CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-656

Generic Name: Morphine Sulfate Extended-Release Tablets, 100mg

Sponsor: Watson Laboratories, Inc.

Approval Dates: January 30, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-656

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APPROVAL LETTER

ANDA 75-656

JAN 30 2001

Watson Laboratories, Inc.
Attention: Ernest Lengle, Ph.D.
311 Bonnie Circle
Corona, CA 92880

Dear Sir:

Reference is made to your abbreviated new drug application dated June 28, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Morphine Sulfate Extended-release Tablets, 100 mg.

Reference is also made to your amendments dated February 14, and November 16, 2000.

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, 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (MS Contin® Controlled-release Tablets of the 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 specifications are as follows:

Dissolution testing should be conducted in 900 mL of water at 37°C using apparatus 1 (Basket) at 50 RPM. The test product should meet the following "interim" dissolution specifications:

Sampling Time	Percent Dissolved
[redacted]	NLT [redacted] and NMT [redacted]
[redacted]	NLT [redacted] and NMT [redacted]
[redacted]	NLT [redacted]

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected 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 information should be submitted in the form of a Prior Approval Supplement.

Under section 505(A) of the Act, 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 that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Sincerely yours,

/S/

1/30/2001

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-656

Final Printed Labeling

MORPHINE SULFATE EXTENDED-RELEASE TABLETS
Rx only

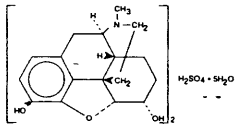
C II

JAN 30 2001

Morphine Sulfate Extended-release Tablets, 100 mg

DESCRIPTION

Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate and has the following structural formula:



APPROVED

Molecular Formula: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4$ Molecular Weight: 668.76

The molecular formula and molecular weight are based on the "anhydrous" form of the drug product.
Each tablet, for oral administration contains 100 mg of morphine sulfate USP. In addition, each tablet contains the following inactive ingredients: Cetostearyl alcohol, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate, polyethylene glycol, polysorbate 80, synthetic black iron oxide, talc and titanium dioxide.

CLINICAL PHARMACOLOGY

Metabolism and pharmacokinetics
Morphine sulfate extended-release tablets are controlled-release tablets containing morphine sulfate. Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is a controlled release or a conventional formulation. Morphine is released from morphine sulfate extended-release 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 that 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 (Vd) 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_a). The formulation employed in morphine sulfate extended-release has not been shown to affect morphine's oral bioavailability, but does decrease its apparent K_a. Other basic pharmacokinetic parameters (e.g., volume of distribution [Vd], elimination rate constant [K_e], 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 morphine sulfate extended-release 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_{ss}) 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_{max}) and minimum (C_{min}) 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 narcotic 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-naive individuals. Dosages of morphine should be chosen and must be titrated on the basis 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 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 $[C_{max}\text{-}C_{min}]/[C_{ss}\text{-average}]$.) 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 a controlled release oral morphine formulation indicated for the relief of moderate to severe pain. They are 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 is contraindicated in patients with known hypersensitivity to the drug, in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

Morphine sulfate extended-release is 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

as great (or greater) than the appropriate dose for opioid-naive individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

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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, 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 may produce orthostatic hypotension in ambulatory patients.

Morphine sulfate extended-release, 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, 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 controlled-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 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.

Selection of patients for treatment with morphine sulfate extended-release 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 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 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 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 abused and should be handled accordingly.

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, 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 extended-release 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 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 from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

Labor and Delivery
Morphine sulfate extended-release is 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 narcotic antagonist, naloxone, should be available for reversal of narcotic-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 extended-release is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving morphine sulfate extended-release since morphine may be excreted in the milk.

Pediatric Use
Use of morphine sulfate extended-release 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 narcotic 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 narcotic 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 narcotic-tolerant cancer patients, the administration of morphine sulfate extended-release 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 is abruptly discontinued, a moderate to severe abstinence syndrome may occur. The opioid agonist abstinence syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep or "yen" 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 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 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. In such cases, an abrupt or complete reversal of narcotic 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 a narcotic 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 of 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 controlled-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 q12h 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

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

4

DOSAGE AND ADMINISTRATION

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

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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 controlled-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 q12h 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 tablet should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. The 30 mg tablet strength is 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, the 30 mg tablet strength is 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 systematic evidence bearing on these types 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 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 a controlled-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. morphine sulfate extended-release tablets are a controlled-release formulation; it does not release morphine continuously over the dosing interval.)

For patients with low daily morphine requirements, the 15 mg tablet should be used.

Conversion from Morphine Sulfate Extended-release Tablets to Parenteral Opioids:
When converting a patient from morphine sulfate extended-release 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 sulfate for IM use, one could employ a conversion of 1 mg of morphine sulfate IM for every 6 mg of morphine sulfate 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, 100 mg are gray, round standard cup film coated tablets, debossed "WATSON" over "617" on one side and plain on the other side. They are available as:

SIZE	WATSON NDC NUMBER
100	52544-617-01
500	52544-617-05

Store at controlled room temperature, 15°C-30°C (59°F-86°F). [See USP].
Dispense in a tight, light-resistant container as defined in the USP.

DEA order form required.

Watson Laboratories, Inc.
Corona, CA 92880

Revised: October 2000

NDC 52544-617-01

WATSON LABORATORIES, INC.

MORPHINE SULFATE EXTENDED-RELEASE TABLETS C II

100 mg

Rx only

100 TABLETS

30 · 2001

Each Tablet Contains:
Morphine sulfate, USP.....100 mg

USUAL DOSAGE:
Read accompanying prescribing literature.
Swallow tablets whole. Do not break, crush or chew.

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

Store at controlled room temperature, 15°C-30°C (59°F-86°F). [See USP].

DEA ORDER FORM REQUIRED.

WATSON LABORATORIES, INC.
Corona, CA 92880

N 3 52544-617-01 6

Lot No.:

Exp.:

APPROVED

NDC 52544-617-05

WATSON LABORATORIES, INC.

MORPHINE SULFATE EXTENDED-RELEASE TABLETS C II

100 mg

Rx only

500 TABLETS

APPROVED

Each Tablet Contains:
Morphine sulfate, USP.....100 mg

USUAL DOSAGE:
Read accompanying prescribing literature.
Swallow tablets whole. Do not break, crush or chew.

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

Store at controlled room temperature, 15°C-30°C (59°F-86°F). [See USP].

DEA ORDER FORM REQUIRED.

WATSON LABORATORIES, INC.
Corona, CA 92880

N 3 52544-617-05 4

Lot No.: MAY 30 2001

Exp.:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-656

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

Wtm9902.004

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75656

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc. (Miami)
16600 NW 54th Ave.
Miami, FL 33014

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MS Contin
Innovator Company: Purdue Frederick
All patents and exclusivities for the drug substance, drug product, dosing schedule, use, and indications have expired.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Morphine Sulfate Tablets CR, 100 mg

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

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
06/28/99	original

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablet; Oral

14. POTENCY
100 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

8/2/99	Receipt acknowledged (Acceptable for filing 6/29/99)
9/15/99	Labeling review #1 (C. Park)
10/19/99	Bioequivalence review #1 (S.P. Shrivastava)

17. COMMENTS
Deficiencies were identified as follows:

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS
The application is deficient and is not recommended for approval. The response to all deficiencies will be considered a MAJOR amendment.

19. REVIEWER:
Mayra L. Piñeiro-Sánchez, Ph.D.

DATE COMPLETED:
December 17, 1999

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

Wtm9902.004

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-656

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc. (Miami)
Attention: Ernest Lengle, Ph.D.
311 Bonnie Circle
Corona, CA 92880

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MS Contin
Innovator Company: Purdue Frederick
All patents and exclusivities for the drug substance, drug product, dosing schedule, use, and indications have expired.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Morphine Sulfate Tablets CR, 100 mg

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

9. AMENDMENTS AND OTHER DATES:
Firm:
June 28, 1999 - Original submission
August 19,1999 - Additional Amendment
February 14,2000 - Bio Amendment
May 4, 2000 - Major amendment (subject of this review)

FDA:
February 7, 2000 - Deficiency letter

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablet; Oral

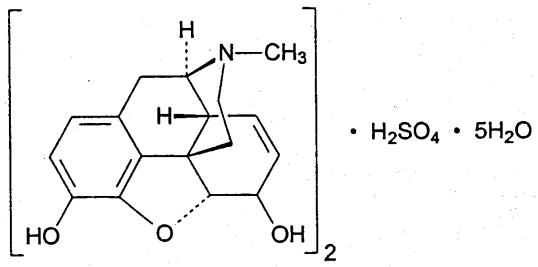
14. POTENCY
100 mg

15. CHEMICAL NAME AND STRUCTURE

Morphine Sulfate.

Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5α,6α)-, sulfate (2:1) (salt), pentahydrate.

$(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$. M.W. = [redacted] CAS No. 6211-15-0.



16. RECORDS AND REPORTS

8/2/99	Receipt acknowledged (Acceptable for filing 6/29/99)
9/15/99	Labeling review #1 (C. Park)
10/19/99	Bioequivalence review #1 (S.P. Shrivastava)
12/17/99	Chemistry Review #1 (M. Piñeiro-Sánchez)

17. COMMENTS

Deficiencies were identified as follows:

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

The application is deficient and is not recommended for approval. The response to all deficiencies will be considered a MINOR amendment.

19. REVIEWER: Mayra L. Piñeiro-Sánchez, Ph.D.

DATE COMPLETED: **August 15, 2000**

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

Wtm9902.004

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 75-656

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc. (Miami)
Attention: Ernest Lengle, Ph.D.
311 Bonnie Circle
Corona, CA 92880

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: MS Contin
Innovator Company: Purdue Frederick
All patents and exclusivities for the drug substance, drug product, dosing schedule, use, and indications have expired.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Morphine Sulfate Tablets CR, 100 mg

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

9. AMENDMENTS AND OTHER DATES:
Firm:
June 28, 1999 - Original submission
August 19,1999 - Additional Amendment
February 14,2000 - Bio Amendment
May 4, 2000 - Major amendment
November 16, 2000 - Minor amendment (subject of this review)

FDA:
February 7, 2000 - Deficiency letter (Chemistry Major)
October 6, 2000 - Deficiency letter (Chemistry Minor)

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablet; Oral

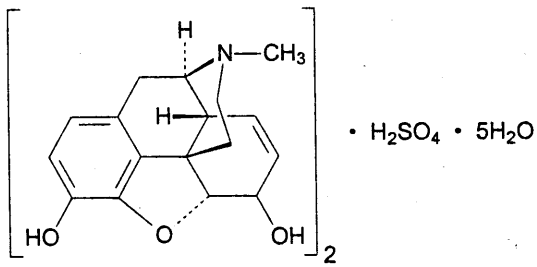
14. POTENCY
100 mg

15. CHEMICAL NAME AND STRUCTURE

Morphine Sulfate.

Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5α,6α)-, sulfate (2:1) (salt), pentahydrate.

$(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$. M.W. = [redacted]. CAS No. 6211-15-0.



16. RECORDS AND REPORTS

8/2/99	Receipt acknowledged (Acceptable for filing 6/29/99)
9/15/99	Labeling review #1 (C. Park)
10/19/99	Bioequivalence review #1 (S.P. Shrivastava)
12/17/99	Chemistry Review #1 (M. Piñeiro-Sánchez)
5/5/00	Bioequivalence review #2 (S.P. Shrivastava)
8/15/00	Chemistry Review #2 (M. Piñeiro-Sánchez)

10/5/00	Labeling review #2 (C. Park)
11/30/00	Labeling review #3 (C. Park)

17. COMMENTS
All deficiencies have been addressed satisfactorily.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval.

19. REVIEWER:
Mayra L. Piñeiro-Sánchez, Ph.D.

DATE COMPLETED:
January 16, 2001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-656

BIOEQUIVALENCE REVIEW

Morphine Sulfate CR 100 mg Tablets
ANDA #75-656
Reviewer: S. P. Shrivastava
File Name:75656o.200

Watson Laboratories, Inc.
Miami, FL
Submission Date:
February 14, 2000
~~**April 10, 2000**~~

REVIEW OF AN AMENDMENT

The firm had submitted single-dose fasting, single-dose non-fasting and multiple-dose studies for its morphine sulfate CR 100 mg tablets (see review by SShrivastava, 11/16/99). The reviewer cited a few deficiencies. The firm responded to the deficiencies (2/14/00). However, one of the files, WTM99023.hai, provided on the diskette could not be read. The firm was requested to submit another copy. The firm provided the second copy (April 10, 2000) of the old data, which was not the updated (with C_{min}, C_{ave}, DF, etc.). Finally, the updated file (2/14/00) was partially recovered. The remaining data/errors were entered/corrected by the reviewer from the hard copy.

1. **Deficiency:** *It is not clear why most of the repeat analyses showed lower concentration than the first analysis for morphine and morphine-6-glucuronide. You should provide some explanation.*

   Response: The firm acknowledges, that in general, results of the repeat analyses are lower than the original. However, those values were over the highest standard curve calibrator, and could not be deemed reliable. Samples were diluted and re-analyzed according to SOP.

   Reviewer's Comment: The response is acceptable.

2. **Deficiency:** *In the fasting study, the reason for repeat analysis for Subject #11, Period 2, 3.5 hr. sample for morphine is labeled "Over the highest calibration standard" even though the result from the first analysis shows a concentration of ——— The highest calibration standard in this case is ——— You should make appropriate corrections and provide necessary explanation.*

   Response: This was a typographical error. The value should read ——— The error has been corrected. This change is in the original data, and does not need any correction in the final data.

   Reviewer's Comment: The explanation is acceptable.

3. **Deficiency:** *In non-fasting study, the reason for repeat analysis for Subject #11, Period 3, 48 hr. sample for morphine is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows a concentration of ——— The highest calibration standard in this case is ——— Similarly, reason for repeat analysis for Subject #14, Period 1, 36 hr. sample for morphine-6-glucuronide is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows*

*a concentration of "Below the Limit of Quantitation (2 ng or code " * "). You should make appropriate corrections and provide necessary explanation.*

Response: This was a typographical error. The error has been corrected. The change is in the original data, and does not need any correction in the final data.

Reviewer's Comment: The explanation is acceptable.

4. **Deficiency:** *In the fasting study, the subjects were dosed in two Groups. The firm should evaluate any Group effects on PK parameters, and include the Group term in the model:*

*Model (Y) = Group Sequence Group*Sequence Subject(Group*Sequence) Period Period*Group Treatment Group*Treatment*

Response: Statistical analyses have been repeated using the suggested model, and revised summary tables and ANOVA output is provided. There are no group effects on PK parameters.

Reviewer's Comment: The single-dose fasting study is acceptable.

5. **Deficiency:** *You have not provided C_{min}, C_{ave} and Degree of Fluctuation (DF) data on the EVA electronic data files or diskette. These values should be entered with PK parameters for proper evaluation.*

Response: The firm has provided the requested PK data on diskette.

Reviewer's Comment: Plasma profiles for test and reference products for morphine sulfate and 6-glucuronide metabolite are given in Fig P-1 and P-2 and Tables 1 and 5. Mean PK parameter values are given in Tables 2-4 and 6-8.

The product meets the 90% CI criteria of 80-125 for LAUC and LC_{max} PK parameters (Tables 4, 8).

6. **Deficiency:** *You should evaluate C_{min} values, obtained at 120, 144 and 156 hrs. sampling time points.*

Response: For C_{min} values, the firm has followed the 1993 Guidance on, "Oral Extended (Controlled) Release Dosage Forms *in vivo* bioequivalence and *in vitro* Dissolution Testing", and has evaluated trough levels from at least three samples collected at the same time of the day on three consecutive days.

Reviewer's Comment: The submitted C_{min} data are acceptable.

FIG P—1. PLASMA MORPHINE SULFATE LEVELS (N= 45)

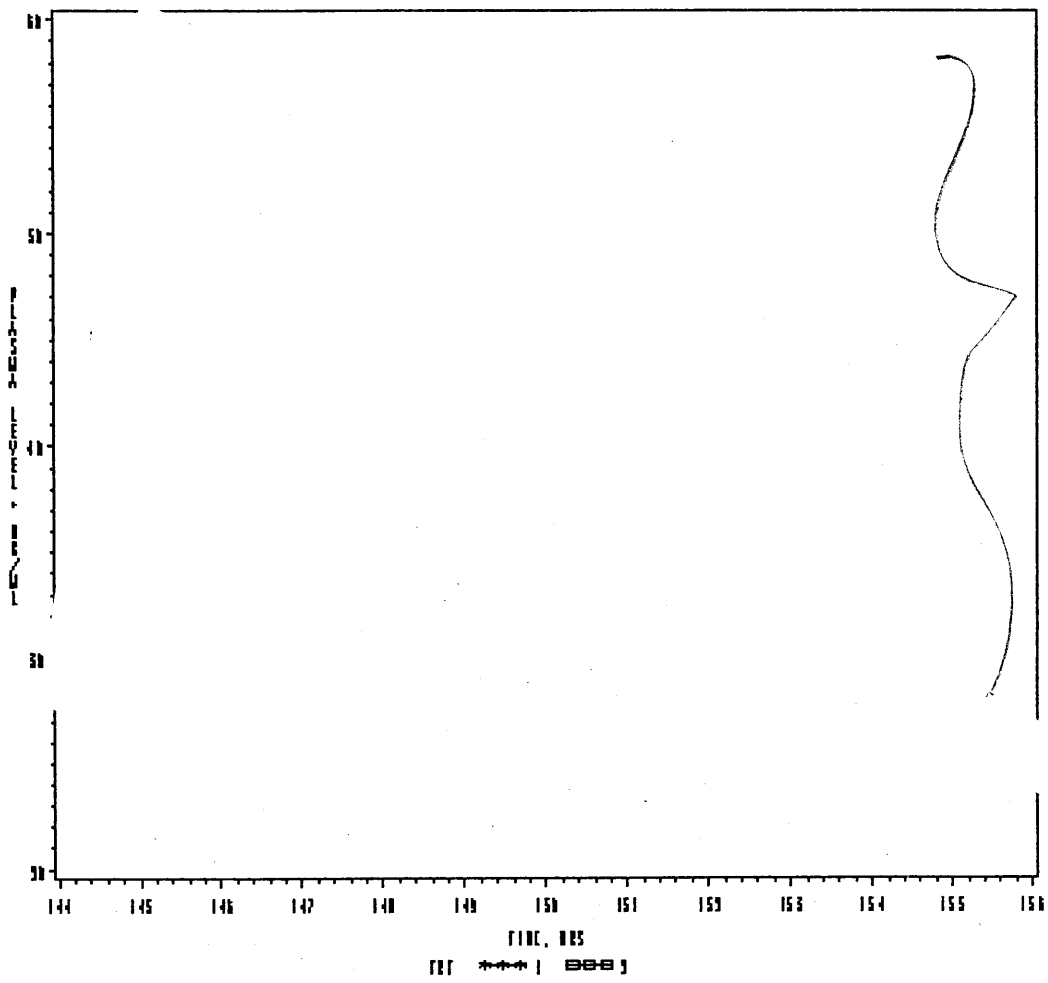

TABLE 1. MEAN PLASMA MORPHINE SULFATE LEVELS FOR TEST AND REFERENCE PRODUCTS

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
144	30.85,	9.24,	28.07,	7.68,	1.10,
144.5	45.26,	12.59,	41.82,	11.23,	1.08,
145	52.22,	14.98,	49.35,	14.21,	1.06,
145.5	55.33,	17.39,	52.10,	14.52,	1.06,
146	57.04,	18.92,	56.95,	13.88,	1.00,
146.5	57.31,	17.92,	55.38,	13.17,	1.03,
147	58.45,	19.01,	54.00,	13.63,	1.08,
147.5	57.18,	17.90,	53.45,	14.46,	1.07,
148	54.38,	16.56,	51.34,	13.51,	1.06,
149	53.37,	15.90,	51.68,	12.87,	1.03,
150	47.01,	16.41,	43.72,	12.40,	1.08,
151	40.61,	13.18,	39.55,	12.52,	1.03,
152	35.74,	11.29,	35.29,	10.68,	1.01,
154	31.01,	9.92,	29.64,	9.86,	1.05,
156	24.29,	8.34,	25.98,	8.15,	0.94,

MEAN1=TEST, MEAN2=REF, RMEAN12=MEAN1/MEAN2; UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 2. ARITHMETIC MEANS AND RATIOS

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	520.80,	146.28,	500.19,	122.57,	1.04,
CAVG	43.40,	12.19,	41.68,	10.21,	1.04,
CMAX	64.32,	18.94,	62.66,	13.67,	1.03,
CMIN	23.41,	7.89,	23.08,	7.70,	1.01,
FLUC1	0.94,	0.18,	0.95,	0.21,	0.99,
LAUCT	498.57,	0.31,	485.84,	0.25,	1.03,
LCAVG	41.55,	0.31,	40.49,	0.25,	1.03,
LCMAX	61.36,	0.33,	61.16,	0.23,	1.00,
LCMIN	22.02,	0.37,	22.57,	0.31,	0.98,
LFLUC1	0.93,	0.19,	0.93,	0.21,	0.99,
LTMAX	146.67,	0.01,	146.82,	0.01,	1.00,
TMAX	146.67,	1.26,	146.83,	1.96,	1.00,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

TABLE 3 LSMEANS AND RATIOS

PARAMETER	LSM1	LSM2	RLSM12
AUCT	519.20,	498.66,	1.04,
CAVG	43.27,	41.55,	1.04,
CMAX	64.15,	62.57,	1.03,
CMIN	22.88,	23.08,	0.99,
FLUC1	0.94,	0.96,	0.99,
LAUCT	497.09,	485.01,	1.02,
LCAVG	41.42,	40.42,	1.02,
LCMAX	61.19,	61.19,	1.00,
LCMIN	21.97,	22.54,	0.97,
LFLUC1	0.93,	0.94,	0.99,
LTMAX	146.82,	146.80,	1.00,
TMAX	146.83,	146.81,	1.00,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

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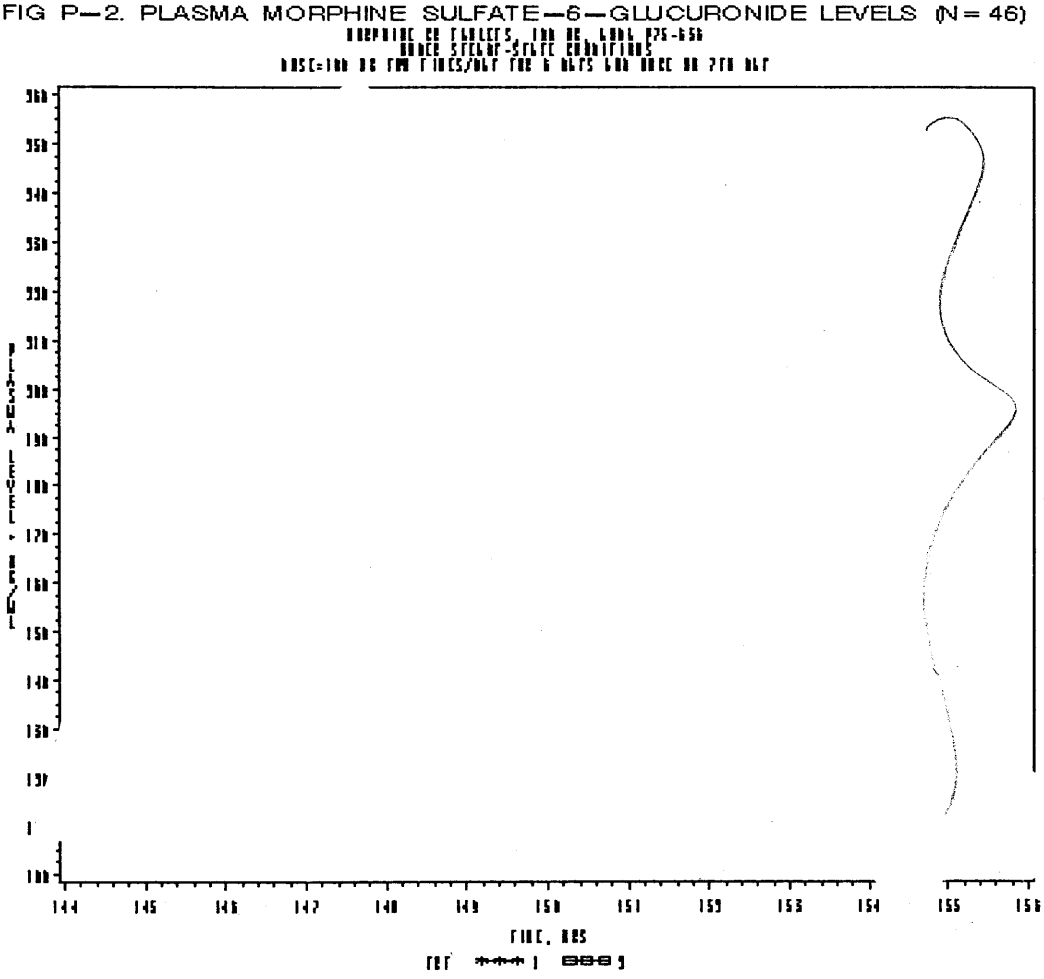
TABLE 4. LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCT	519.20,	498.66,	99.43,	108.80,
CAVG	43.27,	41.55,	99.43,	108.80,
CMAX	64.15,	62.57,	96.98,	108.09,
CMIN	22.88,	23.08,	93.52,	104.67,
FLUC1	0.94,	0.96,	93.08,	104.13,
LAUCT	497.09,	485.01,	97.09,	108.19,
LCAVG	41.42,	40.42,	97.09,	108.19,
LCMAX	61.19,	61.19,	94.11,	106.28,
LCMIN	21.97,	22.54,	91.11,	104.28,
LFLUC1	0.93,	0.94,	93.82,	104.67,
LTMAX	146.82,	146.80,	99.75,	100.27,
TMAX	146.83,	146.81,	99.75,	100.27,

FIG P—2. PLASMA MORPHINE SULFATE—6—GLUCURONIDE LEVELS (N = 46)



1-TEST PRODUCT(WATSON) 2-REFERENCE PRODUCT(PERDUE FREDERICK)

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TABLE 5. MEAN PLASMA MORPHINE SULFATE-6-GLUCURONIDE LEVELS FOR TEST AND REFERENCE

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
144	123.54,	50.46,	113.65,	41.41,	1.09,
144.5	132.74,	50.45,	124.96,	48.53,	1.06,
145	185.12,	88.76,	178.58,	65.97,	1.04,
145.5	212.13,	67.72,	208.84,	51.32,	1.02,
146	236.58,	78.63,	229.56,	46.83,	1.03,
146.5	243.49,	70.71,	250.38,	57.79,	0.97,
147	253.71,	97.71,	251.11,	58.22,	1.01,
147.5	248.87,	80.42,	242.13,	53.60,	1.03,
148	243.31,	69.08,	242.11,	79.93,	1.00,
149	226.60,	80.93,	217.42,	77.68,	1.04,
150	199.64,	71.84,	186.56,	41.89,	1.07,
151	173.55,	49.06,	171.84,	54.31,	1.01,
152	156.22,	49.23,	147.52,	36.32,	1.06,
154	128.44,	45.40,	123.88,	35.51,	1.04,
156	104.16,	37.04,	102.73,	30.79,	1.01,

MEAN1=TEST, MEAN2=REF; UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 6. ARITHMETIC MEANS AND RATIOS

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	2164.86,	591.81,	2100.35,	444.60,	1.03,
CAVG	180.41,	49.32,	175.03,	37.05,	1.03,
CMAX	295.22,	102.20,	285.47,	84.73,	1.03,
CMIN	96.24,	33.53,	93.62,	26.91,	1.03,
FLUC1	1.09,	0.28,	1.09,	0.31,	1.00,
LAUCT	2089.42,	0.27,	2057.49,	0.20,	1.02,
LCAVG	174.12,	0.27,	171.46,	0.20,	1.02,
LCMAX	280.93,	0.31,	275.76,	0.25,	1.02,
LCMIN	90.94,	0.34,	89.43,	0.32,	1.02,
LFLUC1	1.06,	0.24,	1.05,	0.27,	1.01,
LTMAX	147.22,	0.01,	146.90,	0.01,	1.00,
TMAX	147.22,	1.20,	146.90,	0.82,	1.00,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

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TABLE 7. LSMEANS AND RATIOS

PARAMETER	LSM1	LSM2	RLSM12
AUCT	2143.66	2079.89	1.03
CAVG	178.64	173.32	1.03
CMAX	292.17	282.19	1.04
CMIN	95.60	92.76	1.03
FLUC1	1.09	1.09	1.00
LAUCT	2066.82	2037.51	1.01
LCAVG	172.23	169.79	1.01
LCMAX	277.79	272.94	1.02
LCMIN	90.28	88.63	1.02
LFLUC1	1.06	1.05	1.01
LTMAX	147.19	146.87	1.00
TMAX	147.19	146.87	1.00

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

TABLE 8. LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCT	2143.66	2079.89	97.87	108.26
CAVG	178.64	173.32	97.87	108.26
CMAX	292.17	282.19	98.16	108.91
CMIN	95.60	92.76	95.29	110.82
FLUC1	1.09	1.09	93.80	105.92
LAUCT	2066.82	2037.51	96.01	107.17
LCAVG	172.23	169.79	96.01	107.17
LCMAX	277.79	272.94	96.30	107.57
LCMIN	90.28	88.63	93.76	110.68
LFLUC1	1.06	1.05	94.64	107.31
LTMAX	147.19	146.87	99.99	100.45
TMAX	147.19	146.87	99.99	100.45

7. Deficiency: *You have conducted dissolution for 1 hour in SGF (without enzyme) followed by 11 hours in SIF (without enzyme) medium. In order to set appropriate specifications, you should conduct comparative dissolution of the test and reference products in water and additional 4 media at pH 1.2, 4.4, 6.8 and 7.5. The tests should include the following conditions: 12 dosage units each, 900 mL medium at 37 °C, USP Apparatus I (Basket) at 50 rpm, and at least ——— as sampling time points.*

Response: The firm has provided the requested dissolution data in 5 media using Apparatus 1 (Basket) at 50 R.P.M. Results are summarized below.

Method reference: FDA recommendation for ER products
Media: Water, 0.1 N HCl, Acetate buffer at pH 4.4, phosphate buffer at pH 6.8, and phosphate buffer at pH 7.5
Apparatus: USP Apparatus I (Basket) at 50 RPM
Volume: 900 mL
Sampling Times: ———
Assay Procedure: ———

Table 1. Results of *In Vitro* Dissolution/Release Testing: **Medium - Water**						
Sampling Time	Test Product: Watson Laboratories Lot No.: PG-1572 Strength: 100 mg			Reference Product: MS Contin® Lot No: 53J1 Strength: 100 mg		
(hr)	Mean %	Range	% CV	Mean %	Range	% CV
1 Hour	22.6	———	2.6	21.6	———	3.0
2 Hours	35.2	———	2.5	34.6	———	3.0
4 Hours	54.3	———	2.0	53.4	———	2.2
6 Hour	69.2	———	1.8	67.9	———	1.4
8 Hours	81.2	———	1.9	78.6	———	1.1
12 Hour	96.9	———	2.3	93.6	———	1.1
Similarity Factor F2 83.47						

Table 2. Results of *In Vitro* Dissolution/Release Testing: **Medium – 0.1 N HCl**						
Sampling Time	Test Product: Watson Laboratories Lot No.: PG-1572 Strength: 100 mg			Reference Product: MS Contin® Lot No: 53J1 Strength: 100 mg		
(hr)	Mean %	Range	% CV	Mean %	Range	% CV
1 Hour	28.6	———	5.4	30.0	———	1.7
2 Hours	43.1	———	4.6	47.2	———	1.2
4 Hours	65.0	———	3.1	70.5	———	0.9
6 Hour	80.6	———	2.3	85.7	———	0.9
8 Hours	91.5	———	1.6	95.9	———	1.2
12 Hour	100.1	———	1.7	103.0	———	1.1
Similarity Factor F2 68.54						

Table 3. Results of *In Vitro* Dissolution/Release Testing:

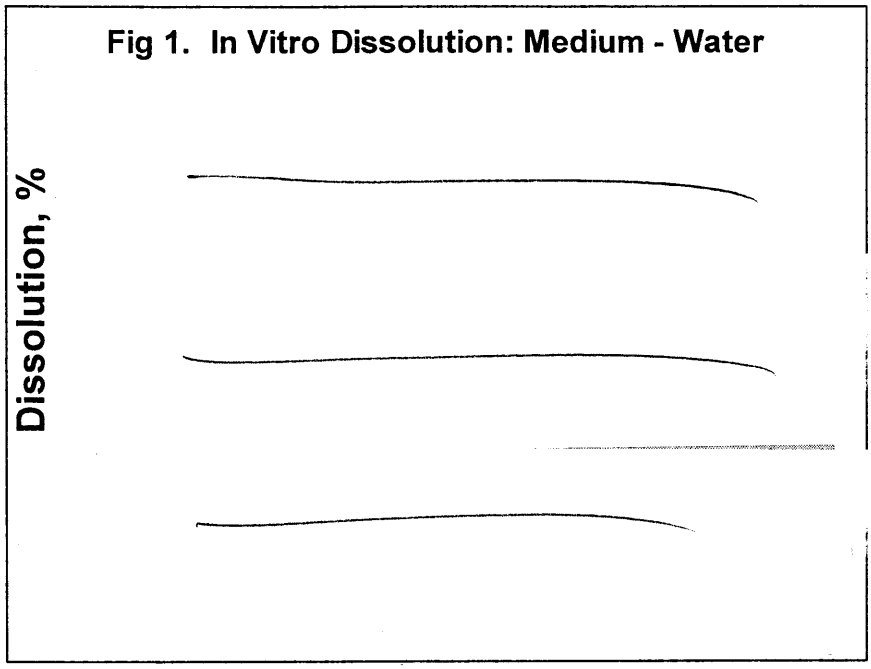
Medium–Acetate Buffer, pH 4.4						
Sampling Time	Test Product: Watson Laboratories Lot No.: PG-1572 Strength: 100 mg			Reference Product: MS Contin® Lot No: 53J1 Strength: 100 mg		
(hr)	Mean %	Range	% CV	Mean %	Range	% CV
1 Hour	23.5	[illegible]	3.4	24.4	[illegible]	3.0
2 Hours	36.2	[illegible]	3.3	37.5	[illegible]	2.5
4 Hours	55.6	[illegible]	3.2	55.5	[illegible]	2.0
6 Hour	70.9	[illegible]	2.4	69.5	[illegible]	1.6
8 Hours	82.6	[illegible]	1.9	80.0	[illegible]	1.3
12 Hour	98.4	[illegible]	1.2	94.9	[illegible]	1.5
Similarity Factor F2 82.72						

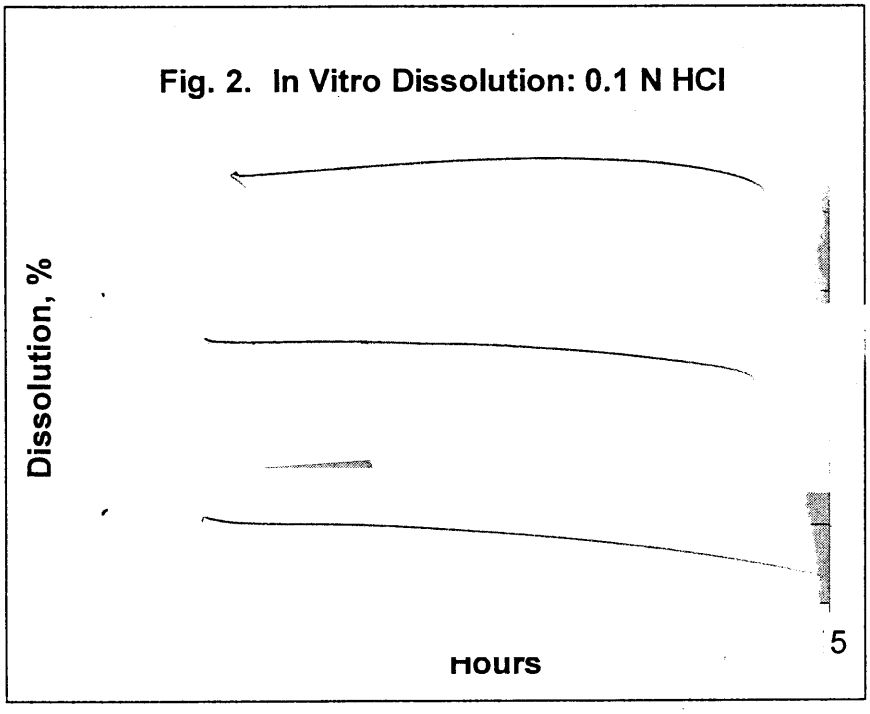
Table 4. Results of *In Vitro* Dissolution/Release Testing: **Medium - Phosphate Buffer pH 6.8**						
Sampling Time	Test Product: Watson Laboratories Lot No.: PG-1572 Strength: 100 mg			Reference Product: MS Contin® Lot No: 53J1 Strength: 100 mg		
(hr)	Mean %	Range	% CV	Mean %	Range	% CV
1 Hour	19.8	[illegible]	1.6	18.7	[illegible]	3.3
2 Hours	30.2	[illegible]	1.7	29.0	[illegible]	2.8
4 Hours	46.2	[illegible]	1.8	44.1	[illegible]	2.3
6 Hour	58.7	[illegible]	1.5	55.4	[illegible]	1.9
8 Hours	68.9	[illegible]	1.7	64.5	[illegible]	1.6
12 Hour	84.4	[illegible]	1.8	78.0	[illegible]	1.6
Similarity Factor F2 71.31						

Table 5. Results of *In Vitro* Dissolution/Release Testing: **Medium - Phosphate Buffer pH 7.5**						
Sampling Time	Test Product: Watson Laboratories Lot No.: PG-1572 Strength: 100 mg			Reference Product: MS Contin® Lot No: 53J1 Strength: 100 mg		
(hr)	Mean %	Range	% CV	Mean %	Range	% CV
1 Hour	15.1	[illegible]	4.6	14.4	[illegible]	1.8
2 Hours	22.8	[illegible]	4.0	21.0	[illegible]	1.5
4 Hours	33.8	[illegible]	3.3	30.2	[illegible]	1.1
6 Hour	42.0	[illegible]	3.3	37.5	[illegible]	1.2
8 Hours	49.2	[illegible]	3.2	44.2	[illegible]	1.2
12 Hour	60.4	[illegible]	3.4	54.9	[illegible]	1.5
Similarity Factor F2 69.65						

Reviewer's Comment

1. Based on the similarity factor F2 (Tables 1-5), and dissolution profiles (Figs. 1-5), water and acetate buffer at pH 4.4 appear to be appropriate media for the product. F2 Values for water and acetate buffer are 83.5 and 82.7, respectively. Since water is simpler medium and F2 value is also highest, tentatively, water is recommended for this product. The medium is also fairly discriminatory. F2 values for 0.1 N HCl, and phosphate buffers at 6.8 and 7.5, are much lower (Attachment-1).





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II. RECOMMENDATIONS

1. The bioequivalence study conducted under fasting conditions by Watson Laboratories, Inc. on its morphine sulfate CR 100 mg tablets, Lot # PG-1572 comparing it to MS Contin® CR tablets 100 mg, Lot #K081 manufactured by Perdue-Frederick has been found acceptable.

2. The bioequivalence study conducted under non-fasting conditions by Watson Laboratories, Inc. on its morphine sulfate controlled release 100 mg tablets, Lot # PG-1572 comparing it to MS Contin® CR tablets 100 mg, lot #k081 manufactured by Perdue-Frederick has been found acceptable.

3. The multiple-dose bioequivalence study conducted by Watson Laboratories, Inc. on its morphine sulfate controlled release 100 mg tablets, lot #GP-1517 comparing it to MS Contin® CR tablets 100 mg, lot #53J1 manufactured by Perdue-Frederick has been found acceptable.

4. The dissolution testing conducted by the firm on its morphine sulfate CR 100 mg Tablets is acceptable.

   Dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37 ^{0}C using apparatus 1 (Basket) at 50 RPM. Tentatively, the test product should meet the following specifications:

   At — hr. sampling time NLT — and NMT —
   At — hrs. sampling time NLT — and NMT —, and
   At — hrs. sampling time NLT — of the labeled amount is dissolved .

   The firm is requested to submit dissolution profiles for 3 production lots for establishing the final dissolution specifications.

From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing, and the application is complete.

/S/

S. P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

/S/

Date 5/8/2000

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-656 SPONSOR : Watson Laboratories, Inc.

DRUG AND DOSAGE FORM : Morphine Sulfate CR Tablets, 100 mg

TYPES OF STUDIES : Fasting , Non-fasting, Multiple-dose studies

CLINICAL STUDY SITE(S) _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : Single-dose fasting, single-dose non-fasting and multiple-dose studies are acceptable.
DISSOLUTION : Dissolution study is acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __No__ New facility __No_ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

INITIAL : /S/ DATE : 5/2/00

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH : II

INITIAL : /S/ DATE : 5/5/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ **DATE :** 6/1/00

Morphine Sulfate CR 100 mg Tablets
ANDA #75-656
Reviewer: S. P. Shrivastava
File Name:75656SD.699

Watson Laboratories, Inc.
Miami, FL
Submission Date:
June 28, 1999

REVIEW OF THREE BIEQUIVALENCE STUDIES AND DISSOLUTION DATA

Indication: Narcotic Analgesic
Submission: Not First Generic
Content of Submission: Single-dose fasting, Single-dose non-fasting, and Multiple-dose studies, and Dissolution Data
ANDA Status: Original submission.
NOTE: Although the Sponsor submitted data on morphine, morphine-3 and morphine-6-glucuronides, since morphine-3-glucuronide is not an active component, the data will not be included, and will not be used for bioequivalence determination.

I. BACKGROUND

Morphine is an opioid analgesic 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. Morphine sulfate is available in oral form as solution, immediate release tablets (IR), controlled release (CR) tablets; rectal suppositories; and for injection which may be given intravenously, intramuscularly, subcutaneously, epidurally or intrathecally. Morphine is rapidly absorbed and is about 35% bioavailable from the gastrointestinal tract. Once absorbed, morphine is distributed to kidneys, skeletal muscle, liver, lungs, spleen and brain. The elimination half-life is normally 2-4 hours. The maximum analgesic effect occurs approximately 60 minutes after administration and the duration of action is four to five hours for immediate release forms. A controlled release tablet is marketed by Purdue Frederick Pharmaceuticals, as scored oral tablets, MS Contin^{R} in 15, 30, 60, 100, and 200 mg strengths.

II. BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

A. Study Information:

Protocol #:	083-64	
IRB Approval:	Yes	
Consent Form Signed:	Yes	
Clinical Site:		
Principal Investigator:		
Analytical Facility:		
Study Dates:	Period I	Grp. 1 - 9/6/98 – 9/8/98; Grp. 2 - 9/13/98 – 9/15/98
	Period II	Grp. 1 - 9/13/98 – 9/15/98 Grp. 2 - 9/20/98 – 9/22/98

Analysis Dates: 10/2/98 – 12/14/98

Study Design: Randomized, two-way crossover design, with seven day washout.

Randomization Scheme: **AB Group 1:** 2, 4, 6, 8, 9, 11, 13, 16, 18, 19, 22, 24, 25
Group 2: 28, 30, 32, 33, 35, 37, 40, 42, 43, 45, 48, 50, 51, 54

BA Group 1: 1, 3, 5, 7, 10, 12, 14, 15, 17, 20, 21, 23, 26, 27

Group 2: 29, 31, 34, 36, 38, 39, 41, 44, 46, 47, 49, 52, 53

Treatments

Test (Treatment A): Morphine Sulfate, 100 mg controlled release tablets, Manufactured by Watson Laboratories, Inc., Lot # PG-1572, Assayed Potency = 97.8%, Batch Size = [redacted] tablets, Manufacture date: 8/27/98.

Reference (Treatment B): MS-Contin^{R} (morphine sulfate controlled-release) 100 mg, Manufactured by Purdue Frederick, Lot No. K081, Assayed Potency = 101.9%, Expiration date: 3/2000.

Naltrexone Hydrochloride: 50 mg tablets, Barr Labs., Inc., Lot # 7H902CK, Exp Date 10/99. In order to suppress the adverse effects of morphine, all subjects received 50 mg doses of naltrexone hydrochloride with 240 mL of water at 15 and 3 hours prior to dosing with morphine sulfate, in each treatment period.

Subjects: 54 Subjects in the age range of 19-50 years were enrolled according to inclusion/exclusion criteria as specified in the protocol, and 52 completed the study. Subjects 14 and 32 vomited within 12 hours of dosing. Therefore, according to protocol, they were dropped

Housing: From 6 hours pre- to 24 hours post-dose

Dosing: Subjects fasted for ten hours overnight before dosing. They were randomized into two equal dosing sequences with twenty-seven subjects per sequence group.

Each subject received 1 x 50 mg naltrexone tablet with 8 fl. Oz. of tap water at 15 hours and three hours prior to morphine dose administration. Naltrexone is a pure opioid receptor antagonist, and was used to suppress the adverse effects of morphine sulfate.

A 100 mg oral dose of morphine sulfate CR (test product or Treatment A) or a 100 mg oral dose of MS-Contin^{R} (reference product or Treatment B)

was administered with 240 mL of water. Subjects continued to fast until 4 hours post dose. Water intake was unrestricted, except for one hour before and two hours after drug administration.

Sampling: [redacted]

Analytical: [redacted]

B. Study Results

1. Clinical: Drop-outs: None

Adverse Events: Adverse events were equally distributed among the test and reference products (see the table below).

Adverse Events	Test	Reference
Nausea	4	8
Headache	4	5
Tired	4	3
Feverish	0	4
Blurred Vision	0	1
Tingling Sensation	0	1
Abdominal Pain/Cramps	1	4
Feel Jittery	0	1
Chest Tightness	1	0
Vomited	2	3
Dizzy	1	0
Light Headed	1	4
Feel Confused	2	0
Shivering/Cold	1	1
Rapid respiratory Rate	1	0
Slow Respiratory Rate	1	0
Dry Heaves	1	0
Loose Stool	0	1

Protocol Deviations: In certain subject blood sampling times were delayed; transfer of samples into freezer was delayed; and a few subjects received medication for headache. The changes were considered not to affect the results.

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b. Morphine-6-glucuronide

The mean plasma concentrations of morphine-6-glucuronide at each time point after test and reference products are shown in Table 4. The plasma concentration-time profiles of morphine for the two products are plotted in Figure P-2 (Attachment-2). The pharmacokinetic parameters are summarized in Tables 5 and 6.

Comments

1. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer. There were statistically significant treatment effect on C_{max} and LC_{max}. However, there were no period, or sequence effects on any of the PK parameters.

2. The elimination constants were calculated for all subjects appropriately.

3. None of the subjects showed 0-hour drug level, first scheduled post-dose time point as T_{max}, or first measurable drug concentration as C_{max}.

4. The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.88 to 1.00 for test and from 0.85 to 0.99 for reference product.

5. ANOVA coefficient of variation for AUC_{0-t}, AUC_{0-inf}, and C_{max} , respectively, were: 10.11, 10.74, and 17.01%.

6. Root Mean Square Error for log transformed parameters were: AUC_{0-t} - 0.102416, AUC_{0-inf} - 0.109024, and C_{max} - 0.131589.

CONCLUSION: Study is incomplete due deficiencies listed in methods validation.

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TABLE 1. MEAN PLASMA MORPHINE SULFATE LEVELS FOR TEST AND REFERENCE PRODUCTS

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.03,	0.19,	0.00,	0.00,	.,
0.5	14.14,	8.66,	13.91,	9.53,	1.02,
1	19.01,	8.66,	22.75,	13.19,	0.84,
1.5	21.40,	8.23,	24.58,	9.00,	0.87,
2	24.34,	8.21,	25.71,	9.58,	0.95,
2.5	26.86,	9.04,	28.07,	10.29,	0.96,
3	25.77,	7.86,	27.96,	8.70,	0.92,
3.5	25.22,	7.25,	27.26,	9.54,	0.93,
4	23.97,	6.78,	26.80,	9.66,	0.89,
5	22.26,	7.51,	25.29,	9.90,	0.88,
6	18.36,	7.28,	20.91,	7.99,	0.88,
7	15.40,	6.22,	17.60,	7.36,	0.87,
8	13.55,	5.07,	15.59,	6.21,	0.87,
10	13.25,	5.09,	14.39,	5.42,	0.92,
12	13.46,	5.55,	13.44,	5.10,	1.00,
16	11.41,	4.65,	10.00,	3.40,	1.14,
24	7.25,	2.92,	6.61,	2.45,	1.10,
30	4.71,	1.94,	4.23,	1.91,	1.11,
36	2.66,	1.31,	2.43,	1.30,	1.09,
48	1.51,	0.92,	1.47,	1.01,	1.03,

MEAN1=TEST, MEAN2=REF; UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

TABLE 2. ARITHMETIC MEANS AND RATIOS

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	447.80,	127.81,	449.07,	132.99,	1.00,
AUCT	419.52,	118.75,	423.55,	119.64,	0.99,
CMAX	30.77,	8.41,	34.78,	12.55,	0.88,
KE	0.07,	0.03,	0.07,	0.02,	1.00,
LAUCI	430.19,	0.29,	428.87,	0.32,	1.00,
LAUCT	402.97,	0.29,	406.06,	0.30,	0.99,
LCMAX	29.64,	0.28,	32.94,	0.33,	0.90,
THALF	11.33,	4.23,	10.98,	3.44,	1.03,
TMAX	3.02,	1.79,	2.89,	1.51,	1.04,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 3. LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
AUCI	447.80,	448.67,	1.00,	96.97,	102.64,
AUCT	419.52,	423.55,	0.99,	96.56,	101.53,
CMAX	30.77,	34.78,	0.88,	82.53,	94.42,
LAUCI	430.19,	429.14,	1.00,	97.26,	103.31,
LAUCT	402.97,	406.06,	0.99,	96.61,	101.94,
LCMAX	29.64,	32.94,	0.90,	84.52,	95.82,

MEAN1=TEST, MEAN2=REF; UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

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TABLE 4. MEAN PLASMA MORPHINE-6-GLUCURONIDE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00,	0.00,	0.00,	0.00,	.,
0.5	25.51,	15.82,	24.22,	16.96,	1.05,
1	100.41,	39.40,	109.74,	39.14,	0.91,
1.5	137.99,	45.74,	158.93,	39.82,	0.87,
2	172.33,	55.89,	177.83,	48.14,	0.97,
2.5	186.38,	58.92,	198.07,	60.29,	0.94,
3	187.58,	47.81,	206.46,	63.25,	0.91,
3.5	195.79,	64.03,	209.11,	86.70,	0.94,
4	193.27,	58.98,	207.99,	86.79,	0.93,
5	154.26,	46.19,	174.04,	57.57,	0.89,
6	127.00,	38.50,	135.60,	43.54,	0.94,
7	100.55,	31.74,	114.64,	44.56,	0.88,
8	87.33,	30.06,	99.09,	37.23,	0.88,
10	82.09,	29.47,	88.34,	30.31,	0.93,
12	78.12,	31.78,	77.86,	31.37,	1.00,
16	66.67,	23.61,	60.35,	25.07,	1.10,
24	40.68,	18.03,	35.90,	14.11,	1.13,
30	25.55,	11.69,	23.16,	10.67,	1.10,
36	15.05,	7.95,	15.23,	7.94,	0.99,
48	7.40,	5.13,	7.91,	5.68,	0.94,

MEAN1=TEST, MEAN2=REF; UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 5. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	2694.18,	692.62,	2769.64,	721.42,	0.97,
AUCT	2573.41,	641.80,	2614.19,	641.11,	0.98,
CMAX	227.08,	68.33,	247.67,	89.54,	0.92,
KE	0.08,	0.03,	0.07,	0.02,	1.12,
LAUCI	2618.23,	0.24,	2686.02,	0.25,	0.97,
LAUCT	2503.98,	0.23,	2543.21,	0.23,	0.98,
LCMAX	218.51,	0.27,	236.31,	0.29,	0.92,
THALF	9.71,	2.85,	10.50,	3.09,	0.92,
TMAX	3.28,	0.97,	3.40,	0.98,	0.97,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 6. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	2694.18,	2752.57,	0.98,	94.16,	101.59,
AUCT	2573.41,	2614.19,	0.98,	95.14,	101.74,
CMAX	227.08,	247.67,	0.92,	86.33,	97.04,
LAUCI	2618.23,	2672.34,	0.98,	94.32,	101.77,
LAUCT	2503.98,	2543.21,	0.98,	95.20,	101.83,
LCMAX	218.51,	236.31,	0.92,	88.55,	96.55,

APPEARS THIS WAY
ON ORIGINAL

III. COMPARATIVE BIOAVAILABILITY UNDER NON-FASTING CONDITIONS

A. Study Information:

Protocol #:	083-65
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	[redacted]
Principal Investigator:	[redacted]
Analytical Facility:	[redacted]
Statistics:	[redacted]
Study Dates:	Period I December 20-21, 1998 Period II December 27-28, 1998 Period III January 3-4, 1999
Analysis Dates:	1/12/99 – 2/24/99
Study Design:	Randomized, three-way crossover design, with seven day washout.
Randomization Scheme:	**ABC**: 6, 7, 13; **BAC**: 1, 8, 16, 19; **CAB**: 4, 12, 15, 20 **ACB:** 5, 10, 18; **BCA**: 3, 9, 17; **CBA**: 2, 11, 14, 21

Treatments

Test (Treatment A): Morphine Sulfate, CR 100 mg, Manufactured for Watson Laboratories, Inc., Lot No. PG-1572, Assayed Potency = %, Batch Size = tablets, Manuf. Date: 8/27/98; administered after a standard breakfast.
Reference (Treatment B): MS-Contin^{R} (morphine sulfate controlled-release) 100 mg, Manufactured by Purdue Frederick, Lot No. K081, Assayed Potency = %, Expiration date: 03/2000, administered after a standard breakfast.
Test (Treatment C): Morphine Sulfate, CR 100 mg, Manufactured for Watson Laboratories, Inc., Lot No. PG-1572. Administered after a 10 hour fast.
Lot numbers of drug products administered in this study are the same as those used for the fasting study.

Subjects

21 Subjects enrolled and 20 completed the study. Subject # 13 did not show up in Period 3.

Dosing

All subjects received 1 x 50 mg naltrexone tablet with 240 mL of water at 15 and 3 hours prior to dosing with morphine in each period. As discussed in fasting study, this was done to suppress the adverse effects of morphine sulfate.

Treatments A and B: After a fast lasting at least 10 hours, subjects were given standardized breakfast 20 minutes before dosing. All subjects completed their entire meal, and the dose was given with 240 mL of water.

Treatment C: Subjects were given a single oral dose of the assigned formulation with 240 mL of water after a fast of at least 10 hours. All subjects fasted for 4 hours after dosing.

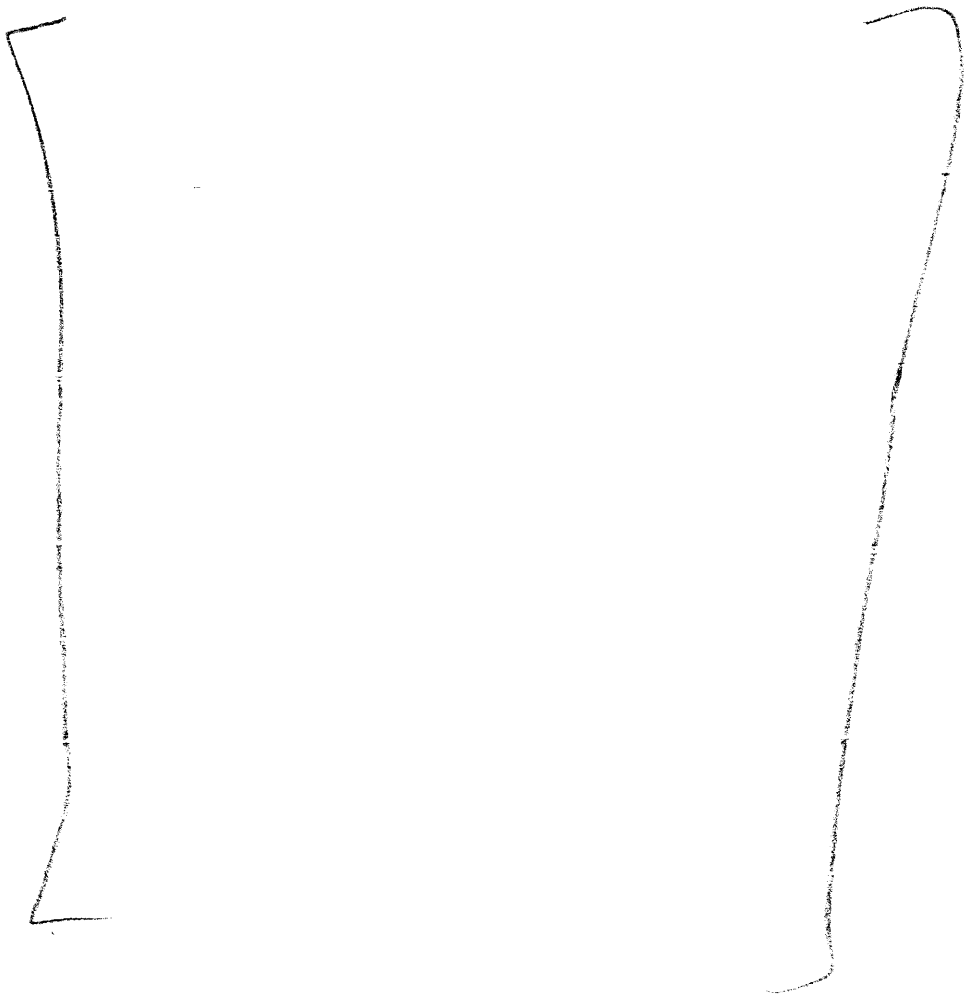
Sample Collection: Same as in fasting study

B. Study Results

1. **Clinical**

   Drop-out: One. Subject # 13 did not show up in Period 3.
   Protocol Deviations: None significant

2. **Analytical**



[redacted]

3. **Pharmacokinetics/Statistics**

a. Morphine

The mean plasma concentration data are given in Fig P-3 (Attachment 3) and Table 7. Pharmacokinetic parameters and ratios of means are given in Tables 8 and 9.

Comments

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.

2. The ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test non-fasting and reference non-fasting are within the 0.80-1.20.

b. Morphine-6-glucuronide

The mean plasma concentration data are given in Fig P-4 (Attachment 4) and Table 10. Pharmacokinetic parameters and ratios of means are given in Tables 11 and 12.

Comments

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.

2. The ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test non-fasting and reference non-fasting are within the 0.80-1.20.

CONCLUSON: The study is incomplete due to deficiencies in methods validation.

TABLE 7. MEAN PLASMA MORPHINE SULFATE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR									
0	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	.,	.,	.,
0.5	8.04,	7.17,	8.27,	8.84,	12.40,	5.77,	0.97,	0.65,	0.67,
1	16.48,	8.58,	16.93,	9.58,	16.77,	4.29,	0.97,	0.98,	1.01,
1.5	22.40,	11.78,	25.16,	10.39,	20.58,	6.76,	0.89,	1.09,	1.22,
2	23.56,	9.68,	26.82,	7.95,	21.07,	5.38,	0.88,	1.12,	1.27,
2.5	26.59,	9.76,	27.66,	9.02,	22.99,	6.53,	0.96,	1.16,	1.20,
3	28.40,	7.84,	27.02,	8.08,	22.52,	6.57,	1.05,	1.26,	1.20,
3.5	28.54,	7.19,	28.36,	9.55,	22.15,	6.67,	1.01,	1.29,	1.28,
4	27.42,	5.69,	27.99,	8.28,	20.95,	6.15,	0.98,	1.31,	1.34,
5	31.75,	8.69,	32.51,	9.65,	20.68,	7.55,	0.98,	1.54,	1.57,
6	26.00,	8.19,	24.65,	7.70,	17.29,	6.14,	1.05,	1.50,	1.43,
7	23.52,	10.27,	20.93,	7.47,	14.15,	5.12,	1.12,	1.66,	1.48,
8	20.36,	9.66,	18.78,	8.18,	12.29,	4.34,	1.08,	1.66,	1.53,
10	15.15,	5.71,	15.73,	6.61,	13.22,	4.80,	0.96,	1.15,	1.19,
12	11.54,	3.84,	10.85,	3.68,	12.11,	4.38,	1.06,	0.95,	0.90,
16	7.30,	2.69,	6.58,	2.47,	8.92,	3.43,	1.11,	0.82,	0.74,
24	4.86,	1.46,	4.68,	1.85,	6.60,	2.06,	1.04,	0.74,	0.71,
30	3.51,	1.66,	3.46,	1.75,	4.14,	1.58,	1.01,	0.85,	0.83,
36	2.00,	1.04,	2.35,	1.31,	2.76,	1.46,	0.85,	0.72,	0.85,
48	1.14,	0.72,	1.04,	0.58,	1.36,	0.95,	1.10,	0.84,	0.77,

MEAN1=TEST FED, MEAN2=REF FED, MEAN3=TEST FAST; UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 8. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER									
AUCI	417.18,	107.15,	408.44,	91.70,	401.19,	109.10,	1.02,	1.04,	1.02,
AUCT	397.60,	93.81,	391.24,	87.24,	375.10,	95.69,	1.02,	1.06,	1.04,
CMAX	36.85,	8.97,	38.17,	9.18,	27.66,	5.37,	0.97,	1.33,	1.38,
KE	0.07,	0.03,	0.07,	0.02,	0.08,	0.04,	1.04,	0.94,	0.90,
LAUCI	405.19,	0.25,	398.58,	0.23,	387.10,	0.28,	1.02,	1.05,	1.03,
LAUCT	387.58,	0.23,	381.95,	0.23,	362.78,	0.27,	1.01,	1.07,	1.05,
LCMAX	35.81,	0.25,	37.12,	0.24,	27.14,	0.20,	0.96,	1.32,	1.37,
THALF	10.75,	3.37,	10.43,	2.31,	10.92,	4.22,	1.03,	0.98,	0.96,
TMAX	3.32,	1.38,	3.48,	1.44,	3.15,	1.18,	0.96,	1.06,	1.10,

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 9. LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	432.53,	421.41,	414.92,	1.03,	1.04,	1.02,
AUCT	409.30,	402.86,	387.50,	1.02,	1.06,	1.04,
CMAX	37.30,	38.53,	28.00,	0.97,	1.33,	1.38,
LAUCI	420.17,	410.99,	400.08,	1.02,	1.05,	1.03,
LAUCT	398.65,	393.30,	374.57,	1.01,	1.06,	1.05,
LCMAX	36.31,	37.58,	27.46,	0.97,	1.32,	1.37,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

APPEARS THIS WAY
ON ORIGINAL

TABLE 10. MEAN PLASMA MORPHINE-6-GLUCURONIDE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR									
0	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	.,	.,	.,
0.5	6.25,	7.26,	7.47,	13.36,	21.24,	16.75,	0.84,	0.29,	0.35,
1	38.20,	29.32,	45.57,	41.32,	73.66,	24.45,	0.84,	0.52,	0.62,
1.5	78.54,	40.26,	87.37,	51.67,	102.82,	22.84,	0.90,	0.76,	0.85,
2	97.54,	45.80,	119.91,	57.59,	132.72,	37.86,	0.81,	0.73,	0.90,
2.5	118.83,	43.73,	139.33,	49.57,	139.63,	31.43,	0.85,	0.85,	1.00,
3	137.07,	51.09,	154.17,	55.07,	148.65,	36.40,	0.89,	0.92,	1.04,
3.5	161.74,	58.50,	162.61,	55.09,	152.06,	35.31,	0.99,	1.06,	1.07,
4	161.60,	52.76,	169.26,	59.52,	144.01,	40.35,	0.95,	1.12,	1.18,
5	157.53,	56.08,	173.16,	68.57,	126.71,	44.48,	0.91,	1.24,	1.37,
6	142.95,	43.74,	147.70,	42.49,	96.15,	32.41,	0.97,	1.49,	1.54,
7	114.43,	42.44,	118.96,	41.87,	78.73,	28.76,	0.96,	1.45,	1.51,
8	107.39,	46.68,	97.43,	42.18,	64.10,	18.82,	1.10,	1.68,	1.52,
10	81.56,	36.29,	79.53,	40.26,	63.58,	23.79,	1.03,	1.28,	1.25,
12	58.57,	27.56,	53.10,	25.75,	65.52,	23.69,	1.10,	0.89,	0.81,
16	38.59,	16.78,	36.71,	15.36,	48.88,	15.90,	1.05,	0.79,	0.75,
24	22.67,	9.21,	22.01,	8.06,	28.98,	11.71,	1.03,	0.78,	0.76,
30	14.71,	6.23,	15.05,	8.16,	18.60,	8.74,	0.98,	0.79,	0.81,
36	8.76,	4.20,	7.93,	4.42,	12.32,	6.92,	1.10,	0.71,	0.64,
48	3.96,	2.92,	4.02,	2.69,	6.10,	4.65,	0.99,	0.65,	0.66,

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 11. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER									
AUCI	1974.34,	585.46,	2023.64,	588.90,	2089.63,	574.83,	0.98,	0.94,	0.97,
AUCT	1928.86,	567.37,	1945.69,	572.40,	1967.00,	497.08,	0.99,	0.98,	0.99,
CMAX	188.20,	49.14,	206.80,	64.55,	169.75,	37.75,	0.91,	1.11,	1.22,
KE	0.08,	0.03,	0.07,	0.02,	0.07,	0.03,	1.11,	1.19,	1.07,
LAUCI	1894.42,	0.30,	1945.99,	0.29,	2017.42,	0.27,	0.97,	0.94,	0.96,
LAUCT	1851.08,	0.30,	1867.99,	0.30,	1908.52,	0.25,	0.99,	0.97,	0.98,
LCMAX	182.06,	0.27,	198.22,	0.29,	165.59,	0.23,	0.92,	1.10,	1.20,
THALF	9.46,	3.34,	9.95,	2.84,	11.12,	3.98,	0.95,	0.85,	0.89,
TMAX	4.33,	1.13,	4.33,	1.58,	3.32,	1.02,	1.00,	1.30,	1.30,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 12. LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	2025.01,	2044.17,	2100.85,	0.99,	0.96,	0.97,
AUCT	1957.99,	1964.20,	1976.64,	1.00,	0.99,	0.99,
CMAX	189.11,	204.72,	166.51,	0.92,	1.14,	1.23,
LAUCI	1950.09,	1967.01,	2028.89,	0.99,	0.96,	0.97,
LAUCT	1881.59,	1887.64,	1919.16,	1.00,	0.98,	0.98,
LCMAX	182.36,	195.82,	162.75,	0.93,	1.12,	1.20,

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

APPEARS THIS WAY
ON ORIGINAL

IV. COMPARATIVE BIOAVAILABILITY: MULTI-DOSE STUDY

A. Study Information:

Protocol #: 083-66
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site: [redacted]
Principal Investigator: [redacted]
Analytical Facility: [redacted]
Statistics: [redacted]
Study Dates: Period I March 25, 1998
Period II April 14, 1998
Analysis Dates: April 15 through April 28, 1998
Study Design: Randomized, multiple-dose, two-treatment, cross-over design with 8 day wash-out period.
Randomization Scheme: **AB**: 2,3,6,8,10,12,14,16,17,19,21,23,25
BA: 1,4,5,7,9,11,13,15,18,20,22,24,26

Treatments

Test Treatment A: Morphine Sulfate, CR 100 mg, Manufactured for Watson Laboratories, Inc.., Lot No. PG-1572

Treatment B: MS-Contin^{R} (morphine sulfate controlled-release) 100 mg, Manufactured by Purdue Frederick, Lot No. 53J1, Assayed Potency = 101.9%, Expiration date: 11/2001.

Lot number of reference drug product administered in this study is not the same as those used for the fasting or non-fasting studies.

Subjects

50 subjects were enrolled and 44 completed the study. Subjects #2 and 38 vomited within 12 hour post-dosing; Subjects # 5, 6, and 24 were dropped due to adverse reactions; and Subject # 29 was dropped due to disruptive behavior.

Dosing

All subjects received a total of 8 oral doses of 50 mg naltrexone HCl tablet per period, taken with 240 mL of water. One tablet was administered at 15 hours prior to the first dose of morphine, then each morning three hours before dosing with morphine.

In each period, the subjects were given 13 consecutive doses of 100 mg morphine every 12 hours. The first dose was given at 10 hours after fasting. All subjects fasted overnight, 4 hours post-dose every morning, and two hours post-dose every evening. Drug was administered with 240 mL of water. Washout period was 7 days.

Sample Collection

B. Study Results

1. Clinical:

Drop-outs: Six
Protocol Deviations: None.

2. **Analytical**

Assay validation for multiple-dose study appears to be adequate. However, explanation on fasting and non-fasting studies is necessary to make appropriate conclusions.

3. **Pharmacokinetics/Statistics**

Comments

1. The firm has not provided C_{min}, C_{ave} and Degree of Fluctuation (DF) data on the EVA electronic data file or diskette for evaluation. Once completed data set is available, ANOVA analyses on multiple dose study will be performed.

2. The firm should evaluate C_{min} values, obtained at 120, 144 and 156 hrs. sampling time points.

CONCLUSION: The study is incomplete due to deficiencies in methods validation.

V. FORMULATION: See the table below.

(NOT FOR RELEASE UNDER F.O.I.)

Test Product Formulation (mg/Tablet)

Core Ingredients	**100 mg**
Morphine Sulfate.5H_2O, USP	[redacted]
Hydroxyethylcellulose, NF	[redacted]
Hydroxypropyl Methylcellulose, NF	[redacted]
Hydroxypropycellulose, NF	[redacted]
Cetostearyl Alcohol, NF	[redacted]
Talc, USP	[redacted]
Magnesium Stearate, NF	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Target Tablet Wt.	**179.0**

Tablet Appearance: Gray round, standard cup film coated, debossed "WATSON" over "617" on one side; Label states – "Morphine sulfate tablets, CR are to be taken whole, and are not to be broken, chewed or crushed". No information on scoring is available in the labels. Contin® CR 100 mg reference is gray colored, round, and non-scored tablet.

VI. *IN VITRO* DISSOLUTION TESTING

Method reference:	FDA recommendation for ER products
Medium:	SGF without enzyme for 1 hour followed by SIF without enzyme for 11 hours (2-12 hrs.)
Apparatus:	USP Apparatus I (Basket) at 50 RPM
Volume:	900 mL
Sampling Times:	[redacted]
Assay Procedure:	[redacted]

I. Results of *In Vitro* Dissolution/Release Testing:						
Sampling Times	Test Product: Watson Laboratories Lot No.: PG-1572 Strength: 100 mg			Reference Product: MS Contin® Lot No.: K081 Strength: 100 mg		
(hr)	Mean %	Range	% CV	Mean %	Range	% CV
1 Hour	29.1		3.2	32.9		2.3
2 Hours	40.4		2.5	44.7		2.3
4 Hours	53.7		2.4	54.5		2.1
6 Hour	62.2		2.3	60.9		2.2
8 Hours	68.2		2.9	65.4		3.0
10 Hour	72.5		2.2	68.5		2.2
12 Hour	76.0		2.0	71.1		2.2

II. Results of *In Vitro* Dissolution/Release Testing:						
Sampling Times	Test Product: Watson Laboratories Lot No.: PG-1572 Strength: 100 mg			Reference Product: MS Contin® Lot No: 53J1 Strength: 100 mg		
(hr)	Mean %	Range	% CV	Mean %	Range	% CV
1 Hour	29.1		3.2	30.5		2.7
2 Hours	40.4		2.5	43.6		2.2
4 Hours	53.7		2.4	54.4		2.2
6 Hour	62.2		2.3	60.9		1.9
8 Hours	68.2		2.9	65.3		1.8
10 Hour	72.5		2.2	68.5		1.9
12 Hour	76.0		2.0	70.9		1.8

Comments

1. The firm has conducted dissolution for 1 hour in SGF (without enzyme) followed by 11 hours in SIF (without enzyme) medium. In order to set appropriate specifications, the firm should conduct comparative dissolution of the test and reference products in water and media at pH 1.2, 4.4, 6.8 and 7.5. The tests should include the following conditions: 12 dosage units each, 900 mL medium at 37 °C, USP Apparatus I (Basket) at 50 rpm, and at least [redacted] as sampling time points.

CONCLUSION: *In vitro* dissolution test is incomplete.

VII. DEFICIENCIES

1. It is not clear why most of the repeat analyses in fasting and non-fasting studies labeled, "Over the highest calibration standard", showed lower concentration than the first analysis for morphine and morphine-6-glucuronide. The firm is requested to provide some explanation.

2. In the fasting study, the reason for repeat analysis for Subject #11, Period 2, 3.5 hr. sample for morphine is labeled "Over the highest calibration standard" even though the result from the first analysis shows a concentration of [redacted] The highest calibration standard in this case is [redacted] The firm should make appropriate corrections and provide necessary explanation.

3. In non-fasting study, the reason for repeat analysis for Subject #11, Period 3, 48 hr. sample for morphine is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows a concentration of [redacted] The highest calibration standard in this case is [redacted] Similarly, reason for repeat analysis for Subject #14, Period 1, 36 hr. sample for morphine-6-glucuronide is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows a concentration of "Below the Limit of Quantitation (2 ng or code " * "). The firm should make appropriate corrections and provide necessary explanation.

4. In the fasting study, the subjects were dosed in two Groups. The firm should evaluate any Group effects on PK parameters, and include the Group term in the model:

Model (Y) = Group Sequence Group*Sequence Subject(Group*Sequence)
Period Period*Group Treatment Group*Treatment

If the Group effect is statistically not significant, the data should be analyzed without the Group term. However, if Group effect is significant, separate 90% confidence interval should be computed for each dose group.

5. The firm has not provided C_{min}, C_{ave} and Degree of Fluctuation (DF) data on the EVA electronic data files or diskette. These values should be entered with PK parameters for proper evaluation.

6. The firm should evaluate both C_{min} values, one obtained before the last dose (144 hrs. sampling time), and one 12 hours after the last dose (156 hrs. sampling time).

7. The firm has conducted dissolution for 1 hour in SGF (without enzyme) followed by 11 hours in SIF (without enzyme) medium. In order to set appropriate specifications, the firm should conduct comparative dissolution of the test and reference products in water and media at pH 1.2, 4.4, 6.8 and 7.5. The tests should include the following conditions: 12 dosage units each, 900 mL medium at 37 °C, USP Apparatus I (Basket) at 50 rpm, and at least [redacted] as sampling time points.

VIII. RECOMMENDATIONS

1. The bioequivalence study conducted under fasting conditions by Watson Laboratories, Inc. on its morphine sulfate CR 100 mg tablets, Lot # PG-1572 comparing it to MS Contin® CR tablets 100 mg, Lot #K081 manufactured by Perdue-Frederick has been

found incomplete by the Division of Bioequivalence due to deficiencies 1-7 cited above.

2. The bioequivalence study conducted under non-fasting conditions by Watson Laboratories, Inc. on its morphine sulfate controlled release 100 mg tablets, Lot # PG-1572 comparing it to MS Contin® CR tablets 100 mg, lot #k081 manufactured by Perdue-Frederick has been found incomplete by the Division of Bioequivalence due to deficiencies 1-7 cited above.

3. The multiple-dose bioequivalence study conducted by Watson Laboratories, Inc. on its morphine sulfate controlled release 100 mg tablets, lot #GP-1517 comparing it to MS Contin® CR tablets 100 mg, lot #53J1 manufactured by Perdue-Frederick has been found incomplete by the Division of Bioequivalence due to deficiencies 1-7 cited above.

4. The dissolution testing conducted by the firm on its morphine sulfate CR 100 mg Tablets is incomplete. The firm is required to conduct additional comparative dissolution testing before a dissolution method and specifications can be proposed.

5. From bioequivalence point of view, the firm has not met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing, and the application is incomplete.

/S/

S. P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 10/19/1999

Concur: /S/ Date 11/5/99
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
CDER, FDA

Attachment – 4
SPS/9-7-99/75656sd.699
cc: ANDA #75-656 (Original, Duplicate) HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 75-656 APPLICANT: Watson Labs.

DRUG PRODUCT: Morphine Sulfate CR tablets, 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. It is not clear why most of the repeat analyses showed lower concentration than the first analysis for morphine and morphine-6-glucuronide. You should provide some explanation.

2. In the fasting study, the reason for repeat analysis for Subject #11, Period 2, 3.5 hr. sample for morphine is labeled "Over the highest calibration standard" even though the result from the first analysis shows a concentration of [redacted]. The highest calibration standard in this case is [redacted] You should make appropriate corrections and provide necessary explanation.

3. In non-fasting study, the reason for repeat analysis for Subject #11, Period 3, 48 hr. sample for morphine is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows a concentration of [redacted] The highest calibration standard in this case is [redacted] Similarly, reason for repeat analysis for Subject #14, Period 1, 36 hr. sample for morphine-6-glucuronide is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows a concentration of "Below the Limit of Quantitation (2 ng or code " * "). You should make appropriate corrections and provide necessary explanation.

4. In the fasting study, the subjects were dosed in two Groups. The firm should evaluate any Group effects on PK parameters, and include the Group term in the model:

   Model (Y) = Group Sequence Group*Sequence Subject(Group*Sequence)
   Period Period*Group Treatment Group*Treatment

5. You have not provided C_{min}, C_{ave} and Degree of Fluctuation (DF) data on the EVA electronic data files or diskette. These values should be entered with PK parameters for proper evaluation.

6. You should evaluate C_{min} values, obtained at 120, 144 and 156 hrs. sampling time points.

7. You have conducted dissolution for 1 hour in SGF (without enzyme) followed by 11 hours in SIF (without enzyme) medium. In order to set appropriate specifications, you should conduct comparative dissolution of the test and reference products in water and additional 4 media at pH 1.2, 4.4, 6.8 and 7.5. The tests should include the following conditions: 12 dosage units each, 900 mL medium at 37 °C, USP

Apparatus I (Basket) at 50 rpm, and at least [redacted] as sampling time points.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with D
HFD-655/SShrivastava /S/ 10/18/99
HFD- /SNerurkar
HFD-617/J. Fan
HFD-650/Dale Conner for Dale 11/16/99

/S/ 10/18/99

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BIOEQUIVALENCY - DEFICIENCIES Submission Date:6/28/99

1. **FASTING STUDY** (STF) Strengths: 100 mg
Clinical: _ **Outcome: IC**
Analytical: _____

2. **FOOD STUDY** (STP) Strengths: 100 mg
Clinical: _ **Outcome: IC**
Analytical _____

3. **MULTIPLE DOSE STUDY** (STM) Strengths: 100 mg
Clinical: _ **Outcome: IC**
Analytical _____

4. **DISSOLUTION DATA** (DIS) Strengths: 100 mg
Outcome: IC

IC - Incomplete

WinBio

APPEARS THIS WAY
ON ORIGINAL

Redacted 4

pages of trade secret and/or confidential commercial information

ANDA/AADA: 75-656 APPLICANT: Watson Labs.

DRUG PRODUCT: Morphine Sulfate CR tablets, 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37 ^{0}C using apparatus 1 (Basket) at 50 RPM. Tentatively, the test product should meet the following specifications:

At – hr. sampling time NLT — and NMT —,
At – hrs. sampling time NLT — and NMT —, and
At – hrs. sampling time NLT — of the labeled amount is dissolved .

The firm is requested to submit dissolution profiles for 3 production lots for establishing the final dissolution specifications.

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

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-656

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: #75-656 DRUG PRODUCT: Morphine Sulfate Tablets CR

FIRM: Watson Laboratories, Inc. (Miami) DOSAGE FORM: Tablet; Oral

311 Bonnie Circle STRENGTH: 100 mg

Corona, CA 92880

CGMP STATEMENT/EIR UPDATE STATUS:

Certifications of CGMP (p. 12613) and of section 306(k) (p. 13380) compliance statement are included.

An acceptable EER was issued on 3/2/00.

Facilities included:

Manufacturing, processing, and testing of the drug product:
Watson Laboratories, Inc.
16600 N.W. 54th Avenue
Miami, FL 33014

Testing of the drug product:
Watson Laboratories, Inc.
5350 N.W. 165th Street
Miami, FL 33014

[redacted]

well as [redacted]

BIO STUDY

Acceptable per S.P. Shrivastava (5/5/00).

VALIDATION

Morphine Sulfate is compendial. Morphine Sulfate Tablets (CR) is a non-compendial drug product. A method validation report for the [redacted] method for assay, dissolution, stability, and [redacted] testing is included (p. 13065-13223). Validation by the Southeast Regional Laboratory found all methods tested suitable for regulatory purposes (September 14, 2000).

Redacted 4

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

ANDA Number: **75-656** Date of Submission: **May 4, 2000**

Applicant's Name: **Watson Laboratories, Inc.**

Established Name: **Morphine Sulfate Extended-release Tablets, 100 mg**

Labeling Deficiencies:

INSERT

a. GENERAL

i. It is difficult to read your insert labeling. Please increase the readability of your insert labeling. We believe that it is important for public health to have insert labeling clearly legible.

ii. Please be reminded that the established name of your drug product is "morphine sulfate extended-release tablets", rather than "[redacted]. Revise [redacted] to read "morphine sulfate extended-release tablets" throughout text, unless otherwise specified.

b. DESCRIPTION

i. Revise the first sentence to be the same as the one proposed in your last submission. [*i.e.*, include "pentahydrate"]

ii. Include "$5H_2O$" in the structural formula.

c. PRECAUTIONS (Pregnancy; Teratogenic Effects; Category C) – First paragraph, second sentence:

...clinical use of morphine sulfate products. [rather than [redacted]

Please revise your insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-656

CORRESPONDENCE

Guidelines Ana. Lab withdrawn from EES
/S/ 1/22/01

WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

November 16, 2000

Gary Buehler, Rh.D., Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
Minor Amendment
N/AM

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 17 2000
OGD

RE: **ANDA 75-656**
Morphine Sulfate Extended-Release Tablets 100 mg

Final Printed Labeling Included

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this amendment to provide a complete response to the comments included in the FDA facsimile dated October 6, 2000 (copy attached) pertaining to Morphine Sulfate Extended-Release Tablets, 100 mg (ANDA 75-656). For convenience of review, your comments are provided in bold face type followed by our response.

Chemistry Deficiencies

[redacted]

/S/ 11-20-00

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

Redacted 1

pages of trade secret and/or confidential commercial information

Labeling Deficiencies

INSERT

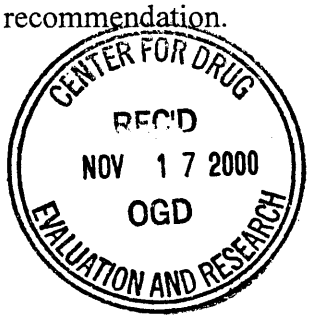
A. GENERAL

i. It is difficult to read your insert labeling. Please increase the readability of your insert labeling. We believe that it is important for public health to have insert labeling clearly legible.

ii. Please be reminded that the established name of your drug product is "morphine sulfate extended-release tablets", rather than ' ' Revise ' ' to read "morphine sulfate extended-release tablets" throughout text, unless otherwise specified.

We have increased the font size of our packaging insert to increase readability. We have revised the established name of our drug product to morphine sulfate extended-release tablets, in accordance with the Agency's recommendation.

B. Description



C. Precautions (pregnancy; teratogenic effects: Category C) – first paragraph, second sentence:

...clinical use of morphine sulfate products (rather than '

Please revise your labeling, as instructed above, and submit in final print.

We have revised our packaging insert as recommended by the Agency. We have included a total of 12 copies of Final Printed Labeling, 11 inserts with the Archival copy and 1 insert with Review copy of the application (see **Exhibit 4).**

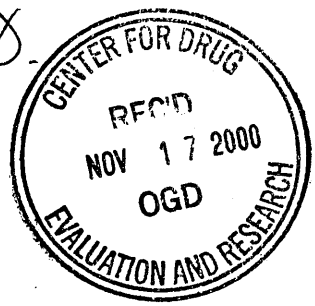
In order to facilitate review of the submission, and in accordance with 21 CFR 314.94 (a)(8)(iv), we have provided a side-by-side comparison of our final printed packaging insert (10/2000) with the previously submitted labeling (4/2000) with all the differences annotated and explained (see **Exhibit 5).**

We have enclosed one volume each of (1) archival, one (1) review copy, and in accordance with 21 CFR § 314.94(d)(5), one (1) field copy of this amendment will be forwarded to the FDA Florida District Office. Watson Laboratories Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this minor amendment.

We believe we have responded to all of FDA's questions/concerns as outlined in their October 6, 2000 letter. Please contact me by phone at (909) 270-1400 or by fax at (909) 278-0967 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest E. Lengle, Ph.D.,
Executive Director
Regulatory Affairs



WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

ORIG AMENDMENT
N/AC

May 4, 2000

Gary Buehler, Rh. D.
Acting Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Morphine Sulfate Extended-release Tablets, 100 mg
ANDA 75-656
Major Amendment

Dear Mr. Buehler:

This is in response to a FDA deficiency letter dated February 7, 2000 regarding Morphine Sulfate Extended-release Tablets, 100 mg (ANDA 75-656). For ease of review, FDA's comments are in bold face followed by our response.

A. Chemistry Deficiencies:

/

\

c. /

JO

311 Bonnie Circle, P.O. Box 1900, Corona, California 92878-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

Redacted 5

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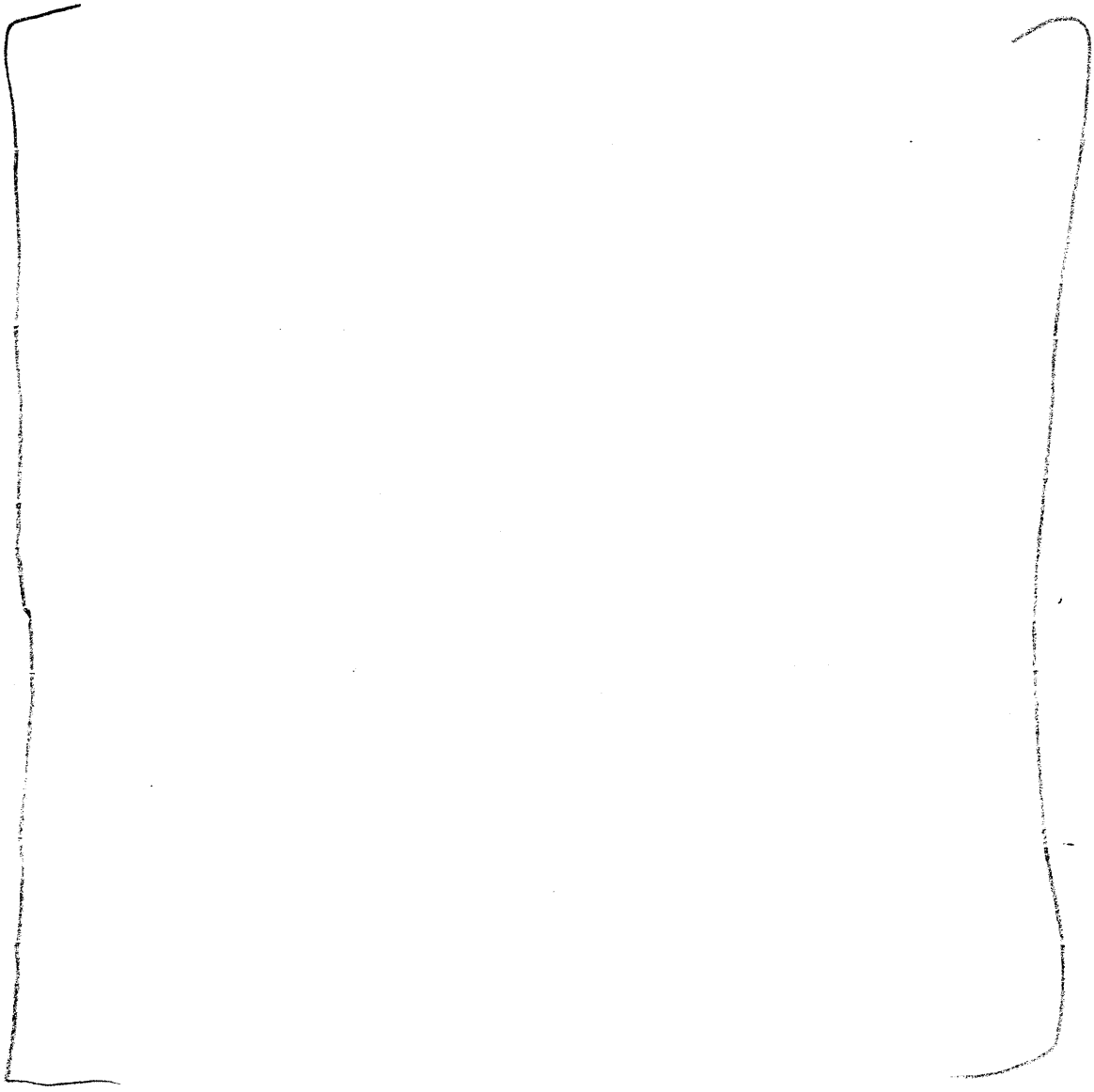
confidential

commercial

information



C. Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please note that the term Controlled-release tablets is not recognized in the USP as one of the solid oral dosage forms. Revise the established name on all labels and labeling to read as follows:

   Morphine Sulfate Extended-release Tablets.

b. Revise the storage requirement to read as follows

...86°F}. {See USP}

2. CONTAINER – 100s & 500s

a. See general comments above.

b. Revise to read as follows and increase the prominence of this statement:

USUAL DOSAGE....Do not break, crush, or chew. {add break}

3. INSERT

a. GENERAL

i. See general comments above.

ii. Subsection heading should be of consistent prominence, usually lesser than section headings throughout the text. Please revise accordingly. (e.g. Drug Interactions vs. Pediatric Use under PRECAUTIONS).

iii. Replace " ——— " with "extended-release morphine sulfate" throughout the text.

b. DESCRIPTION

i. Please specify that the molecular formula and molecular weight are based on the "anhydrous" form of your drug product.

ii. Revise the molecular formula to read as follows"

(C17H19NO3)2*H2SO4

c. CLINICAL PHARMOCOLOGY. Pharmacodynamics

i. Cardiovascular System, - Second sentence

...to opioid-induced... (rather than " ———

ii. Plasma Level-analgesic Relationships

A) First paragraph, last sentence:

...20 ng/mL. (rather than " —

B) ..non-tolerant ... (hyphen in 3 instances)

d. **INDICATIONS AND USAGE**

They are intended ...(rather that " ——— .)

e. **PRECAUTIONS - Pediatric Use:**

... in pediatric patients.

f. **OVERDOSAGE – Second paragraph**

Delete the ——— to read "2 mg".

g. **DOSAGE AND ADMINISTRATION**

i. **General comment**

To facilitate the dosing of this drug product we feel that this section should contain reference to the dosing information for the other strengths (with the exception of 200 mg strength) as appearing in the insert labeling of the reference listed drug. Please revise accordingly and/or comment.

ii. **Conversion form Morphine Sulfate Extended-release Tablets to Parenteral Opiods**

A) Note the upper case letters in the title (see above).

B) Forth sentence

Replace the term " ——— with "morphine sulfate" throughout the sentence (3 instances).

Please revise your labels and labeling, as instructed above, and submit in final print, or in draft if you prefer.

As per your instructions, revised final printed labels and insert are included (see Exhibit 22)

Watson believes that all questions/concerned expressed by OGD regarding this deficiency letter have been resolved. If addition information is required, please call me at (909) 270-1400 or by fax at (909) 278-0967.

Sincerely,

Ernest Lengle, Ph.D.
Sr. Director, Regulatory Affairs

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

February 14, 2000

NDA [illegible] AMENDMENT
AB

Dale P. Conner, Pharm.D.
Director, Division of Bioeoquivalence
OGD, CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Re: Morphine Sulfate Control-release Tablets, 100 mg
ANDA 75-656

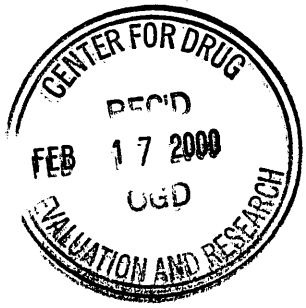
Dear Dr. Conner:

This is in response to a FDA deficiency letter dated November 24, 1999 regarding Morphine Sulfate Controlled-release Tablets, 100 mg (ANDA 75-656). For ease of review, FDA's comments are in bold face type followed by our response.

1. **It is not clear why most of the repeat analyses showed lower concentration than the first analysis for morphine and morphine-6- glucuronide. You should provide some explanation.**

   The _____ used by Watson acknowledges that, in general, it is true that repeated results are lower. The laboratory found that most repeats for morphine and morphine-6-glucuronide were performed because the original results was over the highest standard curve calibrator and could not be deemed reliable. Since the method has not been validated for results above the highest standard curve calibrator, their SOP requires repeat analyses with appropriate dilution to replace such unreliable results. Repeat analyses were performed according to their SOP on sponsor and control samples diluted to concentrations within the standard curve range.

   Results (other than unacceptable _____ not above the standard curve were repeated for pharmacokinetic reasons (reliability of result is suspect by comparison with nearby samples results). Their SOP requires such repeat analysis samples to be run in duplicate and an average of the two closest results to be reported as the final data. This is their means of looking at possible outliers to either confirm the reliability of the original result or to correct unreliable data.



2. **In the fasting study, the reason for repeat analysis for Subject #11, Period 2, 3.5 hr. sample for morphine is labeled "Over the highest calibration standard" even though the result from the first analysis shows a concentration of [redacted] The highest calibration standard in this case is [redacted] You should make appropriate corrections and provide necessary explanation.**

   Regretfully, the first analysis reported concentration ([redacted]) was incorrect and should have been reported as [redacted] Enclosed please fine an amendment for 83-64 that corrects and explains the typographical error (see Exhibit 1). Please note that this correction is to data in the repeat table and does not affect study sample final data.

3. **In non-fasting study, the reason for repeat analysis for Subject #11. Period 3, 48 hr. sample for morphine is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows a concentration of [redacted] The highest calibration standard in this case is [redacted]. Similarly, reason for repeat analysis for Subject #13, Period 1, 36 hr. sample for morphine-6-glucuronide is labeled "Over the highest calibration standard" (Code #2) even though the result from the first analysis shows a concentration of "Below the Limit of Quantitation [redacted] or code "*"). You should make appropriate corrections and provide necessary explanation.**

   The cited reasons for repeat analysis were in error. Attached is an amendment to 83-65 corrects and explains the typographical errors (see Exhibit 2). Please note that these corrections are to information in the repeat tables and do not affect study sample final data.

4. **In the fasting study, the subjects were dosed in two Groups. The firm should evaluate any Group effects on PK parameters, and include the Group term in the model:**

   Model (Y) = Group Sequence Group*Sequence Subject(Group*Sequence)
   Period Period*Group Treatment Group*Treatment

   The existence of group effects on the PK parameters was evaluated in the 083-64(fasting) study. The methods are on page 6 of the report and the results are mentioned on pages 9-12 (for each analyte). The ANOVA output is in Appendix 3. The method used was slightly different from that suggested by the reviewer. The ANOVA model included the following factors: period, treatment, group, treatment-by-group interaction, sequence nested within group, and subject nested within sequence and group. Section 4.4 of the report documents that the interaction and group terms were not significant and were therefore removed from the final model.

The analysis has been repeated using the suggested model. The revised summary tables and ANOVA output are enclosed (see Exhibit 3). It was determined that "group" was not significant. There were not significant changes to the results and no changes to the conclusion.

5. **You have not provided Cmin, Cave and Degree of Fluctuation (DF) data with the electronic data files or diskette. These values should be entered with PK parameters for proper evaluation.**

   Electron data diskette containing the Plasma Pharmacokinetic Datafiles for Morphine Sulfate CR Tablets, 100 mg Study #083-66 is attached (see Exhibit 4). Cmin, Cave and Degree of Fluctuation (DF) data are included as requested by FDA.

6. **You should evaluate Cmin values, obtained at 120, 144 and 156 hrs. sampling time points.**

   In accordance with the 1993 Guidance "Oral Extended (Controlled) Release Dosage Forms in Vivo Bioequivalence and In Vitro Dissolution Testing", we have evaluated the trough values using at least three consecutive days and samples collected at the same time of day in the previously submitted report (083-66). We believe evaluating the 156-hour value would not be appropriate in this case due to the circadian fluctuation of Morphine (Gourlay et al., "Chronopharmacokinetic variablity in plasma morphine concentrations following oral doses of morphine solution". Pain, 61:375-81, 1995)/

7. **You have conducted dissolution for 1 hour in SGF (without enzyme) followed by 11 hours in SIF (without enzyme) medium. In order to set appropriate specifications, you should conduct comparative dissolution of the test and reference products in water and additional 4a media at pH 1.2, 4.4, 6.8 and 7.5. The test should include the following conditions: 12 dosage units each, 900 mL medium at 37C, USP Apparatus I (Basket) at 50 rpm, and at least [redacted] as sampling time points.**

   The dissolution profile comparisons and data in graph form between test sample (Watson's Morphine Sulfate Control-release Tablets, 100 mg (Lot #PG-15172)) and reference sample (Purdue Frederick's MS Contin 100mg, (Lot #53J1)) are given in Exhibit 4

Morphine Sulfate Control-release Tablets, 100 mg
ANDA 75-656
Feb. 14, 2000

We believe that we have addressed all of FDA's concerns. If you have any additional questions or if I can assist you with the review of this amendment, please contact me by telephone at (909) 270-1400 or by facsimile at (909) 278-0967.

Sincerely,

Ernest Lengle, Ph.D.
Senior Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

August 19, 1999

TELEPHONE AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

NDA ORIG AMENDMENT
AA

Reference: Morphine Sulfate Tablets Controlled Release, 100 mg
ANDA 75-656

Gentlemen:

This is in response to your letter, dated August 2, 1999, accepting our Morphine Sulfate Tablets Controlled Release 100 mg, ANDA 75-656 for filing and a telephone call on August 5, 1999 from Jennifer San of your Office.

A disk containing CMC and Bio EVA data is enclosed. Watson Laboratories certifies that, to the best of our abilities, the data on the disk is identical to that in the hard copy that was acceptable for filing June 29, 1999. We apologize for the delay in submitting this disk, but we did not anticipate that it would take about two person-months to complete this arduous task. For your assistance and due to their length, we are enclosing hard copies of the companion documents, which are also found on the disk in electronic format.

Please contact me or Carol Jones at the phone number below, extensions 121 and 131 respectively, if you have any questions or require any further information.

Sincerely,

Loren Gelber

WATSON LABORATORIES, INC.
Loren Gelber, Ph.D.
Vice President Regulatory Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 20 1999
OGD

5350 North West 165th Street, Miami, FL 33014 • Tel: 305-624-1500 • Fax: 305-621-8416
16600 North West 54th Avenue, Miami, FL 33014 • Tel: 305-624-1500 • Fax: 305-625-7487

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

acic for filing
/S/ 7/19/99
505(j)(2)(A)

June 28, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

Gentlemen:

Watson Laboratories, Inc. is submitting an Abbreviated New Drug Application under section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Morphine Sulfate Tablets Controlled Release 100 mg. Please note that Royce Laboratories became a wholly owned subsidiary of Watson Pharmaceuticals in April 1997 and is now doing business as Watson Laboratories, Inc. Miami Florida. Due to this transition, the documents in this application may contain the Royce name, the Watson name, or both names.

This application is organized as suggested in the Guidance for Industry – Organization of an ANDA, OGD #1 Revision 1, February 1999. The archival (blue) copy contains 27 volumes, The Chemistry Section (red) copy contains 3 volumes, and the Bioavailability Section (orange) copy contains 24 volumes. Financial disclosure certifications are found in the biostudy, Volume 2. Generic Enforcement Act and Field Copy Certifications are found in Volume 27, Sections XX and XXI respectively.

Sincerely,

Loren Gelber

WATSON LABORATORIES, INC.
Loren Gelber, Ph.D.
Vice President Regulatory Compliance Miami

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 29 1999
OGD

5350 North West 165th Street, Miami, FL 33014 • Tel: 305-624-1500 • Fax: 305-621-8416
16600 North West 54th Avenue, Miami, FL 33014 • Tel: 305-624-1500 • Fax: 305-625-7487