study period, the subjects received one of two treatments:

### Treatments:

- 1) Treatment A (test), morphine sulfate 60 mg extended-release tablet, 1 X 60 mg, Endo Pharmaceuticals Inc., Lot #LE249

( every 12 hours for 13 doses).

2) Treatment B (reference), MS Contin<sup>R</sup> CR 60 mg tablet, 1 X 60 mg, Purdue Frederick, Lot #J051, Expiry Date: 03/2002.  
( every 12 hours for 13 doses)

Dose:

Beginning on the morning of Day 1, each subject received 13 oral doses of morphine sulfate CR Test or Reference product for the duration of each period. Doses were administered in the morning and 12 hours following the morning dose for Days 1 - 6. A morning dose (test or reference) only was administered on Day 7. Each dose was given with 240 ml of water. All subjects receiving either Treatment A or B were fasted for a minimum of 10 hours prior to dosing.

Date of First Sample Analysis: October 1, 1997  
Dates of Last Sample Analysis: October 21, 1997

Washout Period: Seven days between the last dose of Period 1 and the first dose of Period 2.

Fasting/Meals:

Subjects were required to fast overnight prior to, and for 4.5 hours after, each morning dose. Water was not permitted for 1 hour before and 1 hour after each dose, but was allowed at all other times. Standard meals were provided at 4.5 and 9.5 hours, and snacks were provided at 13.5 hours after dose on each day. All meals and beverages were xanthine and caffeine-free and were identical for both periods.

Blood Sampling:

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adverse events. One hundred and twenty-four (124) adverse events, including mild episodes of sinus bradycardia, headache, nausea, lightheadedness, and vomiting, were experienced by twenty-nine (29) subjects during this study. However, none of these effects were severe, and no medication was required for any clinical complaint. There were few protocol deviations (minor) reported during the study. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters.

Mean plasma Morphine levels of 36 subjects at steady-state are presented in Tables 17 (and in Figure #9 attached).  $AUC_{0-12}$  at steady-state was the sum of the linear trapezoidal estimation of the areas from the time of the 7th dose to 12 hours post 13th dose.  $C_{ss}$  was  $AUC_{0-24}$  divided by the dosing interval (12 hours).  $C_{max}$  and  $T_{max}$  were determined from the observed plasma concentration-time profile over the sampling interval (Day7). Fluct1 was the percent fluctuation calculated as the difference between  $C_{max}$  and  $C_{min}$  divided by  $C_{ss}$ , Fluct2 was the percent fluctuation calculated as the difference between  $C_{max}$  and  $C_{min}$  divided by  $C_{min}$ . Mean pharmacokinetic parameters of Morphine are presented in Table 18.

Mean plasma M-6-G levels at steady-state are presented in Tables 19 (and in Figure #10 attached). Mean pharmacokinetic parameters for M-6-G are presented in Table 20.

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**Table 17**  
**Mean Plasma Morphine Levels (ng/mL)**

Time (hour)	TEST (A) 60 mg Tab. (Endo) Lot #LE249	Reference (B) 60 mg Tab. (MS Contin) Lot #J051
Pre-dose on Day 1	0	0
Pre-dose on Day 2	9.02 (33)	10.29 (32)
Pre-dose on Day 3	13.05 (33)	13.71 (39)
Pre-dose on Day 4	13.50 (31)	14.03 (29)
Pre-dose on Day 5	13.61 (34)	14.83 (31)
Pre-dose on Day 6	13.19 (33)	15.71 (34)
Pre-dose on Day 7	14.59 (30)	16.40 (33)
and post dosing at:		
0.50	23.57 (26)	25.16 (34)
1.00	27.43 (31)	31.42 (30)
1.50	28.28 (29)	29.79 (29)
2.00	29.43 (28)	30.05 (27)
2.50	31.94 (28)	29.93 (31)
3.00	32.38 (26)	29.94 (25)
3.5	30.59 (25)	29.30 (25)
4.0	29.64 (26)	29.53 (25)
5.0	29.87 (27)	32.29 (21)
6.0	26.94 (31)	29.47 (24)
7.0	23.41 (32)	25.92 (27)
8.0	19.76 (29)	21.95 (29)
10.0	14.87 (29)	16.03 (26)
12.0	10.96 (32)	11.58 (27)

Number of Subjects 36

\* Coefficient of Variation

**Table 18**  
**Mean Pharmacokinetic Parameters for Plasma Morphine**

<u>Parameters</u> (Arithmetic Mean)	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B</u>	<u>90% C.I.**</u>
AUC <sub>0-T</sub> (ng.hr/mL)	278.20 (25) *	293.3 (21)		
C <sub>MAX</sub> (ng/mL)	35.98 (25)	37.72 (22)		
Cmin(ng/mL)	10.77 (31)	11.41 (27)		
LnAUC <sub>0-T</sub> Geometric Mean	5.59** 267.74	5.66 287.15	0.93	91; 96
LnC <sub>MAX</sub> Geometric Mean	3.543** 34.57	3.606 36.82	0.93	90; 98
Cmin(ng/mL)	10.72**	11.40	0.94	
T <sub>max</sub> (hour)	2.99 (47)	2.90 (64)		
C <sub>ss</sub> (ng/mL)	23.10**	24.46	0.94	
Fluct1(%)	222.5**	223.0	1.00	
Fluct2(%)	103.2**	103.9	0.99	

Number of Subjects: 36

\* Coefficient of Variation

\*\* Based on Least Squares Means (LSM)

Intra-subject variability for: LnAUC(0-t) =6.96

LnCmax = 10.15

Fluct1 = (Cmax-Cmin)/Cmin

Fluct2 = (Cmax-Cmin)/C<sub>ss</sub>

**Table 19**  
**Mean Plasma Morphine-6-Glucuronide Levels (ng/mL)**

Time (hour)	TEST (A) 60 mg Tab. (Endo) Lot #LE249	Reference (B) 60 mg Tab. (MS Contin) Lot #J051
Pre-dose on Day 1	0	0
Pre-dose on Day 2	45.77 (30)	49.62 (33)
Pre-dose on Day 3	61.84 (29)	64.62 (30)
Pre-dose on Day 4	59.76 (29)	63.13 (29)
Pre-dose on Day 5	54.07 (32)	58.92 (29)
Pre-dose on Day 6	57.50 (28)	66.49 (28)
Pre-dose on Day 7	61.88 (26)	67.64 (32)
and post dosing at:		
0.50	70.36 (22)	73.13 (27)
1.00	113.9 (23)	121.8 (25)
1.50	137.1 (20)	148.0 (23)
2.00	151.1 (21)	162.9 (22)
2.50	166.0 (23)	169.5 (20)
3.00	173.0 (24)	167.2 (20)
3.5	174.2 (22)	168.6 (21)
4.0	167.3 (23)	168.6 (22)
5.0	146.4 (24)	157.2 (28)
6.0	126.2 (23)	141.8 (29)
7.0	111.4 (24)	125.4 (25)
8.0	97.84 (25)	109.5 (27)
10.0	74.75 (21)	79.53 (28)
12.0	58.31 (21)	61.48 (27)

Number of Subjects 36

\* Coefficient of Variation



corresponding reference values. The steady state results for plasma morphine concentrations at 96 (Day 5) hours, 120 (Day 6) hours, and 144 (Day 7) hours are presented in Tables 21 & 22 (attached). Both formulations showed comparable plasma concentrations at 96, 120, and 144 hours. The linear regression analysis also showed that the slope of plasma morphine concentrations at 96, 120, and 144 hours was not significantly different from zero for the test formulation. This indicates attainment of steady state plasma morphine concentrations at 96 hours for the test formulation. Even though the linear regression results for the reference formulation were statistically significant ( $p=0.033$ ), the mean slope was very small (0.0326) and comparable to the mean slope for the test formulation (0.0204).

The ANOVA model included sequence, subject within sequence, period, and treatment. Additional ANOVA analyses were performed to test if the second group was significantly different from the first group with respect to the pharmacokinetic parameters of morphine and M-6-G. The analysis indicated that there was no statistically significant differences between the first group and the make-up group for both compounds.

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In-Vitro Dissolution:

The firm has conducted acceptable dissolution testing on the test and reference products in 0.1N HCl, phosphate buffer and in water. The data are presented in Table 23.

Table 23. In Vitro Dissolution Testing						
<b>Drug:</b> Morphine Sulfate ER Tablets <b>Dose Strengths:</b> 15 mg, 30 mg & 60 mg <b>AND No.:</b> 75-295 <b>Firm:</b> Endo Pharmaceuticals Inc. <b>Submission Date:</b> December 31, 1997						
<b>I. Conditions for Dissolution Testing:</b>						
USP XXIII Paddle RPM: 50 No. Units Tested: 12 Medium: a) 0.1 N HCl, pH 1.2; b) Phosphate buffer, pH 4.5; c) Water Volume: 500 mL (each medium) Specifications: Not Proposed by the firm Assay Methodology: _____						
<b>II(a). Results of In Vitro Dissolution Testing: In 0.1N HCl, pH 1.2</b>						
Sampling Times (Hour)	Test Product			Reference Product		
	Morphine Sulfate ER Tablets of Endo Lot # LE249 Strength 60 mg			Purdue Frederick MS Contin <sup>®</sup> Lot # J051 Strength 60 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
0	0	—	----	0	—	---
0.5	19.9	—	4.7	20.0	—	3.5
1	34.1	—	3.6	32.6	—	3.3
2	54.7	—	2.7	51.0	—	2.9
3	70.0	—	2.2	64.7	—	2.7
4	81.7	—	1.8	76.3	—	2.6
5	89.6	—	1.3	85.5	—	2.4
6	95.0	—	0.9	93.4	—	2.2
8	99.7	—	0.6	103.5	—	1.8
10	101.4	—	0.6	106.4	—	2.0
12	102.0	—	0.6	106.5	—	2.0

II(b). Results of In Vitro Dissolution Testing: In Phosphate Buffer, pH4.5

Sampling Times (Hour)	Test Product			Reference Product		
	Mean %	Range%	%CV	Mean %	Range%	%CV
	Morphine Sulfate ER Tablets of Endo Lot # LE249 Strength 60 mg			Purdue Frederick MS Contin <sup>®</sup> Lot # J051 Strength 60 mg		
0	0	—	---	0	—	---
0.5	16.5	—	8.0	16.6	—	5.1
1	28.2	—	5.5	27.1	—	3.8
2	46.3	—	3.8	42.4	—	2.8
3	60.9	—	3.3	54.0	—	2.2
4	72.9	—	3.0	63.7	—	2.1
5	82.2	—	2.6	72.3	—	1.9
6	88.6	—	2.4	80.1	—	1.9
8	95.3	—	2.1	92.6	—	1.7
10	97.9	—	2.0	100.2	—	1.7
12	99.0	—	1.7	103.4	—	1.5

II(c). Results of In Vitro Dissolution Testing: In Water

Sampling Times (Hour)	Test Product			Reference Product		
	Mean %	Range%	%CV	Mean%	Range%	%CV
	Morphine Sulfate ER Tablets of Endo, Lot # LE249 Strength 60 mg			Purdue Frederick MS Contin <sup>®</sup> Lot # J051 Strength 60 mg		
0	0	—	----	0	—	---
0.5	15.5	—	0.05	16.5	—	0.06
1	26.8	—	0.04	26.9	—	0.04
2	44.2	—	0.03	41.8	—	0.03
3	58.3	—	0.02	53.2	—	0.03
4	70.2	—	0.02	62.9	—	0.03
5	79.6	—	0.01	71.3	—	0.03
6	86.8	—	0.01	78.9	—	0.03
8	94.4	—	0.01	91.3	—	0.02
10	96.9	—	0.01	98.5	—	0.02
12	98.0	—	0.01	101.1	—	0.03

II(a). Results of In Vitro Dissolution Testing: In 0.1N Hcl, pH 1.2						
Sampling Times (Hour)	Test Product			Reference Product		
	Morphine Sulfate ER Tablets of Endo Lot # LB085 Strength 30 mg			Purdue Frederick MS Contin <sup>®</sup> Lot # F05 Strength 30 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
0	0	—	----	0	—	---
0.5	23.4	—	5.3	23.1	—	3.1
1	38.0	—	3.9	36.6	—	2.9
2	58.0	—	3.7	56.1	—	2.7
3	72.1	—	3.5	70.2	—	2.9
4	82.4	—	2.8	81.2	—	3.0
5	89.5	—	2.2	90.1	—	2.8
6	93.8	—	1.8	97.1	—	2.3
8	98.3	—	1.1	103.2	—	2.2
10	100.0	—	1.0	104.4	—	2.3
12	100.7	—	1.0	104.8	—	2.3

II(b). Results of In Vitro Dissolution Testing: In Phosphate buffer, pH4.5						
Sampling Times (Hour)	Test Product			Reference Product		
	Morphine Sulfate ER Tablets of Endo, Lot # LB085 Strength 30 mg			Purdue Frederick MS Contin <sup>®</sup> Lot # F05 Strength 30 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
0	0	—	----	0	—	---
0.5	19.1	—	3.9	21.3	—	6.5
1	31.1	—	3.7	33.6	—	5.3
2	48.5	—	4.0	50.6	—	3.9
3	61.9	—	3.2	62.8	—	3.9
4	72.3	—	3.7	73.3	—	3.5
5	81.3	—	2.8	81.6	—	3.4
6	87.4	—	2.4	88.8	—	3.2
8	94.3	—	1.7	98.6	—	2.2
10	97.8	—	1.8	103.0	—	1.9
12	99.5	—	1.2	104.9	—	1.9

II(c). Results of In Vitro Dissolution Testing: In Water						
Sampling Times (Hour)	Test Product			Reference Product		
	Morphine Sulfate ER Tablets of Endo, Lot # LB085 Strength 30 mg			Purdue Frederick MS Contin <sup>®</sup> Lot # F05 Strength 30 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
0	0	—	----	0	—	---
0.5	19.6	—	0.15	21.1	—	0.05
1	33.3	—	0.08	32.8	—	0.04
2	51.3	—	0.06	48.8	—	0.03
3	65.6	—	0.05	60.7	—	0.02
4	77.2	—	0.04	70.4	—	0.02
5	86.1	—	0.03	78.5	—	0.02
6	92.6	—	0.03	85.3	—	0.01
8	99.1	—	0.03	93.7	—	0.01
10	101.8	—	0.03	97.0	—	0.01
12	102.6	—	0.03	98.5	—	0.01

II(a). Results of In Vitro Dissolution Testing: In 0.1N Hcl, pH 1.2						
Sampling Times (Hour)	Test Product			Reference Product		
	Morphine Sulfate ER Tablets of Endo Lot # LF301 Strength 15 mg			Purdue Frederick MS Contin <sup>®</sup> Lot # J021 Strength 15 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
0	0	—	----	0	—	---
0.5	21.8	—	12.4	24.7	—	4.1
1	34.9	—	6.4	37.7	—	3.9
2	54.5	—	5.1	55.6	—	3.6
3	68.5	—	4.0	68.6	—	2.4
4	79.4	—	3.3	78.9	—	2.0
5	87.4	—	3.1	86.0	—	2.5
6	93.0	—	2.9	92.9	—	1.7
8	98.8	—	2.6	100.0	—	1.7
10	100.7	—	2.8	102.2	—	1.9
12	101.9	—	2.7	102.6	—	2.0

II(b). Results of In Vitro Dissolution Testing: In Phosphate buffer, pH 4.5

Sampling Times (Hour)	Test Product			Reference Product		
	Mean %	Range%	%CV	Mean %	Range%	%CV
0	0	—	----	0	—	---
0.5	19.9	—	8.7	22.5	—	6.7
1	32.2	—	5.7	34.4	—	3.8
2	51.0	—	3.8	50.9	—	2.9
3	65.6	—	3.7	62.8	—	2.8
4	77.1	—	3.1	72.3	—	2.7
5	86.2	—	3.0	79.1	—	2.7
6	92.7	—	2.4	86.5	—	2.3
8	99.7	—	2.4	96.3	—	1.5
10	102.6	—	2.1	99.8	—	1.5
12	104.3	—	1.8	101.7	—	1.6

II(c). Results of In Vitro Dissolution Testing: In Water

Sampling Times (Hour)	Test Product			Reference Product		
	Mean %	Range%	%CV	Mean %	Range%	%CV
0	0	—	----	0	—	---
0.5	18.7	—	0.06	21.2	—	0.04
1	31.8	—	0.04	33.0	—	0.03
2	50.6	—	0.04	48.7	—	0.03
3	64.9	—	0.03	60.1	—	0.02
4	76.4	—	0.03	67.8	—	0.03
5	84.6	—	0.02	76.3	—	0.03
6	90.8	—	0.02	82.8	—	0.02
8	97.5	—	0.02	92.1	—	0.02
10	99.5	—	0.01	95.6	—	0.03
12	101.1	—	0.01	99.6	—	0.02

The firm has also conducted acceptable dissolution testing on the test and reference products (all three strengths) in pH 6.2 phosphate buffer and pH 7.2 phosphate buffer. The comparative dissolution profiles of the test and reference products in different media or in same media at different pHs are presented in Figures 11-15 (attached).

**Compositions:**

The compositions of the test tablets are presented in Table 24 attached herewith.

**Comments:**

1. The bioequivalence studies conducted on (i) the single dose under fasting conditions, on 15 mg and 30 mg tablets, and (ii) single dose under fasting and fed conditions on 60 mg tablets, and (iii) also the multiple dose on 60 mg tablets, using the test product (Morphine Sulfate ER tablets) of Endo Pharmaceuticals Inc. and the reference product (MS Contin<sup>R</sup> ER tablets) of corresponding strengths of Purdue Frederick have been found acceptable by the Division of Bioequivalence.
  
2. The in vitro dissolution testings conducted on the test and reference products in water, 0.1N HCl (pH 1.2) and in phosphate buffer (at pH 4.5, pH 6,2 and pH 7.2) are also acceptable. The firm did not propose the dissolution specification for its test product. Since the approved dissolution medium for the 15, 30 and 60 mg MS Contin<sup>R</sup> Tablets (Purdue Frederick) was water, the tentative specification is the following:  

1 hr NLT	—	and	NMT	—
2 hr NLT	—	and	NMT	—
4 hr NLT	—	and	NMT	—
8 hr NLT	—			
  
3. The formulations for the 15 mg and 30 mg strengths of the test product are proportionally similar to the 60 mg strength of Endo's Morphine Sulfate ER tablets.

**Recommendations:**

1. The single dose bioequivalence studies under fasting conditions, conducted by Endo Pharmaceuticals, Inc., on its test product, Morphine sulfate ER 15 mg Tablets, lot #LF301, comparing it to MS Contin<sup>R</sup> ER 15 mg Tablets manufactured by Purdue Frederick Company, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Endo's Morphine sulfate ER 15 mg Tablets is bioequivalent to the reference product, MS Contin<sup>R</sup> ER 15 mg Tablets manufactured by Purdue Frederick Company.
2. The single dose bioequivalence studies under fasting conditions, conducted by Endo Pharmaceuticals, Inc., on its test product, Morphine sulfate ER 30 mg Tablets, lot #LB085, comparing it to MS Contin<sup>R</sup> ER 30 mg Tablets manufactured by Purdue Frederick Company, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Endo's Morphine sulfate ER 30 mg Tablets is bioequivalent to the reference product, MS Contin<sup>R</sup> ER 30 mg Tablets manufactured by Purdue Frederick Company.
3. The single dose studies under fasting and fed conditions and the multiple dose study under fasting conditions, conducted by Endo Pharmaceuticals, Inc., on its test product, Morphine sulfate ER 60 mg Tablets, lot #LE249, comparing it to MS Contin<sup>R</sup> ER 60 mg Tablets manufactured by Purdue Frederick Company, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Endo's Morphine sulfate ER 60 mg Tablets is bioequivalent to the reference product, MS Contin<sup>R</sup> ER 60 mg Tablets manufactured by Purdue Frederick Company.
4. The dissolution testing conducted by Endo Pharmaceuticals, Inc., on its test product, Morphine sulfate ER 15 mg, 30 mg and 60 mg Tablets, lot #LB085, lot #LE249 and lot #LE249, respectively, is acceptable.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37° C using

USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specification:

1 hr NLT — and NMT —  
2 hr NLT — and NMT —  
4 hr NLT — and NMT —  
8 hr NLT —

/S/

Sikta Pradhan, Ph. D.  
Division of Bioequivalence  
Review Branch I

RD INITIALED YCHUANG  
FT INITIALED YCHUANG

' /S/ '

6/25/98

Concur.

/S/

Date: 6/26/98

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

cc: AND # 75-295 (original, duplicate), HAD-652 (Huang, Pradhan), HAD-650 (Director), Drug File, Division File.

SP/5-4-98//X:\wpfile\Pradhan\75295S5D.D97

# Table - 21

Steady State Slopes for Plasma Morphine Concentrations at 96, 120 and 144 Hours

Subject Number	Treatment Sequence	Study Period	Treatment	Slope
3	BA	1	1 X 60 mg MS Contin Tablet	0.00792
		2	1 X 60 mg DuPont Merck Tablet	0.06917
4	BA	1	1 X 60 mg MS Contin Tablet	-0.03500
		2	1 X 60 mg DuPont Merck Tablet	-0.03417
5	AB	1	1 X 60 mg DuPont Merck Tablet	-0.06875
		2	1 X 60 mg MS Contin Tablet	0.01813
6	BA	1	1 X 60 mg MS Contin Tablet	0.05917
		2	1 X 60 mg DuPont Merck Tablet	-0.07167
7	AB	1	1 X 60 mg DuPont Merck Tablet	0.05792
		2	1 X 60 mg MS Contin Tablet	0.01354
8	BA	1	1 X 60 mg MS Contin Tablet	-0.05500
		2	1 X 60 mg DuPont Merck Tablet	0.04750
9	AB	1	1 X 60 mg DuPont Merck Tablet	-0.07917
		2	1 X 60 mg MS Contin Tablet	0.12417
10	BA	1	1 X 60 mg MS Contin Tablet	0.06292
		2	1 X 60 mg DuPont Merck Tablet	0.06604
11	BA	1	1 X 60 mg MS Contin Tablet	0.08000
		2	1 X 60 mg DuPont Merck Tablet	-0.04104
12	AB	1	1 X 60 mg DuPont Merck Tablet	0.09333
		2	1 X 60 mg MS Contin Tablet	-0.24167
13	BA	1	1 X 60 mg MS Contin Tablet	0.11021
		2	1 X 60 mg DuPont Merck Tablet	0.01979
14	AB	1	1 X 60 mg DuPont Merck Tablet	0.10979
		2	1 X 60 mg MS Contin Tablet	0.10187
15	AB	1	1 X 60 mg DuPont Merck Tablet	0.00042
		2	1 X 60 mg MS Contin Tablet	0.03521
16	BA	1	1 X 60 mg MS Contin Tablet	-0.09625
		2	1 X 60 mg DuPont Merck Tablet	0.02688
17	BA	1	1 X 60 mg MS Contin Tablet	0.05292
		2	1 X 60 mg DuPont Merck Tablet	0.06708
18	BA	1	1 X 60 mg MS Contin Tablet	0.00583
		2	1 X 60 mg DuPont Merck Tablet	0.06417
19	AB	1	1 X 60 mg DuPont Merck Tablet	-0.00875
		2	1 X 60 mg MS Contin Tablet	0.04667
20	AB	1	1 X 60 mg DuPont Merck Tablet	-0.09000
		2	1 X 60 mg MS Contin Tablet	0.02583
21	BA	1	1 X 60 mg MS Contin Tablet	0.02479
		2	1 X 60 mg DuPont Merck Tablet	0.09146
23	BA	1	1 X 60 mg MS Contin Tablet	0.21229
		2	1 X 60 mg DuPont Merck Tablet	0.06354

Table - 21 (cont.)

Steady State Slopes for Plasma Morphine Concentrations at 96, 120 and 144 Hours

Subject Number	Treatment Sequence	Study Period	Treatment	Slope
25	AB	1	1 X 60 mg DuPont Merck Tablet	0.13667
		2	1 X 60 mg MS Contin Tablet	0.20583
26	AB	1	1 X 60 mg DuPont Merck Tablet	0.03854
		2	1 X 60 mg MS Contin Tablet	0.12250
27	BA	1	1 X 60 mg MS Contin Tablet	0.02688
		2	1 X 60 mg DuPont Merck Tablet	0.11042
28	BA	1	1 X 60 mg MS Contin Tablet	0.06437
		2	1 X 60 mg DuPont Merck Tablet	-0.07146
30	BA	1	1 X 60 mg MS Contin Tablet	0.03813
		2	1 X 60 mg DuPont Merck Tablet	0.11979
31	AB	1	1 X 60 mg DuPont Merck Tablet	-0.13750
		2	1 X 60 mg MS Contin Tablet	0.09083
32	AB	1	1 X 60 mg DuPont Merck Tablet	-0.02833
		2	1 X 60 mg MS Contin Tablet	0.03583
33	AB	1	1 X 60 mg DuPont Merck Tablet	0.04188
		2	1 X 60 mg MS Contin Tablet	0.10396
35	BA	1	1 X 60 mg MS Contin Tablet	-0.01875
		2	1 X 60 mg DuPont Merck Tablet	-0.06417
36	BA	1	1 X 60 mg MS Contin Tablet	-0.00771
		2	1 X 60 mg DuPont Merck Tablet	0.02521
37	AB	1	1 X 60 mg DuPont Merck Tablet	0.03375
		2	1 X 60 mg MS Contin Tablet	0.03688
39	BA	1	1 X 60 mg MS Contin Tablet	0.05458
		2	1 X 60 mg DuPont Merck Tablet	0.07500
40	AB	1	1 X 60 mg DuPont Merck Tablet	-0.07438
		2	1 X 60 mg MS Contin Tablet	0.12562
41	BA	1	1 X 60 mg MS Contin Tablet	-0.14542
		2	1 X 60 mg DuPont Merck Tablet	0.11688
42	AB	1	1 X 60 mg DuPont Merck Tablet	0.05500
		2	1 X 60 mg MS Contin Tablet	-0.07438
44	AB	1	1 X 60 mg DuPont Merck Tablet	0.01375
		2	1 X 60 mg MS Contin Tablet	-0.03792

# Table - 22

Steady State Test for Plasma Morphine Concentrations at 96, 120 and 144 hours

Treatment	Number of Subjects	Slope		P-value	
		(Least-Squares Mean)	Mean Slope-0*	TRT A Slope	-TRT B Slope†
1 X 60 mg DuPont Morck Tablet	36	0.01963	0.1787		0.5073
1 X 60 mg MS Contin Tablet	36	0.03318	0.0264		

Note: \* If P-value > 0.05, slope is not statistically different from zero.  
 † If P-value > 0.05, slopes for the two treatments are not significantly different.

*Composites  
and  
Composition  
Table 24*

**Redacted** \_\_\_\_\_

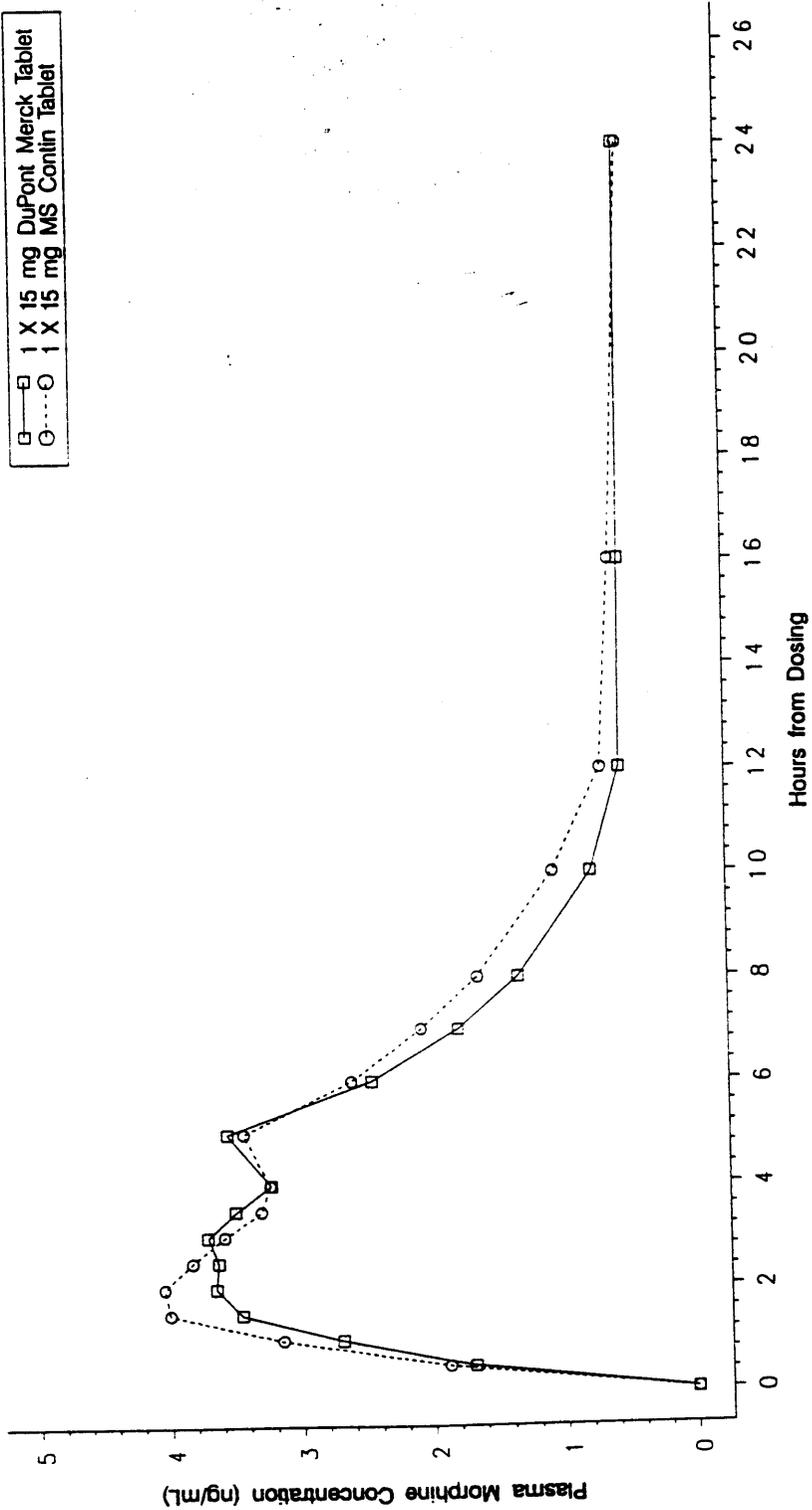
**pages of trade secret and/or**

**confidential**

**commercial**

**information**

Figure 1  
 Mean Plasma Morphine Concentrations (Linear Scale)



The DuPont Merck Pharmaceutical Company  
Morphine Protocol No. EN3174-006  
MDS Harris Project 19862

Figure 2  
Mean Plasma Morphine-6-G Concentrations (Linear Scale)

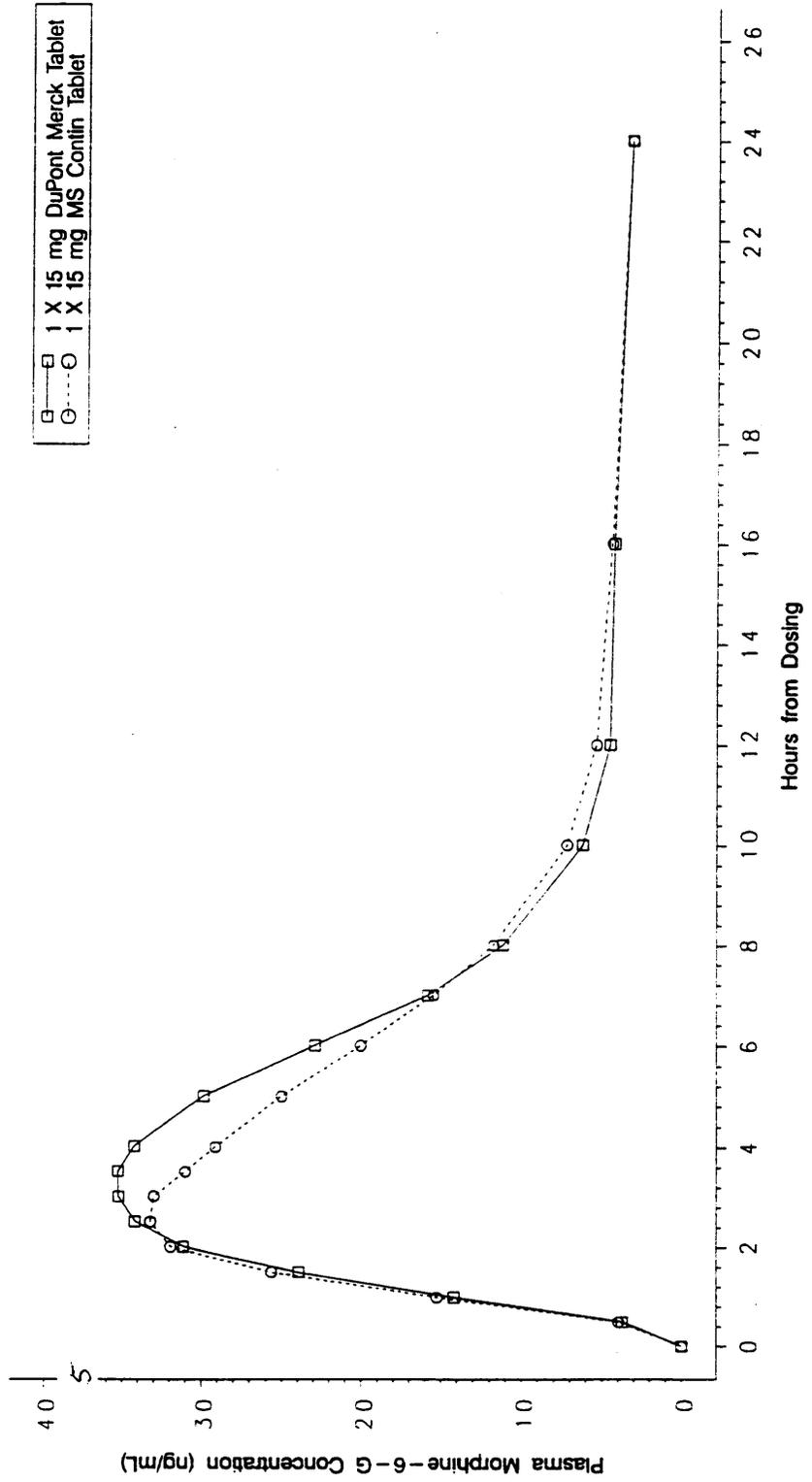
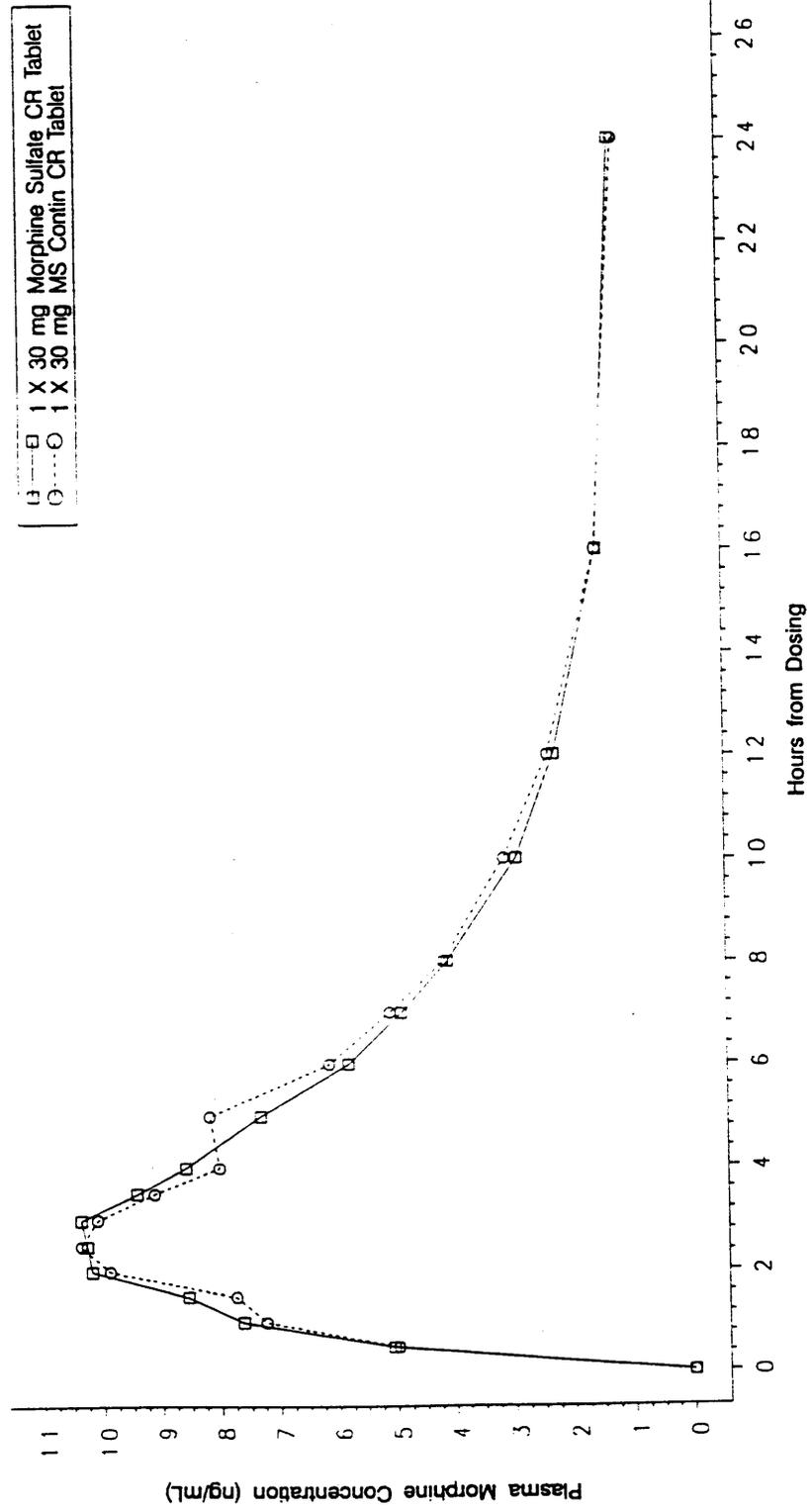


Figure 3  
Mean Plasma Morphine Concentrations Versus Time  
Linear Scale



Merck & Co., Inc.  
Merck Pharmaceutical Company  
Morphine Protocol EN3174-003-001  
MDS Harris Project 19861

Figure 4  
Mean Plasma Morphine-6-glucuronide Concentrations Versus Time  
Linear Scale

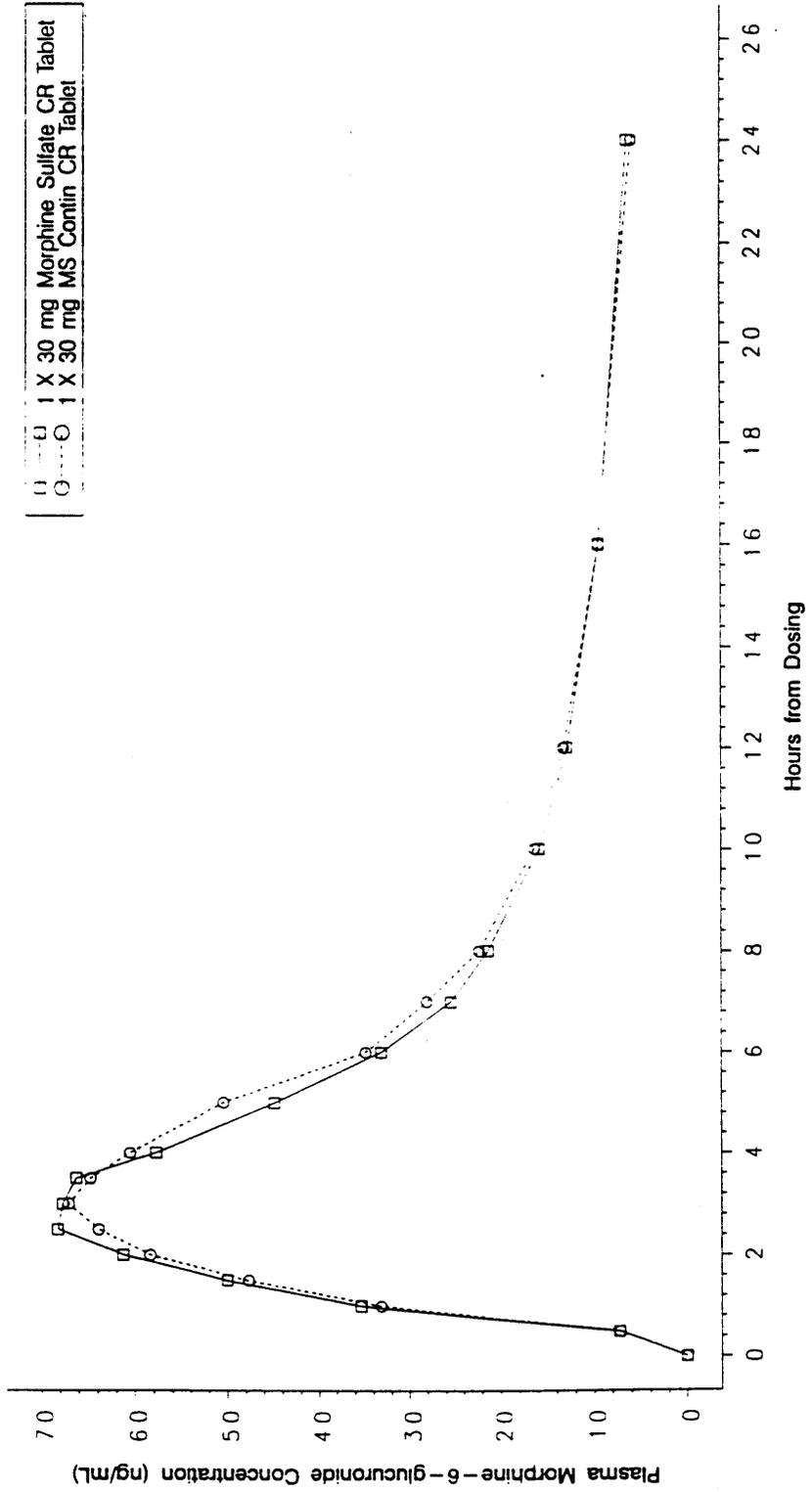
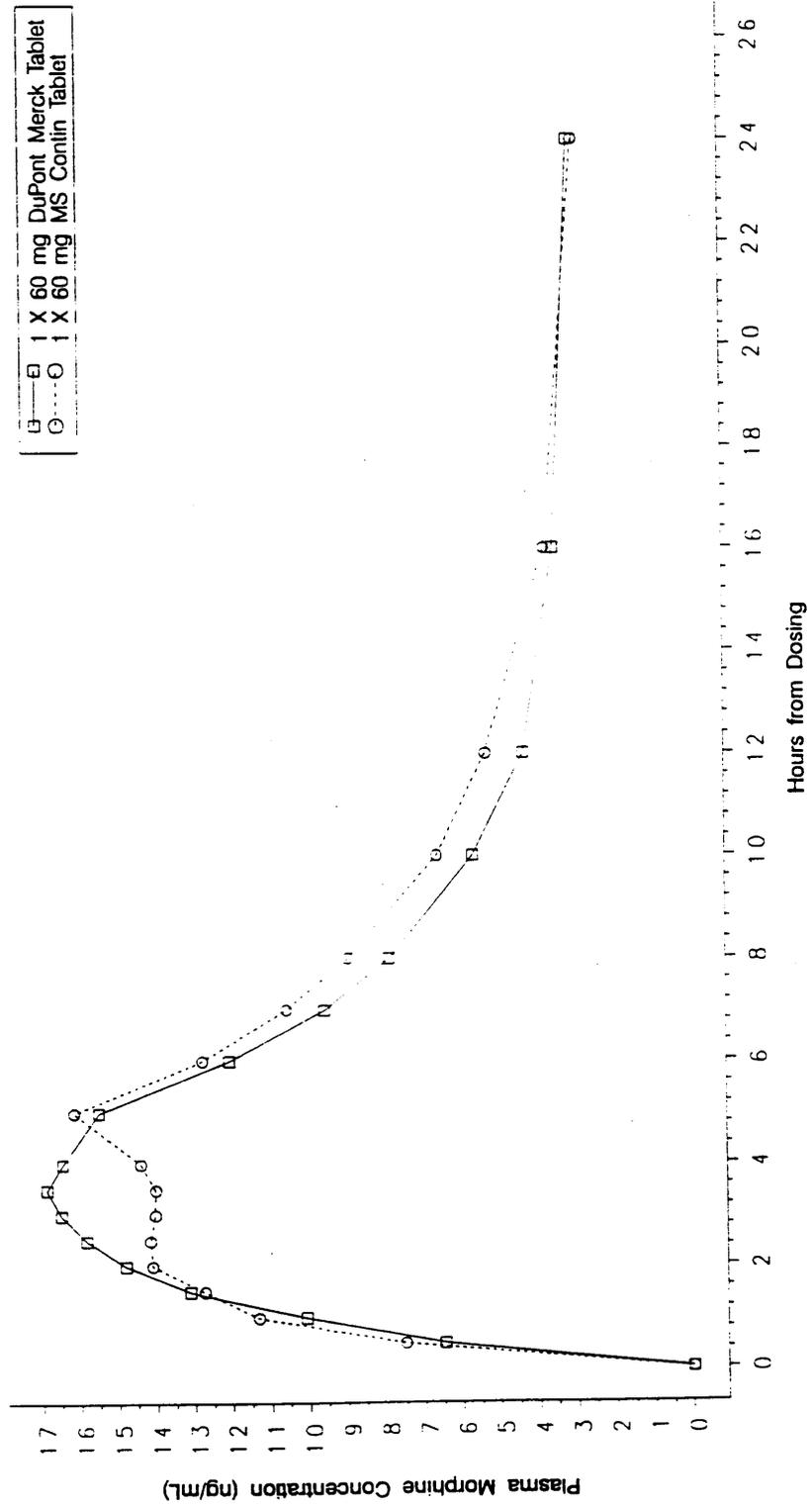
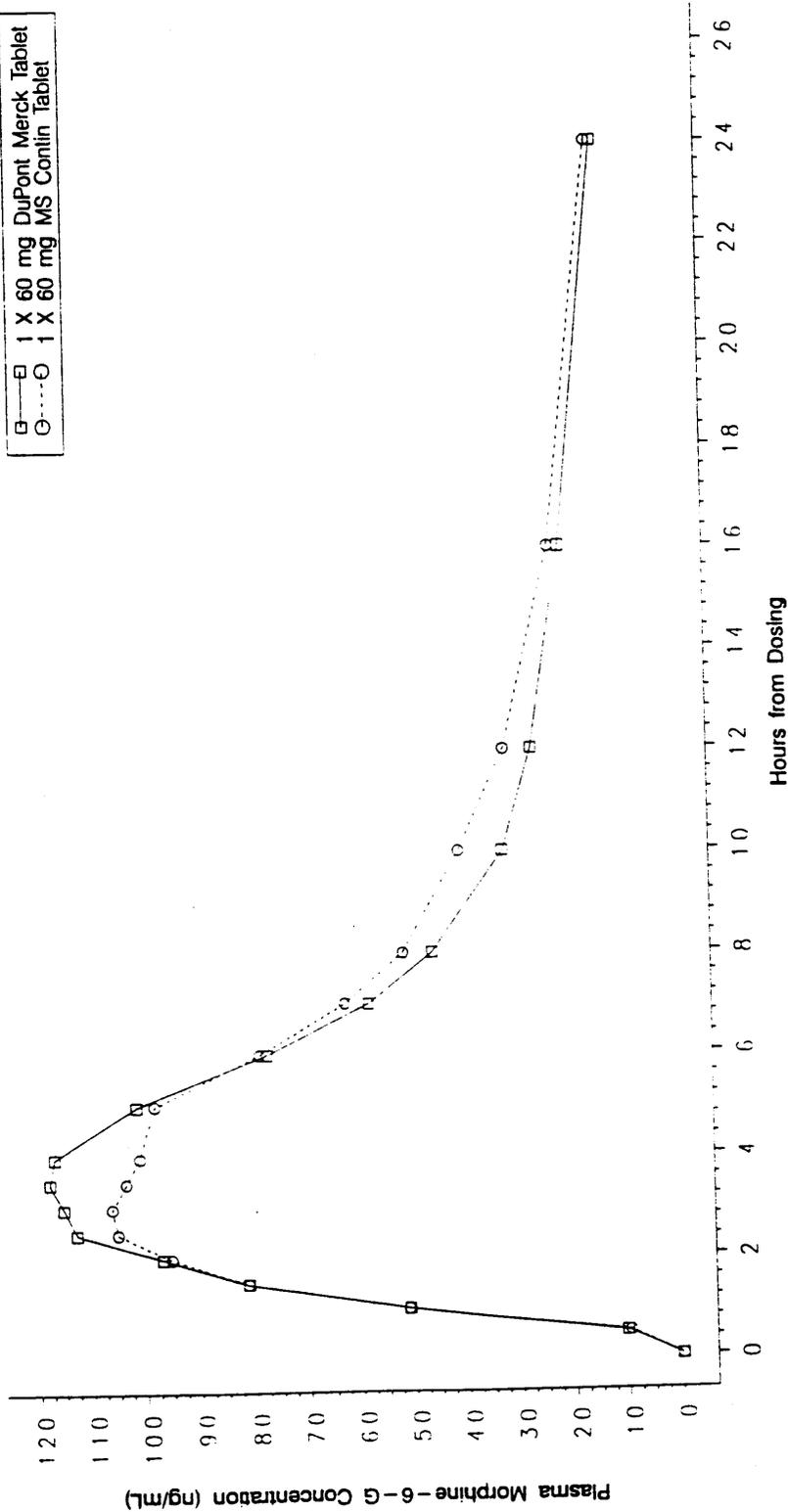


Figure 5  
Mean Plasma Morphine Concentrations (Linear Scale)

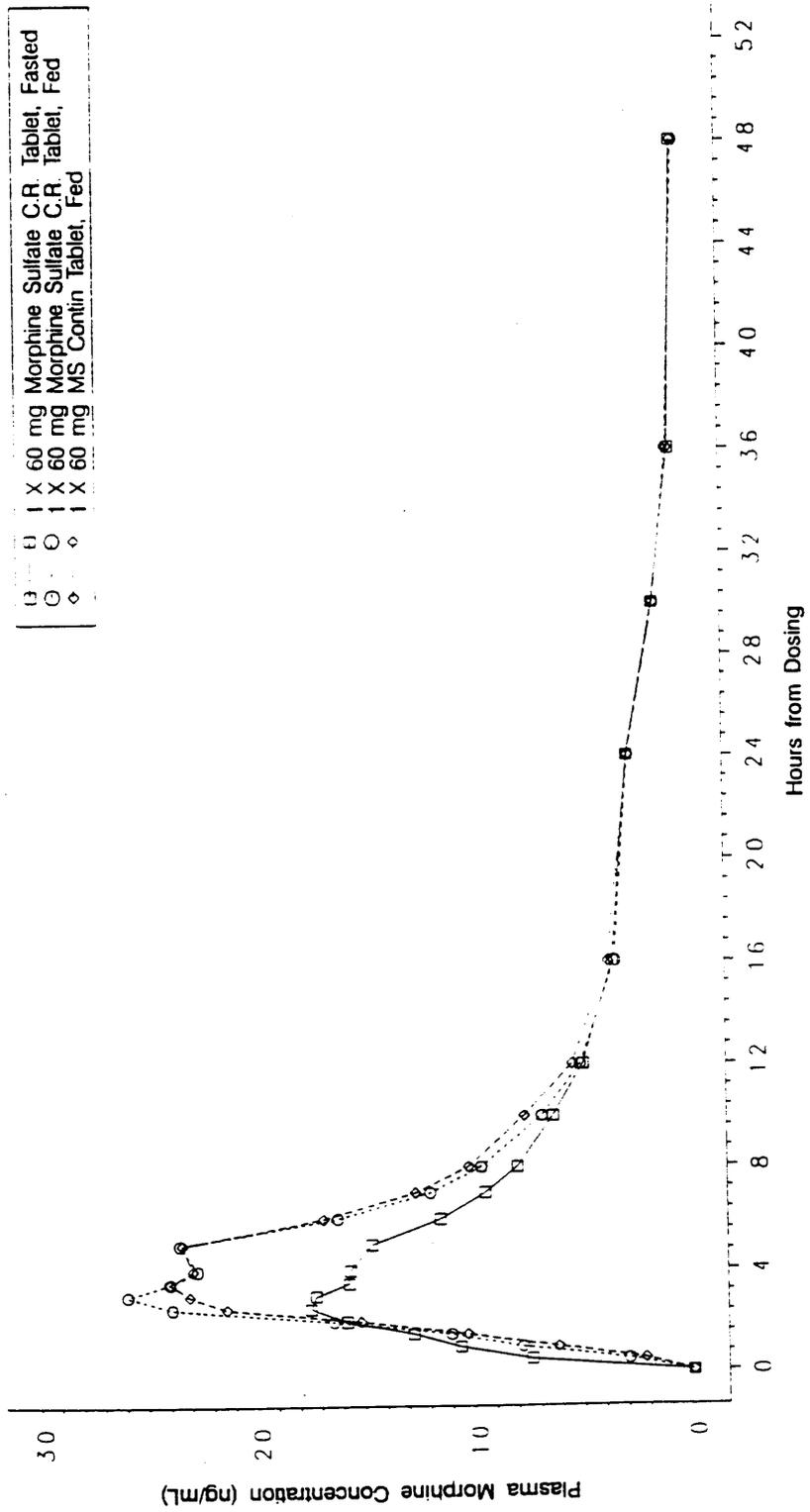


DuPont Merck Pharmaceutical Company  
Morphine Protocol No. EN3174-004  
MDS Harris Project 19858

Figure 6  
Mean Plasma Morphine-6-G Concentrations (Linear Scale)



**Figure 7**  
**Mean Plasma Morphine Concentrations Versus Time**  
**Linear Scale**



**Figure 8**  
**Mean Plasma M-3-G Concentrations Versus Time**  
**Linear Scale**

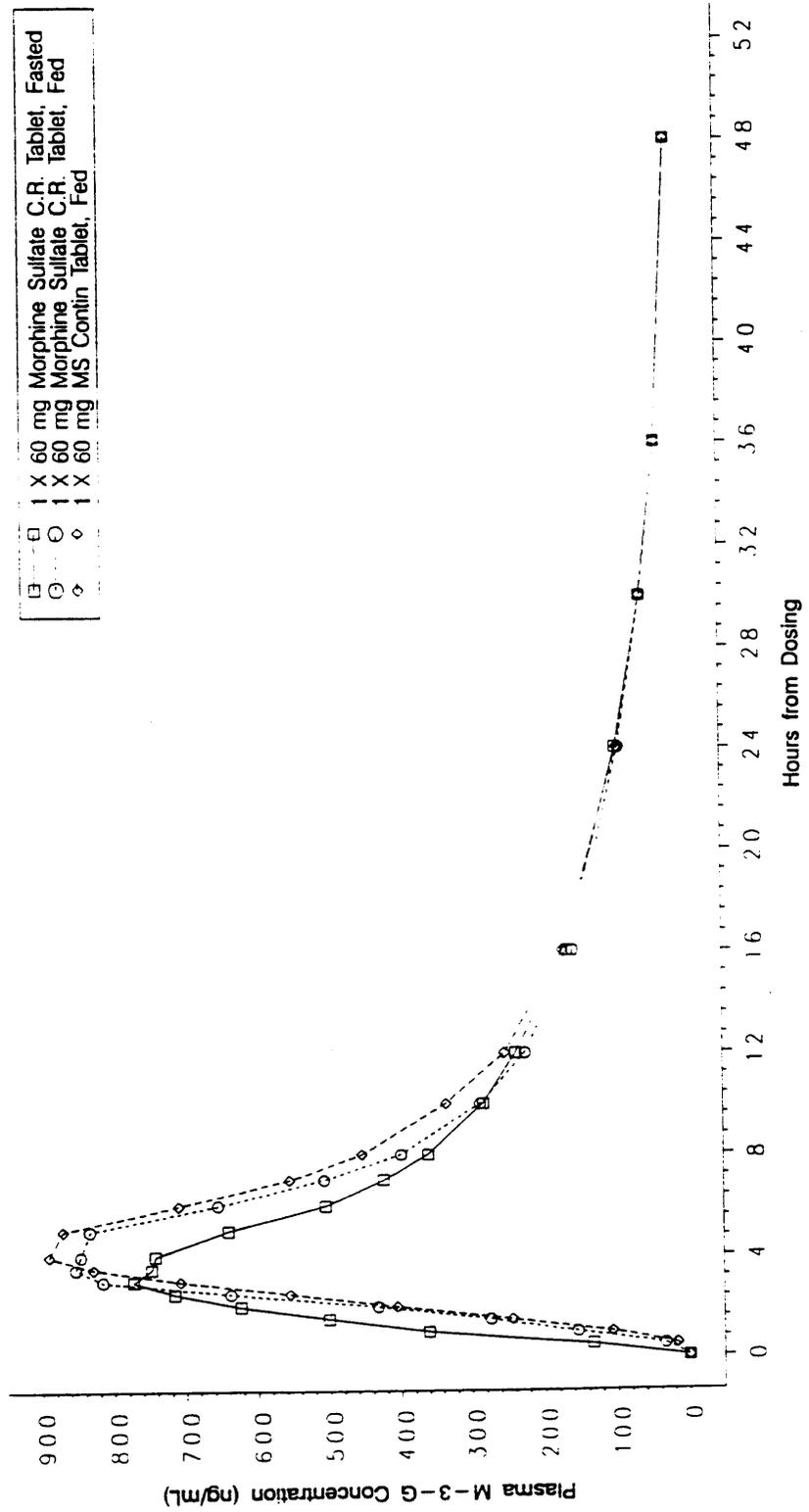


Figure 9  
 Mean Plasma Morphine Concentrations Versus Time (Linear Scale)

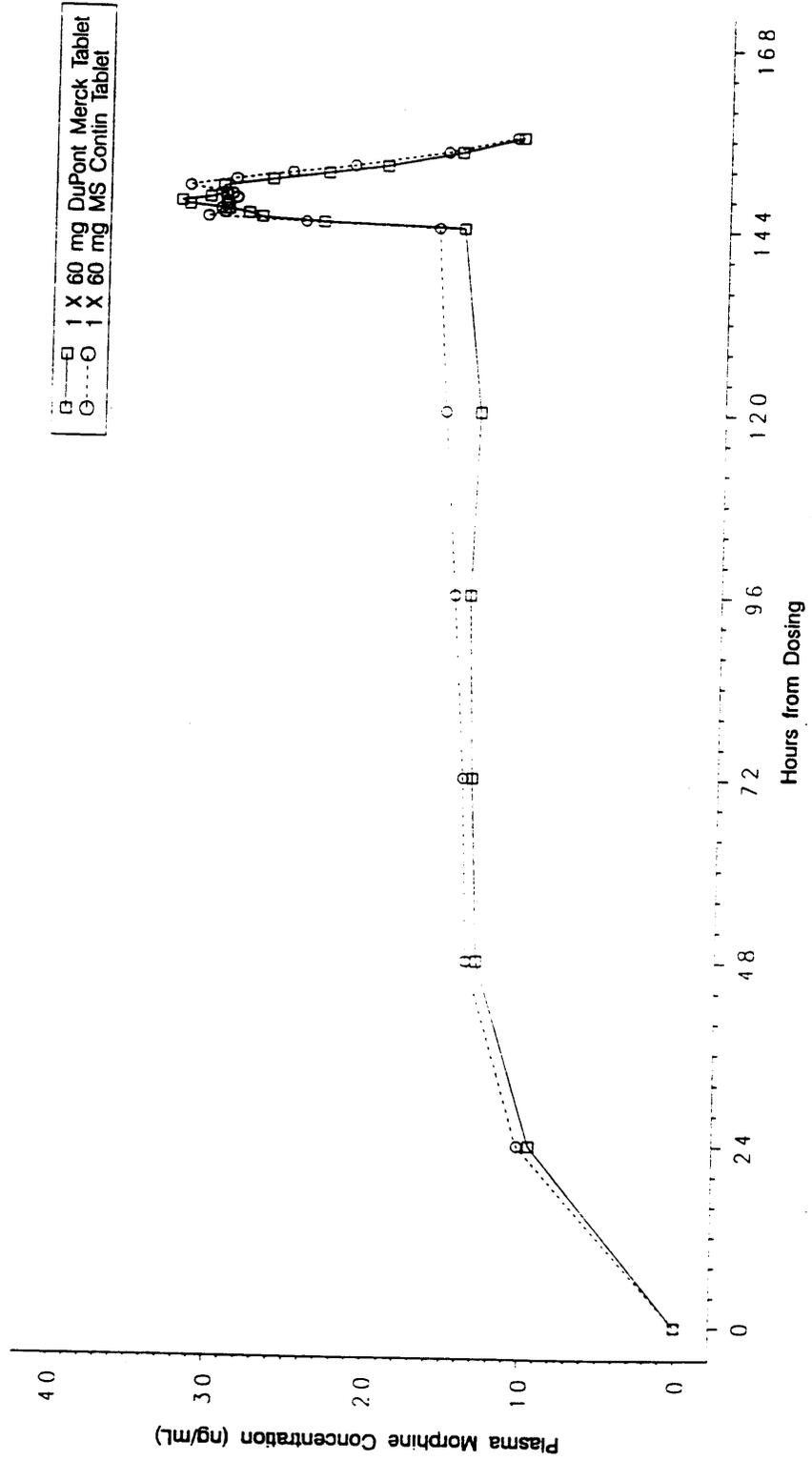
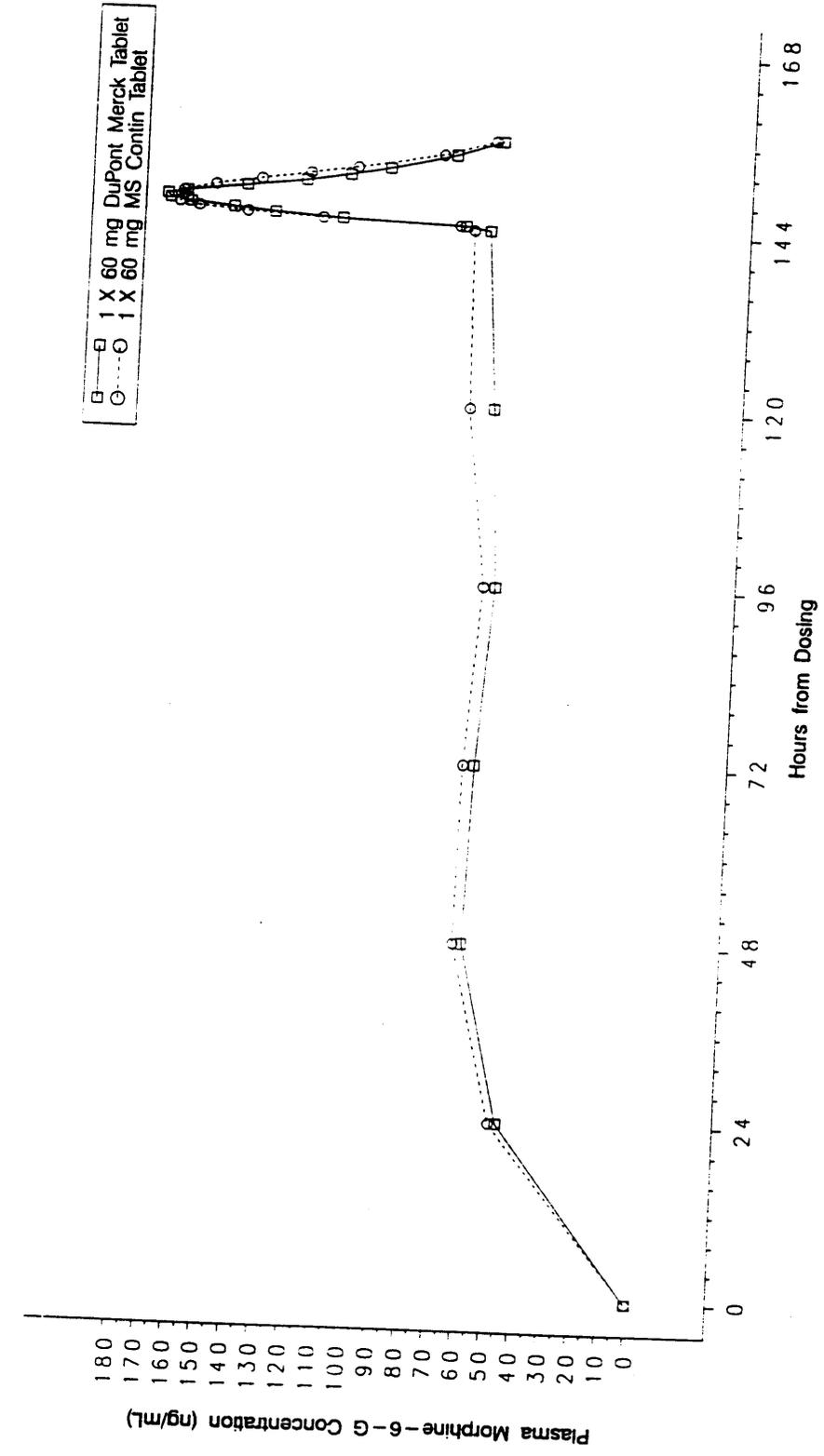


Figure 1C  
 Mean Plasma Morphine-6-G Concentrations Versus Time (Linear Scale)

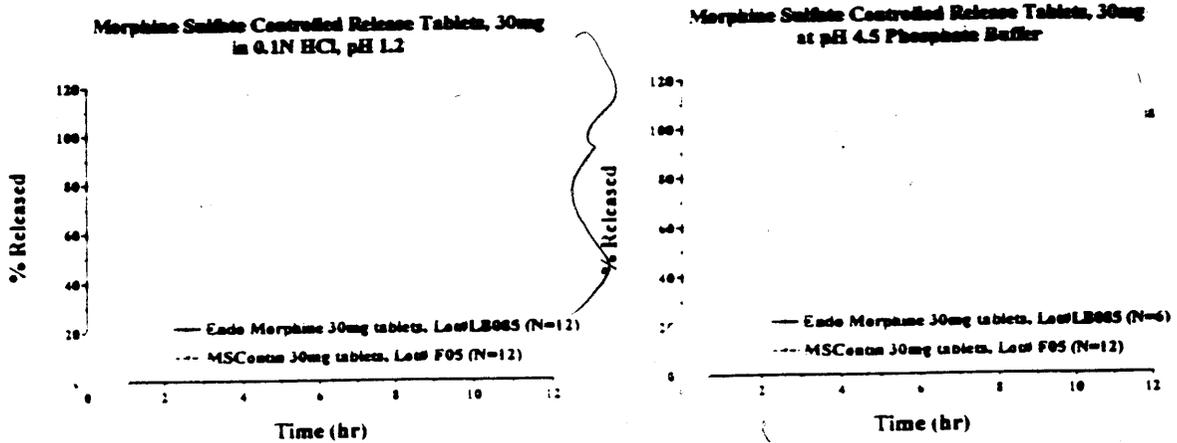


*Figure 11*  
**Endo Pharmaceuticals Inc.**

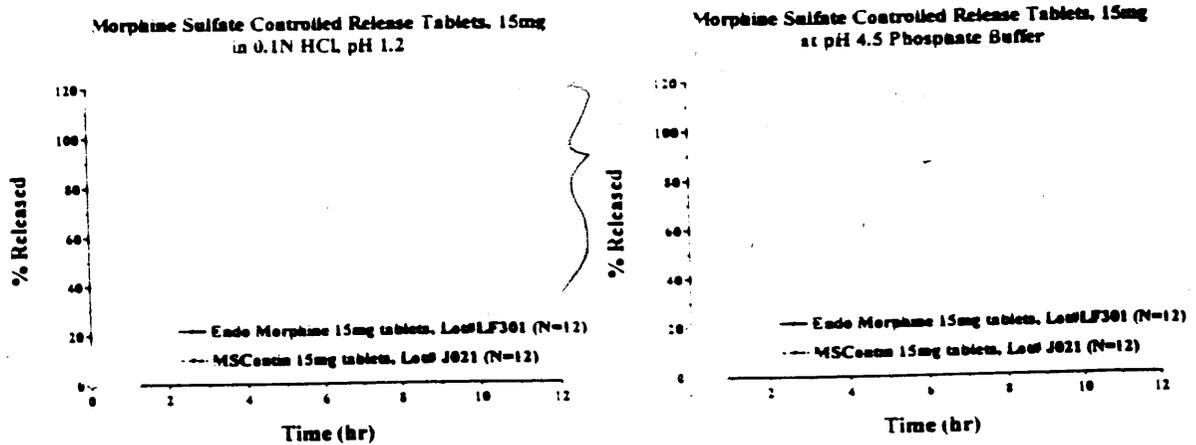
**COMPARISON OF ENDO TEST PRODUCT AND REFERENCE LISTED  
 PRODUCT REPORT  
 MORPHINE SULFATE CONTROLLED RELEASE TABLETS,  
 15 MG, 30 MG and 60 MG**

Document Number ENDO-0994-02

**Morphine Sulfate CR Tablets, 30mg Dissolution Comparison<sup>2</sup>**



**Morphine Sulfate CR Tablets, 15mg Dissolution Comparison<sup>3</sup>**



Reference: Endo tablets, EN0329-86; MSContin, EN0329-59  
 Reference: Endo tablets, EN0301-68; MSContin, EN0329-55

Figure 12  
Endo Pharmaceuticals Inc.

COMPARISON OF ENDO TEST PRODUCT AND REFERENCE LISTED  
PRODUCT REPORT  
MORPHINE SULFATE CONTROLLED RELEASE TABLETS,  
15 MG, 30 MG and 60 MG

Document Number ENDO-0994-02

INTRODUCTION

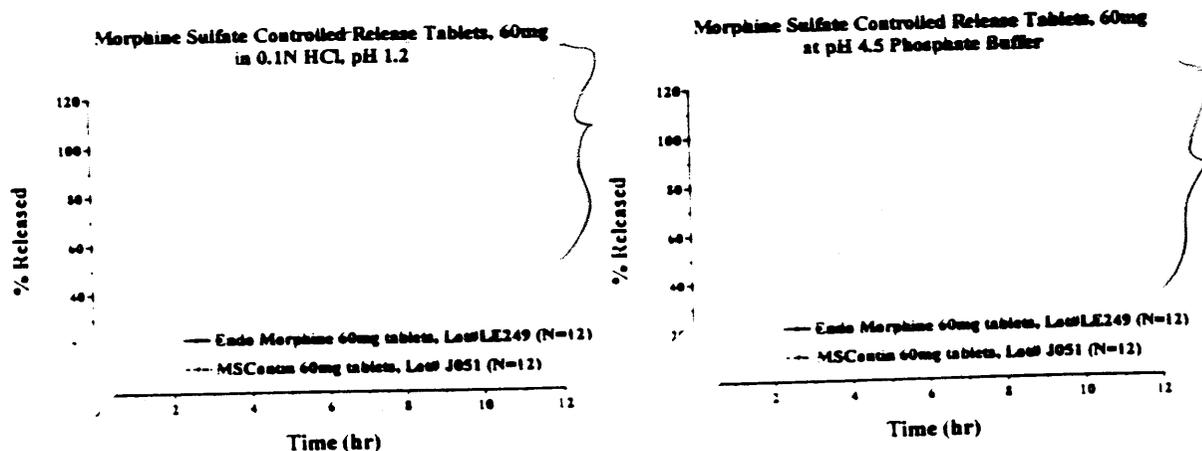
Bioequivalence studies were performed on Endo Morphine Sulfate CR tablets, 15 mg, 30mg, and 60 mg, and all three strengths are bioequivalent to the reference tablets.

RESULTS

Dissolution Profile

Dissolution comparison of Endo's exhibit batches to the Reference Listed Tablets was performed. Individual results are provided in Attachment I.

Morphine Sulfate CR Tablets, 60mg Dissolution Comparison<sup>1</sup>



APPEARS THIS WAY  
ON ORIGINAL

Reference: Endo tablets, EN0301-44; MSC Contin, EN0329-63

Figures 13

Figure 1 Morphine Sulfate CR Tablets, 15 mg, 30 mg and 60 mg Drug Release Profile in Purified Water

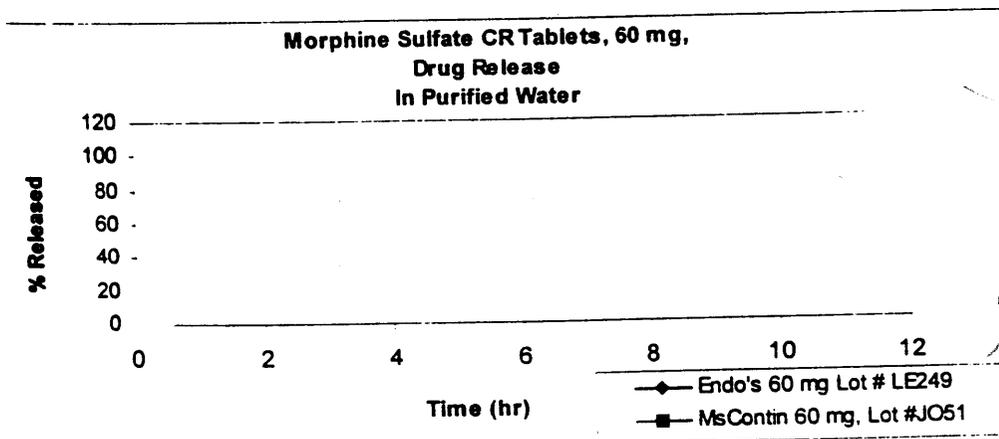
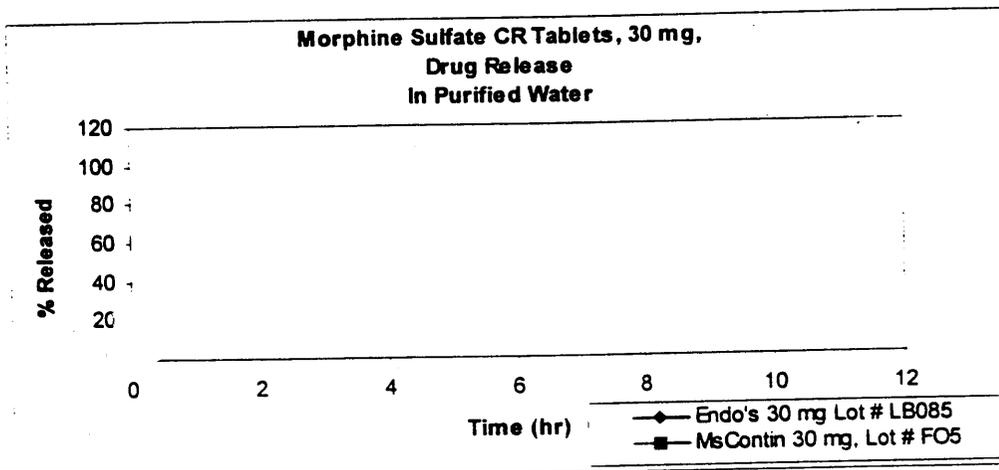
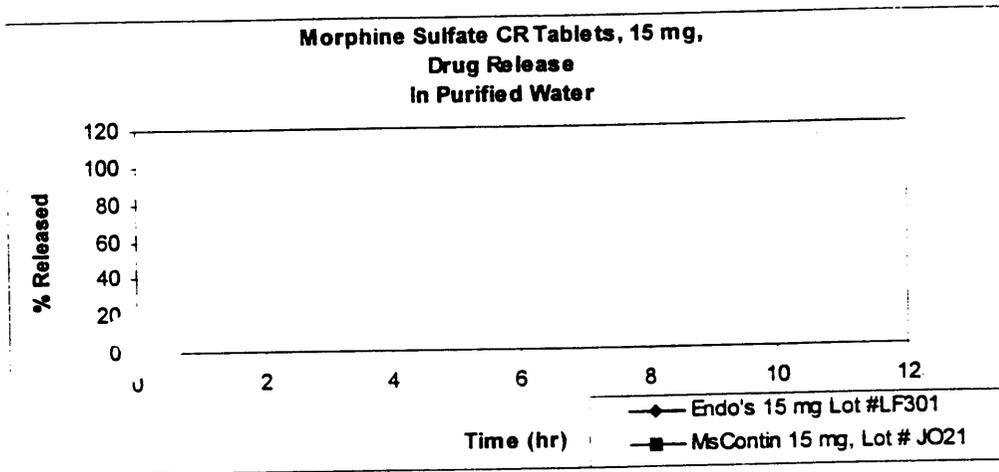
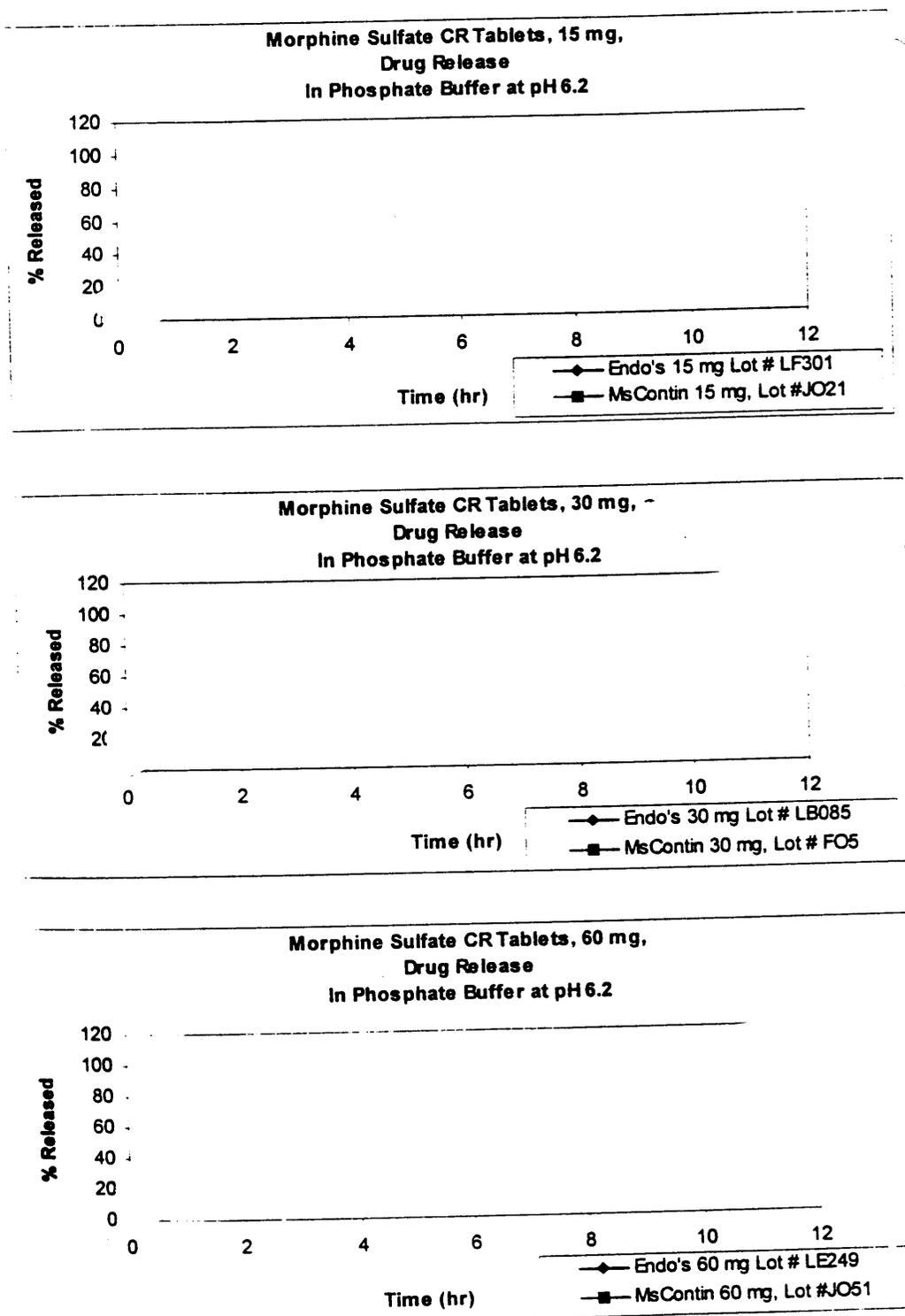
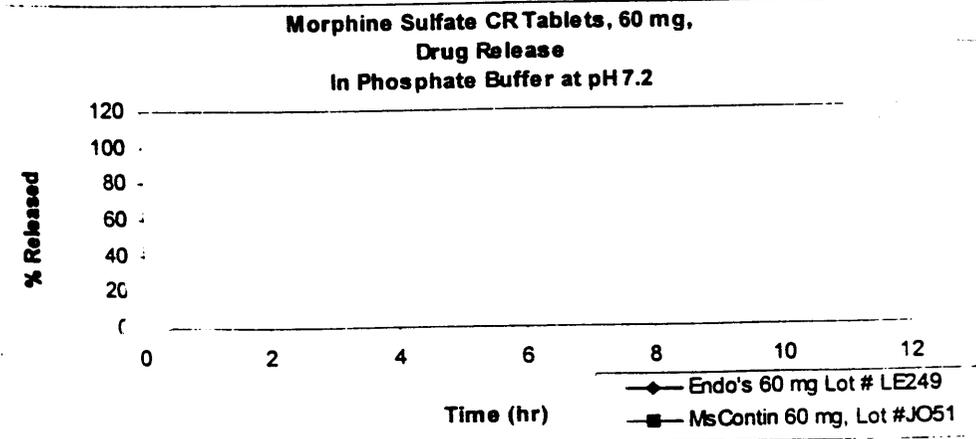
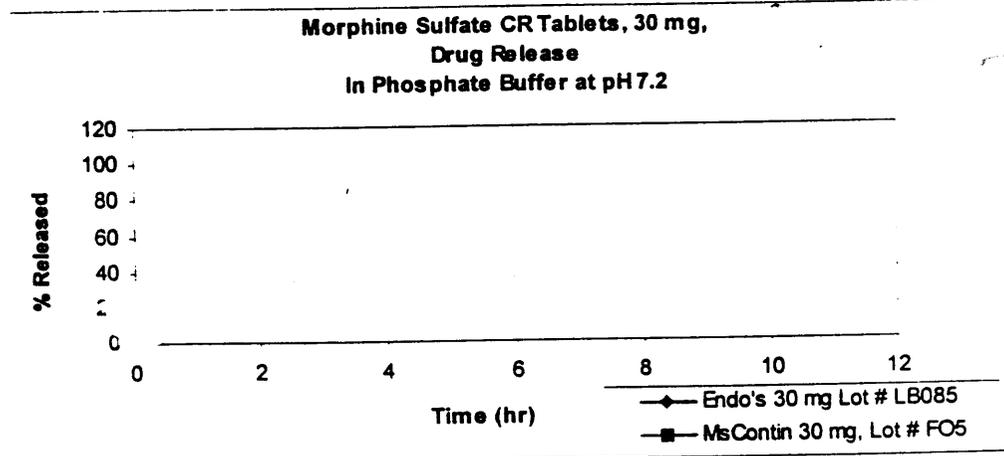
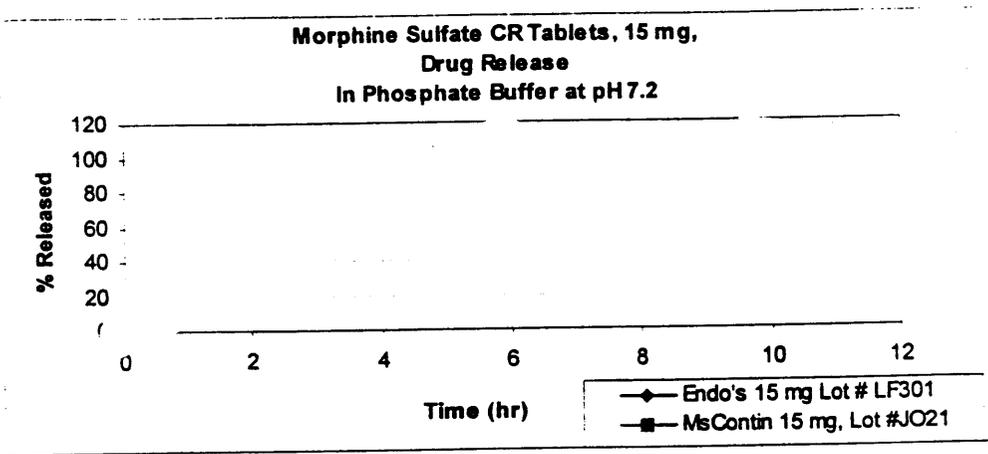


Figure 14 Morphine Sulfate CR Tablets, 15 mg, 30 mg and 60 mg Drug Release Profile in pH 6.2 Phosphate Buffer



**Figure 15 Morphine Sulfate CR Tablets, 15 mg, 30 mg and 60 mg Drug Release profile in pH 7.2 Phosphate Buffer**



**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

***75-295***

**ADMINISTRATIVE  
DOCUMENTS**

ANDA APPROVAL SUMMARY

ANDA: 75-295

DRUG PRODUCT: Morphine Sulfate

M:Endo Pharmaceuticals

DOSAGE FORM: Extended Release Tablet

STRENGTH: 15 mg, 30 mg and 60 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP certification is satisfactory (See Page 428 and 429).

EIR update : Acceptable on October 6, 1998.

BIO STUDY: Satisfactory.

Bioequivalence study of Morphine Sulfate Tablets, 15 mg lot# LF301, 30 mg lot#LB085 and 60 mg lot# LE249 are found acceptable. (see Bio. Review by S. Pradhan on June 24, 1998).

Bio. dissolution specification same as manufacturing:

Medium : 500 ml water, Apparatus II(paddle) at 50 rpm:

Time (hours)	Amount Dissolved
1	NLT <u>      </u> and NMT <u>      </u>
2	NLT <u>      </u> and NMT <u>      </u>
4	NLT <u>      </u> and NMT <u>      </u>
8	NLT <u>      </u>

LIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):  
is pending.

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

Containers used in the stability testing are the same as described in the container section.

Proposed market container/closures:

Strength	Tablet count	Bottle size	Cap/liner
15 mg	60	75cc	33mm cap, <u>                    </u> Liner
	500	150cc	38mm cap, <u>                    </u> Liner
30 mg	60	75cc	33mm cap, <u>                    </u> Liner
	500	150cc	38mm cap, <u>                    </u> Liner
60 mg	100	75cc	33mm cap, <u>                    </u> Liner
	500	300cc	53mm cap, <u>                    </u> Liner

Blister packaging: Withdrawn 10/5/98.

Each strength is packaged at 25 tablets per blister card (10 mil                      foil backing. (4 cards per carton).

**LABELING:**

Satisfactory per A. Vezza on 9-3-98.

**STERILIZATION VALIDATION (IF APPLICABLE):**

**SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):**

15 mg tablet	Lot # LF301	—	—	tablets
30 mg tablet	Lot # LB085	—	—	tablets
60 mg tablet	Lot # LE249	—	—	tablets

Firm's source of NDS OK : Yes (Mallinckrodt. DMF#5857).

**SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):**

15 mg tablet	Lot # LF301	—	—	tablets
30 mg tablet	Lot # LB085	—	—	tablets
60 mg tablet	Lot # LE249	—	—	tablets

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

15 mg tablet:	—	—	tablets)
30 mg tablet:	—	—	tablets)
60 mg tablet:	—	—	tablets)

Manufacturing process is the same as bio.stability.

viewer: S.Basaran

DATE:10/9/98

Team Leader: U.Venkataram

DATE:10/5/98

**IS!**  
**IS!**  
 10/9/98

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**75-295**

**CORRESPONDENCE**



October 5, 1998

**Endo Pharmaceuticals Inc.**

Douglas Sporn  
Director  
Office of Generic Drugs  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II, Room 150  
7500 Standish Place  
Rockville, MD 20855

**NO ORIGINAL AMENDMENT**

*N/A*

**Re: ANDA 75-295; Morphine Sulfate Extended-Release Tablets  
15 mg, 30 mg, 60 mg  
Telephone Amendment**

Dear: Mr. Sporn:

Reference is made to telephone conversations last week with Tim Aimes, Project Manager, regarding the status update of the subject application review.

The discussion centered around the need for an inspection of the auxiliary packaging site ( \_\_\_\_\_ ) for our proposed blister packaging. The manufacturing site and packaging of bottles of the exhibit batches was performed at DuPont Pharmaceuticals, Garden City, New York facility which was inspected in April 1998. Only the blistering operation was performed at the Puerto Rico facility.

Mr. Aimes indicated the inspection of the \_\_\_\_\_ facility was needed for approval of this application and the request for an inspection was submitted to FDA's San Juan District Office in February, 1998. This inspection has not yet been conducted.

In order not to delay approval of this application, Endo Pharmaceuticals Inc. hereby submits this amendment to officially withdraw the blister package only from the original ANDA. It is our understanding that the withdrawal now negates the need for an inspection of the \_\_\_\_\_ facility and the timing of the current review will not be impacted. As per a telephone conversation with Jerry Phillips today, we hereby commit to utilize the approved final printed package insert (6507-00/August, 1998) as submitted on September 1, 1998 with deletion of all reference to the blister package.

*Note: The package insert noted by C. Patterson as having been submitted on 9/1/98 was actually submitted on 8/31/98.*

**RECEIVED**

**OCT 06 1998**

**GENERIC DRUGS**

The following is our understanding of the status of the review of this application:

**Pre-Approval Inspection:** The Pre-Approval Inspection of the manufacturing facility, DuPont Pharmaceuticals, Garden City was performed in April 1998 and approved on April 30, 1998.

**Bioequivalence:** Approval was received on July 1, 1998.

**Labeling:** Final Printed Labeling was submitted on September 1, 1998 and verbal "approval" has been received. As indicated, we will delete all reference to the blister package in that insert.

**Chemistry, Manufacturing and Controls:** A facsimile amendment was submitted on September 24, 1998 and the review was completed and found satisfactory.

**Method Verification:** On September 28, 1998 samples were submitted to the Brooklyn District Laboratory. Unfortunately there was a delay in receipt of the September 1, 1998 letter requesting samples since that correspondence was erroneously sent to DuPont rather than Endo Pharmaceuticals Inc. Should there be any issues, we commit to resolving them with the Brooklyn District Laboratory.

It is our understanding that this information now completes all outstanding items and we now look forward to imminent approval of ANDA 75-295.

If there are any questions regarding this amendment, please contact me at (516) 522-3305.

Sincerely,

A handwritten signature in black ink, appearing to read 'Carol Patterson', with a long horizontal flourish extending to the right.

Carol Patterson, MS  
Manager, Regulatory Affairs.



September 24, 1998

**Endo Pharmaceuticals Inc.**

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II, Room 150  
7500 Standish Place  
Rockville, MD 20855

FA  
NDA OPIC AMENDMENT

**Re: ANDA 75-295; Morphine Sulfate Extended-Release Tablets  
15 mg, 30 mg and 60 mg  
Facsimile Amendment**

Dear Mr. Sporn:

Reference is made to your September 22, 1998 facsimile correspondence which describes chemistry, manufacturing and controls deficiencies in connection with our original application dated December 31, 1997 for the subject product.

We are amending this application with our responses to the Agency's comments. Included in this amendment are the following:

- Completed FDA Form 3439 and Addendum
- Field Copy Certification
- A copy of FDA's September 22, 1998 Facsimile Letter
- CMC Responses and updated stability data

It is our understanding that this amendment completes all outstanding chemistry, manufacturing and controls issues.

If there are any questions regarding this information, please contact me at (516) 522-3309.

**RECEIVED**

Sincerely,

SEP 25 1998

**GENERIC DRUGS** Andrew G. Clair, Ph.D.  
Director, Regulatory Affairs

attachments



**Endo Pharmaceuticals Inc.**

*Labeling Review  
Drafted 9/2/98*

September 1, 1998

~~REVIEW~~ COPY

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

FPL  
NDA ORIG AMENDMENT  
N/AF

**Re: ANDA 75-295; Morphine Sulfate Extended-Release Tablets  
15 mg, 30 mg and 60 mg  
MINOR AMENDMENT**

Dear Mr. Sporn:

Reference is made to the conversation on August 28, 1998 between Adolf Veza, FDA and Carol Patterson, Endo Pharmaceuticals Inc. with regards to the CII position on the labels of the above application.

As requested, we have revised the "overlay" position of the CII on the container and blister labels so that it now appears on the front panel, in prominent bold, black print. In addition, the word,        has been revised to read, "Tablet" on the unit dose blister cell.

Included in this submission are the following:

- FDA 3439 Form
- 12 copies of Final Printed Container Labels
- A side-by-side comparison of the revised container and blister labeling with the previous labeling submitted on August 24, 1998

It is our understanding that this amendment completes all outstanding issues on this application, and we now await the Agency's approval.

If there are any questions regarding this amendment, please contact me at (516) 522-3305.

Sincerely,

Carol Patterson, M.S.  
Manager, Regulatory Affairs

RECEIVED

Enclosures

SEP 01 1998

~~GENERIC DRUGS~~



**Endo Pharmaceuticals Inc.**

August 24, 1998

Review Copy

*Labeling review  
drafted 9/2/98*

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

**NDA ORIG AMENDMENT**

*N/AF*

**Re: ANDA 75-295; Morphine Sulfate Extended-Release Tablets  
15 mg, 30 mg and 60 mg  
MINOR AMENDMENT**

Dear Mr. Sporn:

Reference is made to the August 7, 1998 facsimile letter from the Division of Labeling and Program Support regarding labeling comments for the subject file.

We are amending the application with final printed container labeling which has been revised as per your comments.

Included in this submission are the following:

- Responses to each comment in the August 7, 1998 FDA facsimile letter
- 12 copies of the revised Package Insert
- 12 copies of Final Printed Container Labels
- A side-by-side comparison of the revised labeling with that previously submitted

It is our understanding that this amendment completes all outstanding issues on this application, and we now await the Agency's approval.

If there are any questions regarding this amendment, please contact me at (516) 522-3306.

Sincerely,

*Jeanne Stelter*

Jeanne Stelter  
Regulatory Associate

**RECEIVED**

**AUG 25 1998**

**GENERIC DRUGS**

Enclosures

JS:wj  
FDA-1998.doc



**Endo Pharmaceuticals Inc.**

July 30, 1998

ORIG AMENDMENT

M/AC

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II, Room 150  
7500 Standish Place  
Rockville, MD 20855

**Re: ANDA 75-295; Morphine Sulfate Controlled Release Tablets, USP  
15 mg, 30 mg and 60 mg  
Amendment**

Dear Mr. Sporn:

Reference is made to a telephone conversation with Tim Ames, Project Manager, FDA on July 27, 1998 regarding the subject product.

As per Mr. Ames request, we are providing our Finished Product Monograph that has been revised with the dissolution specifications and conditions outlined in a July 1, 1998 letter from the Division of Bioequivalence (a copy of the letter is enclosed).

In addition, based on FDA comments received in connection with other pending applications, we are providing revised post-approval stability protocols for the annual production lots which includes the 3-month and 9-month testing timepoints. The enclosed post-approval stability protocols are now consistent with the testing timepoints for our validation post-approval stability protocols.

Please note that a "true" copy of this amendment has been forwarded to Ms. Brenda Holman at the New York District Office.

If there are any questions regarding this amendment, please call me at (516) 522-3309.

Sincerely,

Andrew G. Clair, Ph.D.  
Director, Regulatory Affairs

RECEIVED  
JUL 31 1998  
GENERIC DRUGS  
attachments



**Endo Pharmaceuticals Inc.**

June 23, 1998

Dale P. Conner, Ph.D.  
Division Director  
Division of Bioequivalence  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Metro Park North II, Room E-130  
7500 Standish Place  
Rockville, MD 20855

**BIOAVAILABILITY**

**ORIG AMENDMENT**

*NAB*

**Re: Morphine Sulfate Extended-Release Tablets, 15 mg, 30 mg and 60 mg  
ANDA 75-295  
TELEPHONE AMENDMENT**

Dear Dr. Conner:

Reference is made to a telephone conversation on June 19 and 22, 1998 with Nancy Chamberlin regarding the subject file.

Ms. Chamberlin indicated the Division of Bioequivalence had two comments regarding our June 15, 1998 Telephone Amendment.

The comments as communicated to us and our responses are as follows:

**Comment 1**

Regarding the dissolution data submitted in three media: water, pH 6.2 phosphate buffer and pH 7.2 phosphate buffer, provide the volume used for each media.

**Response**

A volume of 500 ml of each of the three dissolution media (water, pH 6.2 phosphate buffer and pH 7.2 phosphate buffer) was used to obtain the dissolution comparison data submitted in Response 1 of the June 15, 1998 amendment.

**RECEIVED**

**JUN 24 1998**

**GENERIC DRUGS**

**Comment 2**

Please provide the start and finish date of sample analyses for all studies. In the June 15, 1998 amendment, the information referenced in Item #3 indicated the receipt date and extraction date for the sample analyses. To clarify, the start and finish date is the date of when the first sample and last sample were analyzed for each study (not the same as receipt date and extraction date).

**Response**

Attached please find a correspondence from \_\_\_\_\_, which provides the analysis dates (time frames for the instrumentation run times) for each of our biostudies, Protocol EN3174-004, -005, -007, -003 and -006. The analysis dates are provided for morphine and \_\_\_\_\_.

We trust these explanations are adequate and will allow the Division of Bioequivalence to finalize review and approve our biostudies in support of the subject file.

If you require additional explanations or need further assistance, please contact me at (516) 522-3309.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrew G. Clair". The signature is fluid and cursive, with a large initial "A" and "C".

Andrew G. Clair, Ph.D.  
Director, Regulatory Affairs



**Endo Pharmaceuticals Inc.**

June 15, 1998

BIOAVAILABILITY

ORIG AMENDMENT

N/AE

Dale P. Conner, Ph.D.  
Division Director  
Division of Bioequivalence  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Metro Park North II, Room E-130  
7500 Standish Place  
Rockville, MD 20855

**Re: Morphine Sulfate Extended-Release Tablets, 15 mg, 30 mg and 60 mg  
ANDA 75-295  
TELEPHONE AMENDMENT**

Dear Dr. Conner:

Reference is made to a telephone conversation on June 1, 1998 with Nancy Chamberlain regarding the subject drug.

Ms. Chamberlain indicated the Division of Bioequivalence had several comments regarding the biostudies submitted in support of the original referenced application, which was accepted for filing on December 31, 1997.

The comments as communicated to us and our responses are as follows:

**Comment 1**

Additional dissolution studies are required for our product and the reference listed drug (all three strengths) in:

- Purified water
- Phosphate buffer; pH 6.0 – 6.5
- Phosphate buffer; pH 7.0 – 7.5

Testing on 12 tablets each is required.

**Response**

Enclosed under Tab 1, "Dissolution" is a report which provides the results of an in-vitro dissolution comparison in three media (purified water, pH 6.2 phosphate buffer and pH 7.2 phosphate buffer) for our product and MS Contin Tablets.

The Similarity Factors ( $f_2$ ) confirm similar dissolution profiles between Endo's tablets and MS Contin.

**RECEIVED**

**JUN 16 1998**

**GENERIC DRUGS**

**Comment 2**

In each biostudy, the actual dosing dates for each period should be identified for each of the submitted studies.

**Response**

Please refer to the attached documentation from \_\_\_\_\_, and their June 3, 1998 cover letter.

Under Item 2 in their cover letter, they identify the location of the actual dosing dates from the 5 biostudy reports previously submitted.

For your convenience, we have provided the applicable report pages that document each dosing date.

This information is enclosed under Tab "Item 2".

**Comment 3**

In each biostudy, for morphine and \_\_\_\_\_ analysis, the actual start and finish date of sample analysis should be provided with the date of preparation of all QC samples.

**Response**

Please refer to the attached documentation from \_\_\_\_\_ and their June 3, 1998 cover letter.

Under Item 3 in their cover letter, they identify the location of the actual start and finish dates from the biostudy reports for these analyses.

For your convenience, we have provided the applicable report pages that document this information.

This information is enclosed under Tab "Item 3".

**Comment 4**

In the single dose 15 mg biostudy, 9 samples for subject 4 (Period 2; 3-16 hours) required repeated analysis due to samples out of order. Please explain. Also, the numbers obtained were very dissimilar (i.e., 747.23 vs. 210.52, 23.84 vs. 201.44, 19.89 vs. 155.73). Please explain these differences.

Please provide the original and repeat chromatograms and justification for repeating the analyses of the 9 morphine samples.

### **Response**

Please refer to the attached documentation from \_\_\_\_\_, and their June 3, 1998 cover letter.

Under Item 4 in their cover letter, they provide an explanation regarding their suspicion that samples from subject 4 were accidentally transferred to the injection vials in reverse order.

In addition, chromatograms for the assays and reassays are provided under the Item 4 Tab entitled, "Original Assays" and "Re-Assays".

### **Comment 5**

In the single dose 30 mg biostudy, 6 samples for subject 32 (Period 2 at 7-24 hours) required repeated analysis due to a processing error. The differences were greater than 50%. Please explain.

In the same study, subject 16 (Period 1 at 8 hours and Period 2 at 3.5 to 7 hours) required repeated analysis for the \_\_\_\_\_ due to samples being out of order. Please explain why the repeated analyses yielded such high differences and why the samples were out of order.

Fifteen analytical runs led to 11 being found unacceptable. Explain the reasons for acceptance or rejection of the analytical runs.

### **Response**

Please refer to the attached documentation from \_\_\_\_\_ and their June 3, 1998 cover letter.

Under Item 5 in their cover letter, they provide an explanation which documents analyst error in preparing internal standards for subject 32. In addition, for subject 16, reassay was necessary due to an internal standard failure rather than the sample being out of order. Furthermore, for subject 16, samples accidentally transferred to injection vials in reverse order led to reassay.

Lastly, \_\_\_\_\_ provides additional explanation regarding the 15 analytical runs and subsequent findings of acceptability.

We trust these explanations are adequate and will allow the Division of Bioequivalence to finalize review and approve our biostudies in support of the subject file.

If you require additional explanations or need further assistance, please contact me at (516) 522-3309.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrew G. Clair". The signature is fluid and cursive, with a large initial "A" and "C".

Andrew G. Clair, Ph.D.  
Director, Regulatory Affairs

attachments

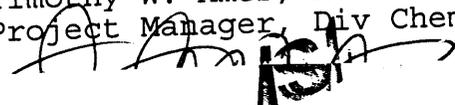
AGC.wj  
FDA-1998.doc

Telephone Conversation Memorandum

ANDA: 75-295  
DRUG: Morphine Sulfate Extended-release Tablets, 30 mg, 60mg  
and 90 mg  
FIRM: Endo Laboratories Inc.  
PERSONS INVOLVED: Andrew Clair, Endo  
Tim Ames, FDA  
PHONE NUMBER: 561-522-3309  
DATE: July 27, 1998

Firm called for status report and indicated that they had received from the Division of Bioequivalence a ~~no~~ further questions ~~letter~~ with the interim dissolution specs, which were different from their previous specs. This was news to me so I informed firm that they needed to incorporate the interim specs into their application. I instructed them to incorporate the new specs into the product release specifications and stability protocol and amend the application accordingly. Mr. Clair indicated he do this immediately.

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

  
cc: ANDA 75-295  
Division file (1)  
HFD-617/TAmes/PHONE.180

File: X:\new\firmam\endo\telecons\phone.180

Endo Pharmaceuticals Inc.  
Attention: Andrew G. Clair, Ph.D.  
500 Endo Blvd.  
Garden City, NY 11530



FEB 6 1998

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: Morphine Sulfate Extended-release Tablets,  
15 mg, 30 mg and 60 mg

DATE OF APPLICATION: December 30, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 31, 1997

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

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

Should you have questions concerning this application, contact:

Tim Ames  
Project Manager  
(301) 827-5849

Sincerely yours,

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



**Endo Pharmaceuticals Inc.**

December 30, 1997

505(j)(1) OK  
1/29/98  
/S/  
v J

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855

**RECEIVED**

DEC 31 1997

**Re: Original Abbreviated New Drug Application  
Morphine Sulfate Controlled Release Tablets  
15 mg, 30 mg and 60 mg**

**GENERIC DRUGS**

Dear Mr. Sporn:

Pursuant to 21 CFR 314.94 and Section 505(j) (1) of the Federal Food, Drug and Cosmetic Act, Endo Pharmaceuticals Inc. hereby submits this original Abbreviated New Drug Application for Morphine Sulfate Controlled Release Tablets 15 mg, 30 mg and 60 mg.

This ANDA consists of a total of fifty-one volumes which are being submitted in duplicate as archival and technical review copies.

To assist the Agency with their review, please note the application consists of the following items:

<b>TECHNICAL INFORMATION</b>	<b>VOLUME</b>	<b>CASE REPORT FORMS</b>
Chemistry, Manufacturing, Control and Labeling	1.1-1.4	-
Bioequivalence Product Information	1.5	-
15 mg Single-Dose Crossover Study (EN3174-006)	1.6-1.10	1.33-1.36
30 mg Single-Dose Crossover Study (EN3174-003-001)	1.11-1.14	1.37-1.40
60 mg Single-Dose Crossover Study (EN3174-004-001)	1.15-1.19	1.41-1.44
60 mg Single-Dose, Three-Way Crossover Study to Determine the Effects of Food on Bioavailability (EN3174-005)	1.20-1.25	1.45-1.47
60 mg Multiple-Dose, Two-Way Crossover Study to Evaluate Steady State Pharmacokinetics (EN3174-007)	1.26-1.32	1.48-1.51

You will note that throughout this application Morphine Sulfate Controlled Release Tablets is also referred to as EN3174.

Regarding the supportive bioequivalence studies, all five *in-vivo* investigations compared the Endo product to the reference product, MS Contin, manufactured by Purdue-Frederick.

As outlined in the September 9, 1993 Guidance for Oral Extended (Controlled) Release Dosage Forms *In-vivo* Bioequivalence and *In-Vitro* Dissolution Testing, the studies conducted included a multiple-dose, steady state two-period crossover study with the 60 mg strength, a single-dose three-way crossover food-effects study with the 60 mg strength and single-dose two-way crossover studies in the fasted state for all three strengths (15 mg, 30 mg and 60 mg). In comparison to the reference product, MS Contin, the Endo product was found:

- To meet the controlled release claim being made for it
- To not exhibit any dose-dumping effect
- To exhibit, as evidenced by the 90% confidence intervals meeting the 80-125% criteria for log-transformed AUCs and C<sub>max</sub>, equivalence between the reference product and the test products following the dosing to steady state and after single-dose administrations
- To be comparable in terms of the impact of food on *in-vivo* bioavailability

Based upon the literature and two pilot studies conducted in-house with the 30 mg strength in both single and multiple dose administrations, nausea and vomiting were the most prevalent adverse events observed. It was felt by our medical staff that the safety of the volunteers should not be compromised in the design of the pivotal studies. Therefore, a decision was made to pre-treat the volunteers in the 30 mg and 60 mg pivotal studies with naltrexone (ReVia, manufactured by DuPont Merck) to block the mu-opioid adverse effects associated with morphine doses. (This was also communicated to us in a letter dated March 19, 1997 from the Division of Bioequivalence). Although nausea and vomiting were still reported by some of the volunteers in these studies, the overall incidence was lower than expected. All subjects were pre-treated with naltrexone to screen out those volunteers who could not safely tolerate doses of naltrexone prior to receiving morphine.

In all five studies, plasma concentrations of free morphine and two morphine metabolites ( \_\_\_\_\_ ) were assayed. Free morphine and both metabolites were found to be equivalent based on meeting the 90% confidence interval criteria for 80-125% for the log-transformed AUCs and Cmax, between the test and reference products in all five studies.

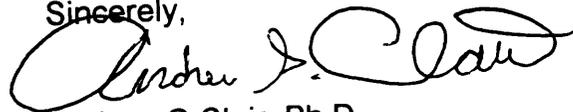
We also wish to bring to the Agency's attention that while the 15 mg and 30 mg finished product were entirely packaged into marketed containers, the 60 mg tablets were partially packaged in accordance with the Office of Generic Drug Policy and Procedure Guide #41-95. This information is outlined in Volume 1.2, page 530.

Endo Pharmaceuticals Inc. is an independent, stand-alone company formed from the recent business divestiture of Endo Laboratories, L.L.C. (formerly a subsidiary of The DuPont Merck Pharmaceutical Company). As a result, The DuPont Merck Pharmaceutical Company functions as a contract firm for Endo Pharmaceuticals Inc. and this information is outlined throughout this application.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the application provision of 19 U.S.C. Section 331(j).

If there are any questions regarding this application, they may be directed to me at (516) 522-3309.

Sincerely,



Andrew G. Clair, Ph.D.  
Director, Regulatory Affairs