

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 200812

Name: Morphine Sulfate Extended-release Capsules USP
20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

Sponsor: Watson Laboratories, Inc-Florida.

Approval Date: November 10, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200812

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200812

APPROVAL LETTER



ANDA 200812

Watson Laboratories, Inc-Florida
Attention: Janet Vaughn,
Director Regulatory Affairs
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 16, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg.

Reference is also made to your amendments dated November 10, December 9, 2010; February 16, May 4, May 17, May 18, June 27, August 11, August 17, September 12, September 13, and November 7 2011.

We have completed the review of this ANDA and have concluded that the criteria for approval in section 505(j) of the FDCA have been met. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Kadian (Morphine Sulfate Extended-release) Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg, of Actavis Elizabeth LLC.

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

Specifications:

Time (hours)	Percent Dissolved
1	NMT 10
4	(b) (4)
6	
9	NLT 85

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 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. On April 19, 2011, you were notified that in accordance with section 505-1 of the FDCA, we determined that a REMS is necessary for certain long-acting and extended-release (LA/ER) opioid products, including Morphine Sulfate Extended-release Capsules, to ensure that the benefits of the drugs continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. You were also notified that in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the LA/ER opioid class.

We acknowledge receipt of your proposed REMS in the amendment dated August 17, 2011, submitted in response to our April 19, 2011 REMS notification letter. At this time, the RLD, Kadian (morphine sulfate extended-release) Capsules, does not have an approved REMS. Therefore, we are not approving a REMS as part of this application approval, but we will act on your REMS proposal at the time we act on the class-wide LA/ER opioid single shared system REMS. We expect you to be working with the Industry Working Group (IWG) to develop the class-wide REMS.

Postmarketing reporting requirements for this ANDA 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.

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

11/10/2011

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200812

LABELING

NDC 0591-3449-30

Morphine Sulfate

Extended-release Capsules, USP

(Once or twice Daily Formulation)

20 mg

Watson

30 Capsules Rx only

Each extended-release capsule contains: 20 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198529

Distributed by: **Watson Pharma, Inc.**

LOT:
EXP:

Product Name: Morphine Sulfate ER Capsules, USP-20 mg-30 Count

Designed by: (b) (6)
Date: 04/27/2011

Proof by:

Proof by:

Pantone

Pantone

(b) (4)

(b) (4)

Black

K

Dieline
Varnish

CMYK
Size: 4.75" x 1.75"

NDC 0591-3449-01

Morphine Sulfate Extended-release Capsules, USP

(Once or twice Daily Formulation)

20 mg



100 Capsules Rx only



Each extended-release capsule contains: 20 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198530

Distributed by: **Watson Pharma, Inc.**



05913449015

LOT:
EXP:

Product Name: Morphine Sulfate ER Capsules, USP-20 mg-100 Count

Designed by: (b) (6) Date: 04/27/2011

Proof by: _____

Proof by: _____

Color Chart:



CMYK

Size: 5.5" x 2.375"

Varnish

NDC 0591-3450-30

Morphine Sulfate
Extended-release Capsules, USP
(Once or twice Daily Formulation)

30 mg

Watson  30 Capsules Rx only



Each extended-release capsule contains: 30 mg morphine sulfate as extended-release pellets.
Usual dosage: See accompanying prescribing information.
The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.
Warning: As with all medication, keep out of the reach of children.
Dispense in a sealed, tamper-evident, childproof, light-resistant container.
Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA 198531

Distributed by: **Watson Pharma, Inc.**

 0591345030 1

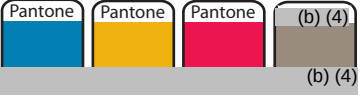
LOT: _____
EXP: _____

Product Name: Morphine Sulfate ER Capsules, USP-30 mg-30 Count

Designed by: (b) (6) Date: 04/27/2011

Proof by: _____

Proof by: _____

Color Chart:  Pantone Pantone Pantone (b) (4) Black (b) (4) K

 CMYK Dieline Varnish

Size: 4.75" x 1.75"

NDC 0591-3450-01

Morphine Sulfate Extended-release Capsules, USP

(Once or twice Daily Formulation)

30 mg



100 Capsules Rx only



Each extended-release capsule contains: 30 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198532

Distributed by: **Watson Pharma, Inc.**



0591345001

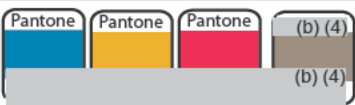
LOT:
EXP:

Product Name: Morphine Sulfate ER Capsules, USP-30 mg-100 Count

Designed by: (b) (6) Date: 04/27/2011

Proof by: _____

Proof by: _____

Color Chart:  Pantone Pantone Pantone (b) (4) Black Dieline CMYK Size: 5.5" x 2.375" Varnish

NDC 0591-3451-30

Morphine Sulfate

Extended-release Capsules, USP

(Once or twice Daily Formulation)

50 mg

Watson

30 Capsules Rx only

Each extended-release capsule contains: 50 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198533

Distributed by: **Watson Pharma, Inc.**

LOT: _____
EXP: _____

Product Name: Morphine Sulfate ER Capsules, USP-50 mg-30 Count

Designed by: (b) (6)
Date: 04/27/2011

Proof by: _____

Proof by: _____

Pantone

Pantone

(b) (4)

Black

Dieline

(b) (4)

K

Varnish

Color Chart:

CMYK

Size: 4.75" x 1.75"

NDC 0591-3451-01

Morphine Sulfate Extended-release Capsules, USP

(Once or twice Daily Formulation)

50 mg



100 Capsules Rx only



Each extended-release capsule contains: 50 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198534

Distributed by: **Watson Pharma, Inc.**



05913451018

LOT:
EXP:

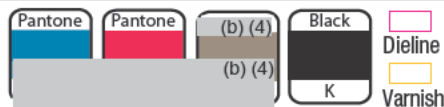
Product Name: Morphine Sulfate ER Capsules, USP-50 mg-100 Count

Designed by: (b) (6) Date: 04/27/2011

Proof by: _____

Proof by: _____

Color Chart:



CMYK

Size: 5.5" x 2.375"

NDC 0591-3452-30

Morphine Sulfate

Extended-release Capsules, USP

(Once or twice Daily Formulation)

60 mg

Watson.

30 Capsules Rx only

Each extended-release capsule contains: 60 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198561

Distributed by: **Watson Pharma, Inc.**

05913452305

LOT: BP:

Product Name: Morphine Sulfate ER Capsules, USP-60 mg-30 Count

Designed by: (b) (6)
Date: 04/27/2011

Proof by:

Proof by:

Pantone

Pantone

Pantone

(b) (4)

Black

Dieline

CMYK

Color Chart:

(b) (4)

K

Varnish

Size: 4.75" x 1.75"

NDC 0591-3452-01

Morphine Sulfate Extended-release Capsules, USP

(Once or twice Daily Formulation)

60 mg



100 Capsules Rx only



Each extended-release capsule contains: 60 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198535

Distributed by: **Watson Pharma, Inc.**



05913452015

LOT:
EXP:

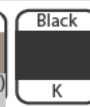
Product Name: Morphine Sulfate ER Capsules, USP-60 mg-100 Count

Designed by: (b) (6) Date: 04/27/2011

Proof by: _____

Proof by: _____

Color Chart:



CMYK
Dieline
Varnish

Size: 5.5" x 2.375"

NDC 0591-3576-30

Morphine Sulfate

Extended-release Capsules, USP

(Once or twice Daily Formulation)

80 mg

Watson.

Each extended-release capsule contains: 80 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198537

Distributed by: **Watson Pharma, Inc.**

0591357630 8

LOT: BP:

30 Capsules Rx only

Product Name: Morphine Sulfate ER Capsules, USP-80 mg-30 Count

Designed by: (b) (6)
Date: 04/27/2011

Proof by:

Proof by:

Pantone

Pantone

Pantone

(b) (4)

Black

Dieline

CMYK

Color Chart:

(b) (4)

K

Varnish

Size: 4.75" x 1.75"

NDC 0591-3576-01

Morphine Sulfate Extended-release Capsules, USP

(Once or twice Daily Formulation)

80 mg



100 Capsules Rx only



Each extended-release capsule contains: 80 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198536

Distributed by: **Watson Pharma, Inc.**



059131576018

LOT:
EXP:

Product Name: Morphine Sulfate ER Capsules, USP-80 mg-100 Count

Designed by: (b) (6) Date: 04/27/2011

Proof by: _____

Proof by: _____

Color Chart:  **CMYK**
Dieline Size: 5.5" x 2.375"
Varnish

NDC 0591-3453-30

Morphine Sulfate
Extended-release Capsules, USP
(Once or twice Daily Formulation)

100 mg

Watson.

30 Capsules Rx only

Each extended-release capsule contains: 100 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198538

Distributed by: **Watson Pharma, Inc.**

059134533012

LOT: BP:

Product Name: Morphine Sulfate ER Capsules, USP-100 mg-30 Count

Designed by: (b) (6)
Date: 04/27/2011

Proof by:

Proof by:

Pantone

Pantone

Pantone

(b) (4)

Black

Dieline

CMYK

Color Chart:

(b) (4)

K

Varnish

Size: 4.75" x 1.75"

NDC 0591-3453-01

Morphine Sulfate Extended-release Capsules, USP

(Once or twice Daily Formulation)

100 mg



100 Capsules Rx only



Each extended-release capsule contains: 100 mg morphine sulfate as extended-release pellets.

Usual dosage: See accompanying prescribing information.

The pellets for Morphine Sulfate Extended-Release capsules should NOT be chewed, crushed or dissolved.

Warning: As with all medication, keep out of the reach of children.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880 USA

198539

Distributed by: **Watson Pharma, Inc.**



05913453012

LOT:
EXP:

Product Name: Morphine Sulfate ER Capsules, USP-100 mg-100 Count

Designed by: (b) (6) Date: 04/27/2011

Proof by: _____

Proof by: _____

Color Chart:



CMYK
Dieline
Size: 5.5" x 2.375"
Varnish

Morphine Sulfate Extended-release Capsules, USP CII

Morphine sulfate extended-release capsules, USP 20 mg
Morphine sulfate extended-release capsules, USP 30 mg
Morphine sulfate extended-release capsules, USP 50 mg
Morphine sulfate extended-release capsules, USP 60 mg
Morphine sulfate extended-release capsules, USP 80 mg
Morphine sulfate extended-release capsules, USP 100 mg

Rx only

WARNING:
Morphine sulfate extended-release capsules contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Morphine sulfate extended-release capsules can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing morphine sulfate extended-release capsules in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Morphine sulfate extended-release capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

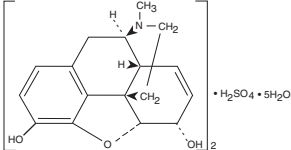
Morphine sulfate extended-release capsules are NOT for use as a prn analgesic.

Morphine sulfate extended-release capsules 100 mg ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. MORPHINE SULFATE EXTENDED-RELEASE CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE PELLETS IN THE CAPSULES ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

DESCRIPTION

Morphine sulfate extended-release capsules, USP are an opioid analgesic supplied in 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg strengths for oral administration.

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



Morphine sulfate is an odorless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol: water partition coefficient of morphine is 1.42 at physiologic pH and the pKb is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). Each morphine sulfate extended-release capsule contains either 20 mg, 30 mg, 50 mg, 60 mg, 80 mg or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: corn starch, diethyl phthalate, ethylcellulose, hypromellose 2910, methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30, and talc. The capsule shells contain black iron oxide, gelatin, propylene glycol and titanium dioxide. In addition, the 20 mg capsule shell contains D&C yellow #10, the 30 mg capsule shell contains FD&C blue #1 and FD&C red #3, the 50 mg capsule shell contains FD&C blue #1, the 60 mg capsule shell contains D&C red #28, FD&C blue #1 and FD&C red #40, the 80 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C red #40 and FD&C yellow #6 and the 100 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C green # 3 and FD&C red #40.

USP Dissolution Test is pending.

CLINICAL PHARMACOLOGY

Morphine is a natural product that is the prototype for the class of natural and synthetic opioid analgesics. Opioids produce a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release and physical dependence.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body. Morphine acts as a pure agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Effects on the 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 brainstem 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, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in the setting of morphine sulfate extended-release overdose (See OVERDOSAGE).

Effects on the 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 the sphincter of Oddi.

Effects on the Cardiovascular System

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

Pharmacodynamics

Plasma Level-Analgesia Relationships

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose.

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 to 50 times as great (or greater) than the appropriate dose for opioid-naïve individuals. Dosages of morphine should be chosen and must be titrated on the 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.

Pharmacokinetics

Morphine sulfate extended-release capsules contain polymer coated extended-release pellets of morphine sulfate that release morphine significantly more slowly than from conventional oral preparations. Morphine sulfate extended-release activity is primarily due to morphine. One metabolite, morphine-6- glucuronide, has been shown to have analgesic activity, but does not readily cross the blood-brain barrier.

Following oral administration of morphine, the extent of absorption is essentially the same for immediate or extended-release formulations, although the time to peak blood level (T_{max}) will be longer and the C_{max} will be lower for formulations that delay the release of morphine in the gastrointestinal tract. Elimination of morphine is primarily via hepatic metabolism to glucuronide metabolites (55 to 65%) which are then renally excreted. The terminal half-life of morphine is 2 to 4 hours, however, a longer term half-life of about 15 hours has been reported in studies where blood has been sampled up to 48 hours.

The single-dose pharmacokinetics of morphine sulfate extended-release are linear over the dosage range of 30 to 100 mg. The single dose and multiple dose pharmacokinetic parameters of morphine sulfate extended-release in normal volunteers are summarized in Table 1.

Table 1: Mean pharmacokinetic parameters (% coefficient variation) resulting from a fasting single dose study in normal volunteers and a multiple dose study in patients with cancer pain.

Regimen/ Dosage Form	AUC _{0-8h} + (ng.h/mL)	C _{max} + (ng/mL)	T _{max} (h)	C _{min} + (ng/mL)	Fluctuation*
Single Dose (n=24)					
Morphine Sulfate Extended-release Capsule	271.0 (19.4)	15.6 (24.4)	8.6 (41.1)	na [^]	na
Extended-ReleaseTablet	304.3 (19.1)	30.5 (32.1)	2.5 (52.6)	na	na
Morphine Solution	362.4 (42.6)	64.4 (38.2)	0.9 (55.8)	na	na
Multiple Dose (n=24)					
Morphine Sulfate Extended-release Capsules q24h	500.9 (38.6)	37.3 (37.7)	10.3 (32.2)	9.9 (52.3)	3.0 (45.5)
Extended-Release Tablet q12h	457.3 (40.2)	36.9 (42.0)	4.4 (53.0)	7.6 (60.3)	4.1 (51.5)

For single dose AUC = AUC_{0-8h}, for multiple dose AUC = AUC_{0-24h} at steady state

+ For single dose parameter normalized to 100 mg, for multiple dose parameter normalized to 100 mg per 24 hours

* Steady-state fluctuation in plasma concentrations = C_{max}-C_{min}/C_{min}

[^] Not applicable

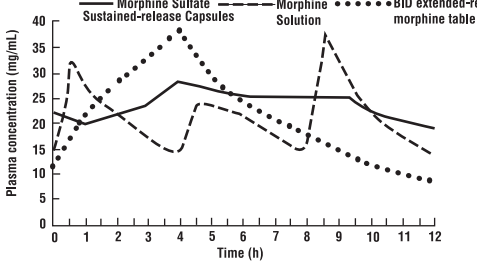
Absorption

Following the administration of oral morphine solution, approximately 50% of the morphine absorbed reaches the systemic circulation within 30 minutes. However, following the administration of an equal amount of morphine sulfate extended-release to healthy volunteers, this occurs, on average, after 8 hours. As with most forms of oral morphine, because of pre-systemic elimination, only about 20 to 40% of the administered dose reaches the systemic circulation.

Food Effects: While concurrent administration of food slows the rate of absorption of morphine sulfate extended-release, the extent of absorption is not affected and morphine sulfate extended-release can be administered without regard to meals.

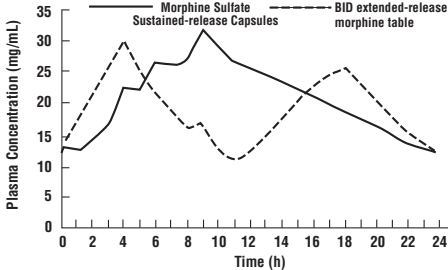
Steady State: When morphine sulfate extended-release is given on a fixed dosing regimen to patients with chronic pain due to malignancy, steady state is achieved in about two days. At steady state, morphine sulfate extended-release will have a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution and some other extended-release preparations (see Graph 1).

Graph 1 (Study # MOB-1/90): Mean steady state plasma morphine concentrations for morphine sulfate extended-release capsule (twice a day), extended-release morphine tablet (twice a day) and oral morphine solution (every 4 hours); plasma concentrations are normalized to 100 mg every 24 hours, (n=24).



When given once-daily (every 24 hours) to 24 patients with malignancy, morphine sulfate extended-release had a similar C_{max} and higher C_{min} at steady state in clinical usage, when compared to twice-daily (every 12 hours) extended-release morphine tablets, given at an equivalent total daily dosage (see Graph 2 and Table 1). Drug-disease interactions are frequently seen in the older and more gravely ill patients, and may result in both altered absorption and reduced clearance as compared to normal volunteers (see **Geriatric, Hepatic Failure, and Renal Insufficiency** sections).

Graph 2 (Study # MOR-9/92): Dose normalized mean steady state plasma morphine concentrations for morphine sulfate extended-release (once a day), and an equivalent dose of a 12-hour, extended-release morphine tablet given twice a day. Plasma concentrations are normalized to 100 mg every 24 hours, (n=24).



Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. The volume of distribution of morphine is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier. Morphine also crosses the placental membranes (see **PRECAUTIONS - Pregnancy**) and has been found in breast milk (see **PRECAUTIONS - Nursing Mothers**).

Metabolism

The major pathway of the detoxification of morphine is conjugation, either with D-glucuronic acid in the liver to produce glucuronides or with sulfuric acid to give morphine-3-etheral sulfate. Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%). Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar after both single doses and at steady state for morphine sulfate extended-release, 12-hour extended-release morphine sulfate tablets and morphine sulfate solution.

M3G has no significant analgesic activity. M6G has been shown to have opioid agonist and analgesic activity in humans.

Excretion

Approximately 10% of morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven to 10% of administered morphine is excreted in the feces.

The mean adult plasma clearance is about 20 to 30 mL/minute/kg. The effective terminal half-life of morphine after IV administration is reported to be approximately 2.0 hours. Longer plasma sampling in some studies suggests a longer terminal half-life of morphine of about 15 hours.

Special Populations

Geriatric: The elderly may have increased sensitivity to morphine and may achieve higher and more variable serum levels than younger patients. In adults, the duration of analgesia increases progressively with age, though the degree of analgesia remains unchanged. Morphine sulfate extended-release pharmacokinetics have not been investigated in elderly patients (>65 years) although such patients were included in the clinical studies.

Nursing Mothers: Morphine is excreted in the maternal milk, and the milk to plasma morphine AUC

ratio is about 2.5:1. The amount of morphine received by the infant depends on the maternal plasma concentration, amount of milk ingested by the infant, and the extent of first pass metabolism. Pediatric: Infants under 1 month of age have a prolonged elimination half-life and decreased clearance relative to older infants and pediatric patients. The clearance of morphine and its elimination half-life begin to approach adult values by the second month of life. Pediatric patients old enough to take capsules should have pharmacokinetic parameters similar to adults, dosed on a per kilogram basis (see **PRECAUTIONS - Pediatric Use**).

Gender: No meaningful differences between male and female patients were demonstrated in the analysis of the pharmacokinetic data from clinical studies.

Race: Pharmacokinetic differences due to race may exist. Chinese subjects given intravenous morphine in one study had a higher clearance when compared to caucasian subjects (1852 ± 116 mL/min versus 1495 ± 80 mL/min).

Hepatic Failure: The pharmacokinetics of morphine were found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these patients indicating a decrease in metabolic activity.

Renal Insufficiency: The pharmacokinetics of morphine are altered in renal failure patients. AUC is increased and clearance is decreased. The metabolites, M3G and M6G accumulate several fold in renal failure patients compared with healthy subjects.

Drug-Drug Interactions: The known drug interactions involving morphine are pharmacodynamic, not pharmacokinetic (see **PRECAUTIONS - Drug Interactions**).

INDICATIONS AND USAGE

Morphine sulfate extended-release capsules, USP are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time (see **CLINICAL PHARMACOLOGY**).

Morphine sulfate extended-release capsules, USP are NOT intended for use as a prn analgesic.

Morphine sulfate extended-release capsules, USP are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. Morphine sulfate extended-release capsules, USP are only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

Morphine sulfate extended-release capsules are contraindicated in patients with a known hypersensitivity to morphine, morphine salts or any of the capsule components, or in any situation where opioids are contraindicated. This includes in patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute or severe bronchial asthma or hypercarbia. Morphine sulfate extended-release capsules are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

Morphine sulfate extended-release capsules are to be swallowed whole and are not to be chewed, crushed, or dissolved. Taking chewed, crushed, or dissolved morphine sulfate extended-release capsules, USP leads to rapid release and absorption of a potentially fatal dose of morphine.

Morphine sulfate extended-release capsules 100 mg ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This capsule strength may cause fatal respiratory depression when ingested or administered to patients who are not previously exposed to opioids.

Care should be taken in the prescribing of this capsule strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Morphine sulfate extended-release contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing morphine sulfate extended-release in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Abuse of morphine sulfate extended-release by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS and DRUG ABUSE AND DEPENDENCE**)

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Morphine sulfate extended-release may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Impaired Respiration

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs more frequently in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction (when even moderate therapeutic doses may significantly decrease pulmonary ventilation).

Morphine sulfate extended-release 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 (e.g. severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

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 a pre-existing increase in intracranial pressure. Morphine sulfate extended-release produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries. Morphine should only be administered under such circumstances when considered essential and then with extreme care.

Hypotensive Effect

Morphine sulfate extended-release may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has already been compromised by a reduced 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 and syncope in ambulatory patients.

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

Interactions with other CNS Depressants

Morphine sulfate extended-release 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.

Gastrointestinal Obstruction

Morphine sulfate extended-release should not be given to patients with gastrointestinal obstruction, particularly paralytic ileus, as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine formulations diarrhea may reduce morphine absorption.

Other

Although extremely rare, cases of anaphylaxis have been reported.

PRECAUTIONS

General

Morphine sulfate extended-release is intended for use in patients who require continuous, around-the-clock opioid analgesia for an extended period of time. As with any potent opioid, it is critical to

adjust the dosing regimen for morphine sulfate extended-release for each patient, 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 of morphine sulfate extended-release, attention should be given to the points under **DOSAGE AND ADMINISTRATION**.

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Selection of patients for treatment with morphine sulfate extended-release should be governed by the same principles that apply to the use of any 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; 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 sulfate extended-release may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Morphine sulfate extended-release may aggravate pre-existing convulsions in patients with convulsive disorders.

Cordotomy

Patients taking morphine sulfate extended-release who are scheduled for cordotomy or other interruption of pain transmission pathways should have morphine sulfate extended-release ceased 24 hours prior to the procedure and the pain controlled by parenteral short-acting opioids. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes.

Use in Pancreatic/Biliary Tract Disease

Morphine sulfate extended-release may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Special Risk Groups

Morphine sulfate extended-release should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxedema; hypothyroidism; prostatic hypertrophy or urethral stricture.

Caution should also be exercised in the administration of morphine sulfate extended-release to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens, and convulsive disorders.

Driving and Operating Machinery

Morphine sulfate extended-release may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of morphine sulfate extended-release with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol (see **Drug Interactions**).

Information for Patients

If clinically advisable, patients receiving morphine sulfate extended-release, or their caregivers should be given the following information by the physician, nurse, or pharmacist:

1. Patients should be advised that morphine sulfate extended-release contains morphine and should be taken only as directed.
2. Patients should be advised that morphine sulfate extended-release capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternately, morphine sulfate extended-release capsules, USP may be opened and the entire contents sprinkled on a small amount of apple sauce immediately prior to ingestion. Morphine sulfate extended-release capsules, USP or the contents of the capsules must not be chewed or crushed due to a risk of fatal overdose.
3. Patients should be advised that morphine sulfate extended-release capsules, 100 mg are for use only in opioid-tolerant patients. Special care must be taken to avoid accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.
4. Patients should be advised that the dose of morphine sulfate extended-release should not be adjusted without consulting the prescribing health care provider.
5. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should be advised that morphine sulfate extended-release 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.
7. Patients should be advised that morphine sulfate extended-release should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) except by the orders of the prescribing healthcare provider because dangerous additive effects may occur resulting in serious injury or death.
8. Women of childbearing potential who become or are planning to become pregnant, should consult their prescribing healthcare provider prior to initiating or continuing therapy with morphine sulfate extended-release.
9. Patients should be advised that if they have been receiving treatment with morphine sulfate extended-release for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the morphine sulfate extended-release dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their prescribing healthcare provider should provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be advised that morphine sulfate extended-release is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
11. Patients should be advised that severe constipation could occur as a result of taking morphine sulfate extended-release and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.
12. Patients should be instructed to keep morphine sulfate extended-release in a secure place out of the reach of children. When morphine sulfate extended-release is no longer needed, the unused capsules should be destroyed by flushing down the toilet.

Drug Interactions

CNS Depressants: Morphine should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the initial dose of one or both agents should be reduced by at least 50%.

Muscle Relaxants: morphine sulfate extended-release may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.

Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and buproporphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as morphine sulfate extended-release. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of morphine sulfate extended-release c and/or may precipitate withdrawal symptoms in these patients.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and significant depression of respiration or coma.

NON TEXT AREA

Morphine sulfate extended-release should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

Cimetidine: There is an isolated report of confusion and severe respiratory depression when a hemodialysis patient was concurrently administered morphine and cimetidine.

Diuretics: Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. There are no reports of carcinogenic effects in humans. *In vitro* studies have reported that morphine is non-mutagenic in the Ames test with *Salmonella*, and induces chromosomal aberrations in human leukocytes and lethal mutation induction in *Drosophila*. Morphine was found to be mutagenic *in vitro* in human T-cells, increasing the DNA fragmentation. *In vivo*, morphine was mutagenic in the mouse micronucleus test and induced chromosomal aberrations in spermatids and murine lymphocytes. Chronic opioid abusers (e.g., heroin abusers) and their offspring display higher rates of chromosomal damage. However, the rates of chromosomal abnormalities were similar in nonexposed individuals and in heroin users enrolled in long term opioid maintenance programs.

Pregnancy

Teratogenic Effects (Pregnancy Category C)

Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurological, soft and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often maternally toxic and were 0.3 to 3-fold the maximum recommended human dose (MRHD) on a mg/m² basis. The relative contribution of morphine-induced maternal hypoxia and malnutrition, each of which can be teratogenic, has not been clearly defined. Treatment of male rats with approximately 3-fold the MRHD for 10 days prior to mating decreased litter size and viability.

Nonteratogenic Effects

Morphine given subcutaneously, at non-maternally toxic doses, to rats during the third trimester with approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, and testes size and body weight in the offspring, and decreased fertility in female offspring. The offspring of rats and hamsters treated orally or intraperitoneally throughout pregnancy with 0.04-to 0.3-fold the MRHD of morphine have demonstrated delayed growth, motor and sexual maturation and decreased male fertility. Chronic morphine exposure of fetal animals resulted in mild withdrawal, altered reflex and motor skill development, and altered responsiveness to morphine that persisted into adulthood.

There are no well-controlled studies of chronic *in utero* exposure to morphine sulfate in human subjects. However, uncontrolled retrospective studies in human neonates chronically exposed to other opioids *in utero*, demonstrated reduced brain volume which normalized over the first month of life. Infants born to opioid-abusing mothers are more often small for gestational age, have a decreased ventilatory response to CO₂, and increased risk of sudden infant death syndrome. Morphine sulfate extended-release should only be used during pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus.

Labor and Delivery

Morphine sulfate extended-release is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Neonatal Withdrawal Syndrome

Chronic maternal use of opiates or opioids during pregnancy coexists the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration, and severity of the disorder differ based on such factors as the addictive drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital.

Nursing Mothers

Low levels of morphine sulfate have been detected in human milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Because of the potential for adverse reactions in nursing infants from morphine sulfate extended-release, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety of morphine sulfate extended-release, both the entire capsule and the pellets sprinkled on apple sauce, have not been directly investigated in pediatric patients below the age of 18 years. The range of doses available is not suitable for the treatment of very young pediatric patients or those who are not old enough to take capsules safely. The apple sauce sprinkling method is not an appropriate alternative for these patients.

Geriatric Use

Clinical studies of morphine sulfate extended-release did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Serious adverse reactions that may be associated with morphine sulfate extended-release therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock (see **OVERDOSAGE, WARNINGS**).

The less severe adverse events seen on initiation of therapy with morphine sulfate extended-release are also typical opioid side effects. These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include drowsiness, dizziness, constipation and nausea. In many cases, the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large rapid swings in plasma concentrations of the opioid. Many of these adverse events, will cease or decrease as morphine sulfate extended-release therapy is continued and some degree of tolerance is developed, but others may be expected to remain troublesome throughout therapy.

Management of Excessive Drowsiness

Most patients receiving morphine sulfate extended-release will experience initial drowsiness. This usually disappears within 3 to 5 days and is not a cause of concern unless it is excessive, or accompanied by unsteadiness or confusion. Dizziness and unsteadiness may be associated with postural hypotension, particularly in elderly or debilitated patients, and has been associated with syncope and falls in non-tolerant patients started on opioids.

Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, intolerance to the dose used (especially in older patients), disease severity and the patient's general condition.

The dosage should be adjusted according to individual needs, but additional care should be used in the selection of initial doses for the elderly patient, the cachectic or gravely ill patient, or in patients not already familiar with opioid analgesic medications to prevent excessive sedation at the onset of treatment.

Management of Nausea and Vomiting

Nausea and vomiting are common after single doses of morphine sulfate extended-release or as an early undesirable effect of chronic opioid therapy. The prescription of a suitable antiemetic should be considered, with the awareness that sedation may result (see **Drug Interactions**). The frequency of nausea and vomiting usually decreases within a week or so but may persist due to opioid-induced gastric stasis. Metoclopramide is often useful in such patients.

Management of Constipation

Virtually all patients suffer from constipation while taking opioids, such as morphine sulfate extended-release, on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients may become impacted. Tolerance does not usually develop for the constipating effects of opioids.

Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be used prophylactically from the beginning of opioid therapy.

Adverse Events Probably Related to morphine sulfate extended-release Administration

In clinical studies in patients with chronic cancer pain the most common adverse events reported by patients at least once during therapy were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from morphine sulfate extended-release or seen in less than 3% of patients in the clinical studies were:

Body as a Whole: Asthenia, accidental injury, fever, pain, chest pain, headache, diaphoresis, chills, flu syndrome, back pain, malaise, withdrawal syndrome

Cardiovascular: Tachycardia, atrial fibrillation, hypotension, hypertension, pallor, facial flushing, palpitations, bradycardia, syncope

Central Nervous System: Confusion, dry mouth, anxiety, abnormal thinking, abnormal dreams, lethargy, depression, tremor, loss of concentration, insomnia, amnesia, paresthesia, agitation, vertigo, foot drop, ataxia, hypesthesia, slurred speech, hallucinations, vasodilation, euphoria, apathy, seizures, myoclonus

Endocrine: Hyponatremia due to inappropriate ADH secretion, gynecomastia

Gastrointestinal: Vomiting, anorexia, dysphagia, dyspepsia, diarrhea, abdominal pain, stomach atony disorder, gastro-esophageal reflux, delayed gastric emptying, biliary colic

Hemic & Lymphatic: Anemia, leukopenia, thrombocytopenia

Metabolic & Nutritional: Peripheral edema, hyponatremia, edema

Musculoskeletal: Back pain, bone pain, arthralgia

Respiratory: Hiccup, rhinitis, atelectasis, asthma, hypoxia, dyspnea, respiratory insufficiency, voice alteration, depressed cough reflex, non-cardiogenic pulmonary edema

Skin and Appendages: Rash, decubitus ulcer, pruritus, skin flush

Special Senses: Amblyopia, conjunctivitis, miosis, blurred vision, nystagmus, diplopia

Urogenital: Urinary abnormality, amenorrhea, urinary retention, urinary hesitancy, reduced libido, reduced potency, prolonged labor

Post-marketing Adverse Events Probably Related to Morphine Sulfate Extended-Release

The safety of morphine sulfate extended-release has been evaluated in a randomized, prospective, open-label, 4-week treatment period, post-marketing study consisting of 1418 patients ages 18 to 85 with chronic, non-malignant pain (e.g., back pain, osteoarthritis, neuropathic pain). No control arm was included in this study. The most common adverse events reported at least once during therapy were constipation (12%), nausea (9%) and somnolence (3%). Other less common side effects occurring in less than 3% of patients were vomiting, pruritus, dizziness, sedation, dry mouth, headache, fatigue and rash.

DRUG ABUSE AND DEPENDENCE

Morphine sulfate extended-release is a mu-agonist opioid with an abuse liability similar to other opioid agonists and is a Schedule II controlled substance. Morphine sulfate extended-release and other opioids used in analgesia can be abused and are subject to criminal diversion.

Morphine sulfate extended-release is an opioid with no approved use in the management of addiction disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

“Drug-seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Morphine sulfate extended-release, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Morphine sulfate extended-release is intended for oral use only. Abuse of chewed, crushed, or dissolved capsules or pellets poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. Due to the presence of talc as one of the excipients in capsules, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

OVERDOSAGE

Symptoms

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, pulmonary edema, bradycardia, hypotension and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

Treatment

Primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Gastric contents may need to be emptied to remove unabsorbed drug when an extended-release formulation such as morphine sulfate extended-release has been taken. Care should be taken to secure the airway before attempting treatment by gastric emptying or activated charcoal.

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

The pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression which results from opioid overdose. Since the duration of reversal would be expected to be less than the duration of action of morphine sulfate extended-release, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Morphine sulfate extended-release will continue to release and add to the morphine load for up to 24 hours after administration and the management of an overdose should be monitored accordingly. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed by the manufacturer of the product.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Such agents 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 opioid effects may precipitate an acute abstinence syndrome.

Opioid Tolerant Individuals: In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal. The severity of the withdrawal produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

DOSAGE AND ADMINISTRATION

Morphine sulfate extended-release capsules may be administered once or twice daily.

Morphine sulfate extended-release capsules should be swallowed whole. The pellets in morphine sulfate extended-release capsules should not be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Alternatively, morphine sulfate extended-release capsules may be administered as a sprinkle on apple sauce or through a 16 French gastrostomy tube (see ALTERNATIVE METHODS OF ADMINISTRATION section).

The 100 mg capsules are for use only in opioid-tolerant patients.

Morphine sulfate extended-release capsules are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain), or for pain in the

immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in these settings have not been established.

Morphine sulfate extended-release capsules are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

Patients who are already receiving morphine sulfate extended-release capsules as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention.

Initiating Therapy with Morphine sulfate extended-release Capsules

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring.

It is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of morphine sulfate extended-release capsules, USP, attention should be given to:

- the total daily dose, potency and kind of opioid the patient has been taking previously;
- the reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed (Note: potency estimates may vary with the route of administration);
- the patient's degree of opioid experience and opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medication;
- the type and severity of the patient's pain.

Care should be taken to use low initial doses of morphine sulfate extended-release capsules in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS).

During periods of changing analgesic requirements including initial titration, frequent communication is recommended between physician, other members of the healthcare team, the patient, and the caregiver/family.

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

Conversion from Other Oral Morphine Formulations to Morphine sulfate extended-release capsules

Patients on other oral morphine formulations may be converted to morphine sulfate extended-release capsules by administering one-half of the patient's total daily oral morphine dose as morphine sulfate extended-release capsules every 12 hours (twice-a-day) or by administering the total daily oral morphine dose as morphine sulfate extended-release capsules every 24 hours (once-a-day). Morphine sulfate extended-release capsules should not be given more frequently than every 12 hours.

Conversion from Parenteral Morphine or Other Parenteral or Oral Opioids to Morphine sulfate extended-release capsules

Morphine sulfate extended-release capsules can be administered to patients previously receiving treatment with parenteral morphine or other opioids. While there are useful tables of oral and parenteral equivalents in cancer analgesia, there is substantial interpatient variation in the relative potency of different opioid drugs and formulations. For these reasons, it is better to underestimate the patient's 24-hour oral morphine requirement and provide rescue medication, than to overestimate and manage an adverse event. The following general points should be considered:

- Parenteral to Oral Morphine Ratio: It may take anywhere from 2 to 6 mg of oral morphine to provide analgesia equivalent to 1 mg of parenteral morphine. A dose of oral morphine three times the daily parenteral morphine requirement may be sufficient in chronic use settings.
- Other Parenteral or Oral Opioids to Oral Morphine Sulfate: There is lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, 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 safest to give half of the estimated daily morphine demand as the initial dose, and to manage inadequate analgesia by supplementation with immediate-release morphine. (See discussion which follows.)

The first dose of morphine sulfate extended-release capsules may be taken with the last dose of any immediate-release (short-acting) opioid medication due to the long delay until the peak effect after administration of morphine sulfate extended-release capsules.

Use of morphine sulfate extended-release capsules as the First Opioid Analgesic

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

Individualization of Dosage

The best use of opioid analgesics in the management of chronic malignant and non-malignant pain is challenging, and is well described in materials published by the World Health Organization and the Agency for Health Care Policy and Research which are available from Alphaarma Pharmaceuticals LLC upon request. Morphine sulfate extended-release capsules, USP are a third step drug which is most useful when the patient requires a constant level of opioid analgesia as a “floor” or “platform” from which to manage breakthrough pain. When a patient has reached the point where comfort cannot be provided with a combination of non-opioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24 hour oral morphine equivalent.

Morphine sulfate extended-release capsules should be started by administering one-half of the estimated total daily oral morphine dose every 12 hours (twice-a-day) or by administering the total daily oral morphine dose every 24 hours (once-a-day). The dose should be titrated no more frequently than every-other-day to allow the patients to stabilize before escalating the dose. If breakthrough pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of a short-acting analgesic. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to twice-a-day dosing.

Patients who do not have a proven tolerance to opioids should be started only on the 10 mg or 20 mg strength, and usually should be increased at a rate not greater than 20 mg every-other-day. Most patients will rapidly develop some degree of tolerance, requiring dosage adjustment until they have achieved their individual best balance between baseline analgesia and opioid side effects such as confusion, sedation and constipation. No guidance can be given as to the recommended maximal dose, especially in patients with chronic pain of malignancy. In such cases the total dose of morphine sulfate extended-release capsules should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions intervene.

Alternative Methods of Administration

In a study of healthy volunteers, morphine sulfate extended-release pellets sprinkled over apple sauce were found to be bioequivalent to morphine sulfate extended-release capsules swallowed whole with apple sauce under fasting conditions. Other foods have not been tested. Patients who have difficulty swallowing whole capsules or tablets may benefit from this alternative method of administration.

- Sprinkle the pellets onto a small amount of apple sauce. Apple sauce should be room temperature or cooler.
- The patient must be cautioned not to chew the pellets which could result in the immediate release of a potentially dangerous, even fatal dose of morphine.
- Use immediately.
- Rinse mouth to ensure all pellets have been swallowed.
- Patients should consume entire portion and should not divide apple sauce into separate doses. The entire capsule contents may alternatively be administered through a 16 French gastrostomy tube.

- Flush the gastrostomy tube with water to ensure that it is wet.
- Sprinkle the morphine sulfate extended-release pellets into 10 mL of water.
- Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel.
- Rinse the beaker with a further 10 mL of water and pour this into the funnel.
- Repeat rinsing until no pellets remain in the beaker.

THE ADMINISTRATION OF MORPHINE SULFATE EXTENDED-RELEASE PELLETS THROUGH A NASOGASTRIC TUBE SHOULD NOT BE ATTEMPTED.

Considerations in the Adjustment of Dosing Regimens

If signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, if breakthrough pain occurs when morphine sulfate extended-release capsules are administered on an every 24 hours dosing regimen, consideration should be given to dosing every 12 hours. If breakthrough pain occurs on a 12 hour dosing regimen a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments in both dose and dosing interval can be made to obtain an appropriate balance between pain relief and opioid side effects. To avoid accumulation the dosing interval of morphine sulfate extended-release capsules should not be reduced below 12 hours.

Cessation of Therapy

When the patient no longer requires therapy with morphine sulfate extended-release capsules, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Morphine Sulfate Extended-Release Capsules to Other Extended-Release Oral Morphine Formulations

Morphine sulfate extended-release capsules are not bioequivalent to other extended-release morphine preparations. Although for a given dose the same total amount of morphine is available from morphine sulfate extended-release capsules as from morphine solution or extended-release morphine tablets, the slower release of morphine from morphine sulfate extended-release capsules results in reduced maximum and increased minimum plasma morphine concentrations than with shorter acting morphine products. Conversion from morphine sulfate extended-release capsules to the same total daily dose of other extended-release morphine preparations may lead to either excessive sedation at peak or inadequate analgesia at trough and close observation and appropriate dosage adjustments are recommended.

Conversion from Morphine Sulfate Extended-Release Capsules to Parenteral Opioids

When converting a patient from morphine sulfate extended-release capsules to parenteral opioids, it is best to calculate an equivalent parenteral dose, and then initiate treatment at half of this calculated value. For example, to estimate the required 24 hour dose of parenteral morphine for a patient taking morphine sulfate extended-release capsules, one would take the 24 hour morphine sulfate extended-release capsules dose, divide by an oral to parenteral conversion ratio of 3, divide the estimated 24 hour parenteral dose into six divided doses (for a four hour dosing interval), then halve this dose as an initial trial.

For example, to estimate the required parenteral morphine dose for a patient taking 360 mg of morphine sulfate extended-release capsules a day, divide the 360 mg daily oral morphine dose by a conversion ratio of 1 mg of parenteral morphine for every 3 mg of oral morphine. The estimated 120 mg daily parenteral requirement is then divided into six 20 mg doses, and half of this, or 10 mg, is then given every 4 hours as an initial trial dose.

This approach is likely to require a dosage increase in the first 24 hours for many patients, but is recommended because it is less likely to cause overdose than trying to establish an equivalent dose without titration.

Safety and Handling

Morphine sulfate extended-release capsules contain morphine sulfate which is a controlled substance under Schedule II of the Controlled Substances Act. Morphine, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any morphine sulfate extended-release capsules that are no longer needed.

Morphine sulfate extended-release capsules may be targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Morphine sulfate extended-release capsules consists of closed hard gelatin capsules containing polymer coated morphine sulfate pellets that pose no known handling risk to health care workers. Morphine sulfate extended-release capsules are liable to diversion and misuse both by the general public and health care workers, and should be handled accordingly.

HOW SUPPLIED

Morphine sulfate extended-release capsules, USP contain white to off-white pellets of morphine sulfate and are available in six dose strengths:

20 mg size “4” CS, hard gelatin capsules, yellow opaque cap printed with “**WATSON/3449**” and white opaque body printed with “**20 mg**”, containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3449-30) and 100 (NDC 0591-3449-01).

30 mg size “3” CS, hard gelatin capsules, blue violet opaque cap printed with “**WATSON/3450**” and white opaque body printed with “**30 mg**”, containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3450-30) and 100 (NDC 0591-3450-01).

50 mg size “2” CS, hard gelatin capsules, light blue opaque cap printed with “**WATSON/3451**” and white opaque body printed with “**50 mg**”, containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3451-30) and 100 (NDC 0591-3451-01).

60 mg size “1” CS, hard gelatin capsules, pink opaque cap printed with “**WATSON/3452**” and white opaque body printed with “**60 mg**”, containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3452-30) and 100 (NDC 0591-3452-01).

80 mg size “0” CS, hard gelatin capsules, flesh opaque cap printed with “**WATSON/3576**” and white opaque body printed with “**80 mg**”, containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3576-30) and 100 (NDC 0591-3576-01).

100 mg size “0” CS, hard gelatin capsules, blue-green opaque cap printed with “**WATSON/3453**” and white opaque body printed with “**100 mg**” containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3453-30) and 100 (NDC 0591-3453-01).

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Dispense in a sealed tamper-evident, childproof, light-resistant container.

CAUTION: DEA Order Form Required.

Manufactured by:

Watson Laboratories, Inc.
Corona, CA 92880 USA

Distributed by:

Watson Pharma, Inc.
Corona, CA 92880 USA

Rev. date: 05/2011

198528

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 200812

LABELING REVIEWS

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

ANDA Number: 200812

Date of Submission: December 16, 2009

Applicant's Name: Watson Laboratories, Inc

Established Name: Morphine Sulfate Extended-Release Capsules USP, 80 mg and 100 mg

Labeling Deficiencies;

1. GENERAL COMMENT

Please note that the term "(b) (4)" is not an official USP dosage form. Please revise the name of the drug product to read "Morphine Sulfate Extended-Released Capsules, USP" in all labeling pieces. Please also be advised that the reference listed drug, Kadian® Capsules, uses "Morphine Sulfate Extended-Released Capsules, USP" as the established name.

1. CONTAINER- 30s and 100s

- a. See GENERAL COMMENT above.
- b. We ask that you include the phrase "(Once or twice Daily Formulation)" in a prominent manner immediately above the drug product name. We believe that inclusion of this phrase help to distinguish your drug product from the morphine sulfate extended-release capsules modeled after other reference listed drug products.
- c. Please be advised that your drug product is a controlled substance. Please include the controlled substance symbol on the label, preferably in association with the drug product name. The symbol on labels shall be clear and large enough to afford easy identification of the schedule of the controlled substance upon inspection without removal from the dispenser's shelf.
- d. Decrease prominence of company logo and move further down the label.
- e. Increase prominence of net quantity statement and "Rx only"
- f. Please revise the net quantity statement to read "30 Capsules" rather than "(b) (4)"
- g. Please include a statement "Protect from light and moisture" in association with the storage temperature statement.
- i. We encourage you to include pictorial of the capsule like the RLD. The picture of your drug product is to reflect the actual product including unique markings rather than a simulated drawing of the product.
- j. 1st line of the side panel- Revise to read:

"Each extended-release capsule contains..." [note "extended- release" inserted]

- k. Please ensure that you complete the bar code when submitting the final printed labels.
- l. Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please ensure that these criteria are met prior to submission of final print.
- m. Please complete the address of the distributor.

2. INSERT

a. GENERAL

- i. See GENERAL COMMENT above.
- ii. We recommend that you allow one line space between paragraphs to increase the readability of your labeling.

b. WARNING

Please put the warning statement in a box. We refer you to the Kadian labeling.

c. DESCRIPTION

- i. We note that your drug product is the subject of a USP monograph. Please verify that your dissolution test meets the USP specification.
- ii. Please note that you have included the strengths that you are not proposing. Please delete the strengths from the DESCRIPTION section other than 80 mg and 100 mg.
- iii. We encourage you to revise the chemical name using letter "α" rather than using "a".
- iv. We note that you included "corn starch" in the listing of inactive ingredients, which is not included in your Composition section. Please delete this and/or comment.
- v. We recommend that you revise the last sentence to read as follows:

"The capsule shells contain black iron oxide,...FD&C red #40. The 80 mg capsule shell also contain FD&C yellow #6 and the 100 mg capsule shell contains FD&C green #3. "
- vi. We note that your coating material contains iron complex. In accordance with the 21 CFR 73.1200(c), the amount of elemental iron contained in the formulation cannot exceed 5 mg per day at the maximum recommended dosage, which is two capsules per day for this drug product. Is the elemental iron of this product consumed at the maximum daily recommended dosage under 5 mg per day? Please comment.

d. CLINICAL PHARMACOLOGY

- i. Pharmacokinetics:

Please insert solid lines on Table 1 to improve readability. We refer you to RLD labeling.

ii. Absorption

Graph 1 (Study # MOB-1/90) - Revise to read:

...for morphine sulfate extended-release capsule (twice-a-day), extended-release morphine tablet... [note "capsule" inserted]

e. DOSAGE AND ADMINISTRATION

i. Individualization of Dosage - 2nd paragraph, 1st sentence:

Please note that twice-a-day is not spaced out in the sentence. Please revise to read "(twice-a-day)".

ii. Conversion from morphine sulfate extended-release capsules, USP to other Extended-Release Oral Morphine Formulations

A. The statement "morphine sulfate extended-release capsules, USP" should be presented in bold face type. Please revise accordingly.

B. Last sentence - Revise to read:

...the same total daily dose if other extended-release morphine... [note the word "other" inserted]

f. HOW SUPPLIED

We note that you stated "(b) (4) dose strengths" are available in this section while you are proposing only two strengths. Please revise accordingly.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Soon Oh at 240-276-8996 or send e-mail to Soon.oh@fda.hhs.gov.

{See appended electronic signature page}

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs

FOR THE RECORD:

1. Model Labeling: Kadian (Morphine Sulfate Extended-Release) Capsules (NDA 20-616/S-025), approved on 04/20/2007. There is no pending labeling supplement after SLR-025. Kadian has strengths of 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg. There is no safety information posted on the MedWatch website.

There is another RLD, Avinza for morphine sulfate extended-release capsules. Avinza has been approved for the 30 mg, 45 mg, 60 mg, 75 mg, 90 mg and 120 mg.

2. This drug product is the subject of a USP monograph.
3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of Composition section. See comment 3(c)(iv) above.

4. Patent Data

There is no unexpired patent and exclusivity for this product.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

ANDA: Store at 20 to 25°C (68 to 77°F). [see USP Controlled Room Temperature] See comment 2(e) above.

USP - Packaging and storage— Preserve in tight, light-resistant containers, and store at controlled room temperature.

6. DISPENSING STATEMENT

RLD - Dispense in a sealed tamper-evident, childproof, light-resistant container.

ANDA - Dispense in a sealed tamper-evident, childproof, light-resistant container.

7. PACKAGING CONFIGURATIONS

RLD - 100S

ANDA - 30s and 100s

8. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206.

80 mg size "0" CS, hard gelatin capsules, flesh opaque cap printed with "WATSON/3576" and white opaque body printed with "80 mg", containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3576-30) and 100 (NDC 0591-3576-01).

100 mg size "0" CS, hard gelatin capsules, blue-green opaque cap printed with "WATSON/3453" and white opaque body printed with "100 mg" containing white to off-white pellets. Capsules are supplied in bottles of 30 (NDC 0591-3453-30) and 100 (NDC 0591-3453-01).

9. CONTAINER/CLOSURE

3.2.P.7.1 Summary of Container Closure System

The packaging systems for Morphine Sulfate Sustained-release Capsules, USP, 80 mg and 100 mg are described in detail in the specifications and drawings included in this section. They consist of the following:

Container: white, straight-sided, round bottom, high-density polyethylene (HDPE) bottle

Closure: white, ribbed sides, child-resistant plastic closure with a heat induction liner

Filler: (b) (4) coil, (b) (4) white filament like hairs.

10. Manufacturer - Watson Laboratories, Inc.

- There are two RLD for the morphine sulfate E-R capsules, Avinza® and Kadian® Capsules. The following email was sent to Lillie Golson at the time of review of ANDA (b) (4).
- "A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules, Sprinkled on Applesauce, Under Fasting Conditions" has been submitted by the firm. (see email from Bio reviewer)
- The statement "morphine sulfate extended release capsules contain polymer coated extended release pellets" complies with CMC information. (see email from chemistry reviewer)
- This is the only application that firm has submitted for extended-release capsule. (80 mg and 100 mg)

From: Park, Chan H
Sent: Tuesday, June 22, 2010 8:56 AM
To: Golson, Lillie D
Cc: Park, Chan H
Subject: morphine sulfate E-R capsules
Importance: High

Hi Lillie,

It is my understanding that the generic labeling does not have to specify the RLD (which RLD the generic is modeled after) when there are more than one RLD available with different formulation methods. For example, refer to the following two RLDs for the **morphine sulfate E-R capsules**. When we consider the conversion statements below, however, it appears that the generic drug should specify the RLD on the container labels. What do you think? If so, how do we go about doing this? Do you have a good example? Thank you for your feedback,

Chan

KADIAN[®] capsules contain polymer coated extended-release pellets of morphine sulfate release morphine significantly more slowly than from conventional oral preparation.

AVINZA capsules consist of two components, an immediate release component that rapidly achieves plateau morphine plasma concentrations and an extended release component plasma concentrations throughout the 24-hour dosing interval.

Conversion from KADIAN[®] to Other Extended-Release Oral Morphine Form

KADIAN[®] is not bioequivalent to other extended-release morphine preparations. Although for a given dose the same total amount of morphine is available from KADIAN[®] as from morphine solution or extended-release morphine tablets, the slower release of morphine from KADIAN results in reduced maximum and increase minimum plasma morphine concentrations than with solution or extended-release morphine tablets, the slower release of morphine concentrations than with shorter acting morphine products. Conversion from Kadian to the same total daily dose of extended-release morphine preparations may lead to either excessive sedation at peak or inadequate analgesia at trough and close observation and appropriate dosage adjustments are recommended.

Conversion from AVINZA to Other Controlled-Release Oral Morphine Formulations

For a given dose, the same total amount of morphine is available from AVINZA as from oral morphine solution or controlled-release morphine tablets. The extended duration of release of morphine from AVINZA results in reduced maximum and increased minimum plasma morphine concentrations than with shorter acting morphine products. Conversion from AVINZA to the same total daily dose of another controlled-release morphine formulation could lead to either excessive sedation at peak serum levels or inadequate analgesia at trough serum levels. Dosage adjustment with close observation is recommended.

From: Golson, Lillie D
Sent: Tuesday, June 22, 2010 3:02 PM
To: Park, Chan H
Cc: Golson, Lillie D
Subject: RE: morphine sulfate E-R capsules

Hi Chan,

I know I've had a lengthy discussion with someone on these products, but can't find my notes. In looking at the D&A section, the best way to differentiate these products would be to put "Once daily" or "Once daily formulation" on the Avinza and "Once or twice daily" or "Once or twice daily formulation" on the Kadian. This is what we've done with the diltiazems, methylphenidates, etc. One thing that helps here is that these products only have two overlapping strengths, 30 mg and 60 mg. So, one differentiation should be made with the product's strengths. Are you okay with this?

Thanks

From: Park, Chan H
Sent: Wednesday, June 23, 2010 7:49 AM
To: Golson, Lillie D

Cc: Park, Chan H
Subject: RE: morphine sulfate E-R capsules

Hi Lillie,

thank you very much for your help. It sounds very reasonable to me. Although only two strengths have overlapping, I would have all strengths to contain "Once Daily Formulation" for generics modeled after Avinza and "Once or twice Daily Formulation" for the other ones. thanks,

Chan

From: Samaan, Nashed
Sent: Tuesday, June 29, 2010 12:34 PM
To: Oh, Soon
Subject: RE: 200812

Hi Soon,

Sorry for the delay.
Yes, the description is correct as submitted in the CMC information.

Thanks,
Nashed Samaan

From: Oh, Soon
Sent: Thursday, June 24, 2010 11:08 AM
To: Samaan, Nashed
Cc: Park, Chan H
Subject: 200812

Dear Nashed,
I am a new labeling reviewer and Chan Park is training me. I am reviewing morphine sulfate extended release capsule, application # 200812.
The sponsor claims that **morphine sulfate extended release capsules contain polymer coated extended release pellets**. I would like to confirm this statement complies with chemistry information they submitted. Please advise. Thanks.
Soon

From: Kaur, Paramjeet
Sent: Thursday, June 24, 2010 10:39 AM
To: Oh, Soon
Subject: RE: 200812

Good Morning Soon:

I have not started reviewing this application yet. I will start working on this one next week.

From the submitted study tables, it appears that they have done " A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN[®] Capsules, Sprinkled on Applesauce, Under Fasting Conditions".

Thanks
Paramjeet

From: Oh, Soon
Sent: Thursday, June 24, 2010 9:41 AM
To: Kaur, Paramjeet
Cc: Park, Chan H
Subject: 200812

Dear Paramjeet,

I am a new labeling reviewer and Chan Park is training me. I am reviewing morphine sulfate extended release capsule, application # 200812.

The sponsor claims that the entire contents can be sprinkled on apple sauce. I just want to confirm if the sponsor submitted the data to verify this statement. Please advise. Thanks.

Soon

Date of Review: 07/02/10

Date of Submission: 10/9/09

Primary Reviewer: Soon Oh

Date:

Team Leader: Lillie Golson

Date:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-200812	ORIG-1	WATSON LABORATORIES INC	MORPHINE SULFATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOON M OH
07/14/2010

LILLIE D GOLSON
07/14/2010

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

ANDA Number: 200812

Date of Submission: September 30, 2010

Applicant's Name: Watson Laboratories, Inc.

Established Name: Morphine Sulfate Extended-Release Capsules USP, 20 mg, 30 mg, 50 mg,
60 mg, 80 mg, and 100 mg

Labeling Deficiencies;

1. GENERAL COMMENT

We note that you did not include the point-to-point responses to the Agency's comments. Please include this in your future submissions.

2. CONTAINER- 30s and 100s

- a. Please put the text "Once or Twice Daily Formulation" in a parenthesis and relocate so that it is more closely associated with the drug product name.
- b. We note that you used blue color background for all strengths for the bar appearing at the bottom of the label. If feasible, we recommend that you use the same color as the specific one used for the background for the expression of strength to make further distinction between labels of various strengths.
- c. Your labels do not appear to reflect actual size. As addressed in the last deficiency letter, please be advised that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please ensure that these criteria are met prior to submission of final print.
- d. We believe that your drug product is light sensitive. Please verify that your container/closure system is light-resistant.

3. INSERT

a. GENERAL

- i. We note that you did not include the Structured Product Labeling (SPL) in your submission. You are required to submit SPL prior to approval as well as post-approval. Please refer to the guidance at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072331.pdf>.
- ii. We note that the breakdown of the paragraphs in your proposed labeling is not consistent with that of the Kadian® labeling. Please revise accordingly.
- iii. The sub-section titles are dissociated with the corresponding text in numerous places throughout the insert labeling. Please revise so that the sub-section titles appear immediately before the text.

- iv. It is not necessary to include the term "USP" in association with the drug product name throughout the text. Please delete this except in the TITLE, DESCRIPTION, INDICATIONS AND USAGE, and HOW SUPPLIED sections.
 - v. Please ensure that all text associated with graphs appear sufficiently legible throughout the insert labeling.
 - vi. It is preferable to use the term "to" rather than a hyphen when expressing a numerical range.
 - vii. We recommend that the font size of the final printed labeling not be less than 6 pts.
- b. DESCRIPTION - Last paragraph, 4th sentence:
- i. You made references to 80 mg and 100 mg strengths only. Please include additional strengths you are proposing.
 - ii. We note that you included "corn starch" in the listing of inactive ingredients and "propylene glycol" as a component of capsule shell, which are not included in your "Description and Composition" section. Please delete these and/or comment.
- c. CLINICAL PHARMACOLOGY - Table 1:
- i. 1st column, 2nd item:
"Extended-Release" rather than "(b) (4)"
 - ii. 1st column, 4th item:
"Morphine Sulfate Extended-Release Capsules" rather than "KADIAN® Capsules"

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Chan Park at 240-276-8951 or send e-mail to Chan.park@fda.hhs.gov.

{See appended electronic signature page}

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

FOR THE RECORD:

1. Model Labeling: Kadian (Morphine Sulfate Extended-Release) Capsules (NDA 20-616/S-025), approved on 04/20/2007. There is no pending labeling supplement after SLR-025. Kadian has strengths of 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg. There is no safety information posted on the MedWatch website. No new labeling information can be found in the PF, except an additional dissolution test information.

There is another RLD, Avinza for morphine sulfate extended-release capsules. Avinza has been approved for the 30 mg, 45 mg, 60 mg, 75 mg, 90 mg and 120 mg.

2. This drug product is the subject of a USP monograph.
3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of Composition section. See comment 3(b)(ii) above.

4. Patent Data

There is no unexpired patent and exclusivity for this product.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] Protect from light and moisture.

ANDA: Store at 20 to 25°C (68 to 77°F). [see USP Controlled Room Temperature] Protect from light and moisture.

USP - Packaging and storage— Preserve in tight, light-resistant containers, and store at controlled room temperature.

6. DISPENSING STATEMENT

RLD - Dispense in a sealed tamper-evident, childproof, light-resistant container.

ANDA - Dispense in a sealed tamper-evident, childproof, light-resistant container.

7. PACKAGING CONFIGURATIONS

RLD - 100S

ANDA - 30s and 100s

8. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.

20 mg size “4” CS, hard gelatin capsules, yellow opaque cap printed with “WATSON/3449” and white opaque body printed with “20 mg”, containing white to off-white pellets.

30 mg size “3” CS, hard gelatin capsules, blue violet opaque cap printed with “WATSON/3450” and white opaque body printed with “30 mg”, containing white to off-white pellets.

50 mg size “2” CS, hard gelatin capsules, light blue opaque cap printed with “WATSON/3451” and white opaque body printed with “50 mg”, containing white to off-white pellets.

60 mg size “1” CS, hard gelatin capsules, pink opaque cap printed with “WATSON/3452” and white opaque body printed with “60 mg”, containing white to off-white pellets.

80 mg size “0” CS, hard gelatin capsules, flesh opaque cap printed with “WATSON/3576” and white opaque body printed with “80 mg”, containing white to off-white pellets.

100 mg size “0” CS, hard gelatin capsules, blue-green opaque cap printed with “WATSON/3453” and white opaque body printed with “100 mg” containing white to off-white pellets.

9. CONTAINER/CLOSURE

The packaging systems for Morphine Sulfate Extended-release Capsules, USP, 20 mg, 30 mg, 50 mg, 60 mg and 80 mg are described in detail in the specifications and drawings included in this section. They consist of the following:

Container: white, straight-sided, round bottom, high-density polyethylene (HDPE) bottle

Closure: white, ribbed sides, child-resistant plastic closure with a heat induction liner

Filler: (b) (4) coil, (b) (4), white filament like hairs.

10. Manufacturer - Watson Laboratories, Inc.

11. There are two RLD for the morphine sulfate E-R capsules, Avinza® and Kadian® Capsules. The following email was sent to Lillie Golson at the time of review of ANDA (b) (4)
(b) (4)

From: Park, Chan H
Sent: Tuesday, June 22, 2010 8:56 AM
To: Golson, Lillie D
Cc: Park, Chan H
Subject: morphine sulfate E-R capsules
Importance: High

Hi Lillie,

It is my understanding that the generic labeling does not have to specify the RLD (which RLD the generic is modeled after) when there are more than one RLD available with different formulation methods. For example, refer to the following two RLDs for the **morphine sulfate E-R capsules**. When we consider the conversion statements below, however, it appears that the generic drug should specify the RLD on the container labels. What do you think? If so, how do we go about doing this? Do you have a good example? Thank you for your feedback,

Chan

KADIAN[®] capsules contain polymer coated extended-release pellets of morphine sulfate release morphine significantly more slowly than from conventional oral preparation.

AVINZA capsules consist of two components, an immediate release component that rapidly achieves plateau morphine plasma concentrations and an extended release component plasma concentrations throughout the 24-hour dosing interval.

Conversion from KADIAN® to Other Extended-Release Oral Morphine Form

KADIAN® is not bioequivalent to other extended-release morphine preparations. Although for a given dose the same total amount of morphine is available from KADIAN® as from morphine solution or extended-release morphine tablets, the slower release of morphine from KADIAN results in reduced maximum and increase minimum plasma morphine concentrations than with solution or extended-release morphine tablets, the slower

release of morphine concentrations than with shorter acting morphine products. Conversion from Kadian to the same total daily dose of extended-release morphine preparations may lead to either excessive sedation at peak or inadequate analgesia at trough and close observation and appropriate dosage adjustments are recommended.

Conversion from AVINZA to Other Controlled-Release Oral Morphine Formulations

For a given dose, the same total amount of morphine is available from AVINZA as from oral morphine solution or controlled-release morphine tablets. The extended duration of release of morphine from AVINZA results in reduced maximum and increased minimum plasma morphine concentrations than with shorter acting morphine products. Conversion from AVINZA to the same total daily dose of another controlled-release morphine formulation could lead to either excessive sedation at peak serum levels or inadequate analgesia at trough serum levels. Dosage adjustment with close observation is recommended.

From: Golson, Lillie D
Sent: Tuesday, June 22, 2010 3:02 PM
To: Park, Chan H
Cc: Golson, Lillie D
Subject: RE: morphine sulfate E-R capsules

Hi Chan,

I know I've had a lengthy discussion with someone on these products, but can't find my notes. In looking at the D&A section, the best way to differentiate these products would be to put "Once daily" or "Once daily formulation" on the Avinza and "Once or twice daily" or "Once or twice daily formulation" on the Kadian. This is what we've done with the diltiazems, methylphenidates, etc. One thing that helps here is that these products only have two overlapping strengths, 30 mg and 60 mg. So, one differentiation should be made with the product's strengths. Are you okay with this?

Thanks

From: Park, Chan H
Sent: Wednesday, June 23, 2010 7:49 AM
To: Golson, Lillie D
Cc: Park, Chan H
Subject: RE: morphine sulfate E-R capsules

Hi Lillie,

thank you very much for your help. It sounds very reasonable to me. Although only two strengths have overlapping, I would have all strengths to contain "Once Daily Formulation" for generics modeled after Avinza and "Once or twice Daily Formulation" for the other ones. thanks,

Chan

12. It was confirmed with chemist, Nashed Samaan, on 6/29/10 that the sponsor's description that the capsule contains polymer coated extended release pellets is accurate.
13. It was verified with the Bio reviewer, Paramjeet Kaur, on 6/24/10 that the applicant submitted "A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus Kadian® Capsules, Sprinkled on Applesauce, Under Fasting Condition".

14. The applicant amended this application on 9/30/10 in order to add new strengths of 20 mg, 30mg, 50 mg, and 60 mg.

Date of Review: 11/4/10

Date of Submission: 9/30/10

Primary Reviewer: Chan Park

Date:

Team Leader: Lillie Golson

Date:

C:\Documents and Settings\parkc\My Documents\200812.NA2.L.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHAN H PARK
12/07/2010

LILLIE D GOLSON
12/08/2010

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **200812**

Date of Submission: **May 4, 2011**

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

Established Name: **Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg**

REMS required?

☐ Yes ☒ No

MedGuides and/or PPIs (505-1(e)) ☐ Yes ☒ No

Communication plan (505-1(e)) ☐ Yes ☒ No

Elements to assure safe use (ETASU) (505-1(f)(3)) ☐ Yes ☒ No

Implementation system if certain ETASU (505-1(f)(4)) ☐ Yes ☒ No

Timetable for assessment (505-1(d)) ☐ Yes ☒ No

ANDA REMS acceptable?

☐ Yes ☐ No ☒ n/a

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? NO - ELECTRONIC

Container Labels: 30s and 100s

Professional Package Insert Labeling:

	SUBMIT	ACTION
Label		
30s	5-4-11	APPROVE
100s	5-4-11	APPROVE
INSERT	5-4-11	APPROVE

Revisions needed post-approval: PI – DESCRIPTION – Delete “2910”, “6000” and “K-30” – CLINICAL PHARMACOLOGY – Table 1 – “Extended-release” rather than “Extended-Release”

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Kadian

NDA Number: 20-616

NDA Drug Name: Kadian (morphine sulfate extended-release) Capsules

NDA Firm: Alpharma

Date of Approval of NDA Insert: 4-20-07 [S-025]

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Kadian® [NDA 20-616/S-025]; approved 4/20/07.

2. Patent/ Exclusivities

Patent Data – 20-616

No	Expiration	Use Code	Use	Labeling Impact	File
None					

Exclusivity Data – 20-616

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

3. Storage Conditions:

NDA – Store at 25°C (77°F); excursions permitted between 15° to 30°C (59°-86°F) [see USP Controlled Room Temperature] Protect from light and moisture.

ANDA – Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature] Protect from light and moisture.

USP – Preserve in tight, light-resistant containers, and store at controlled room temperature. Not USP

4. Product Line:

The innovator markets their product in bottles of 100s.

The ANDA wishes to market in HDPE bottles of 30s (CRC) and 100s (CRC).

30s container seal - 33 mm, white, ribbed sides, child resistant plastic closure with aluminum foil coated

(b) (4) liner

100s container seal - 45 mm, white, ribbed sides, child resistant plastic closure with aluminum foil coated

(b) (4) liner

The aluminum foil coated liner meets the requirements for tamper-evident seal for controlled drug products.

5. The insert describes the capsules accurately.

CAPSULE COLORS

	ANDA	RLD
10 mg	N/A	Light blue
20 mg	Yellow	Yellow
30 mg	Blue-violet	Blue-violet
50 mg	Light blue	Blue
60 mg	Pink	Pink
80 mg	Flesh	Light orange
100 mg	Blue-green	Green
200 mg	N/A	Light brown

6. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.
7. Watson Laboratories, Inc. – USA - is the manufacturer.
8. There are two RLD for the morphine sulfate E-R capsules, Avinza® and Kadian® Capsules. The following email was sent to Lillie Golson at the time of review of ANDA (b) (4) (b) (4).

From: Park, Chan H
Sent: Tuesday, June 22, 2010 8:56 AM
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Cc: Park, Chan H
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Importance: High

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Conversion from AVINZA to Other Controlled-Release Oral Morphine Formulations

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Conversion from AVINZA to the same total daily dose of another controlled-release morphine formulation could lead to either excessive sedation at peak serum levels or inadequate analgesia at trough serum levels. Dosage adjustment with close observation is recommended.

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Sent: Tuesday, June 22, 2010 3:02 PM
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Cc: Golson, Lillie D
Subject: RE: morphine sulfate E-R capsules

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formulation" on the Avinza and "Once or twice daily" or "Once or twice daily formulation" on the Kadian. This is what we've done with the diltiazems, methylphenidates, etc. One thing that helps here is that these products only have two overlapping strengths, 30 mg and 60 mg. So, one differentiation should be made with the product's strengths. Are you okay with this?
Thanks

From: Park, Chan H
Sent: Wednesday, June 23, 2010 7:49 AM
To: Golson, Lillie D
Cc: Park, Chan H
Subject: RE: morphine sulfate E-R capsules

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9. It was confirmed with chemist, Nashed Samaan, on 6/29/10 that the sponsor's description that the capsule contains polymer coated extended release pellets is accurate.
10. It was verified with the Bio reviewer, Paramjeet Kaur, on 6/24/10 that the applicant submitted "A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus Kadian® Capsules, Sprinkled on Applesauce, Under Fasting Condition".
11. The applicant amended this application on 9/30/10 in order to add new strengths of 20 mg, 30mg, 50 mg, and 60 mg.

Date of Review: 5-6-11

Date of Submission: 5-4-11

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Koung Lee

Date:

cc: ANDA: 200812
DUP/DIVISION FILE
HFD-613/AVezza/KLee (no cc)
aev/5/6/11|C:\OldComputer\cdw5106378\C-
drive\FIRMSNZ\WATSON\LTRS&REV\200812AP.LABELING.doc
Review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADOLPH E VEZZA
05/11/2011

KOUNG U LEE
05/12/2011
For Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200812

CHEMISTRY REVIEWS

ANDA 200-812

**Morphine Sulfate Extended-Release Capsules USP
(80 mg and 100 mg)**

Watson Laboratories, Inc.

**Nashed I. Samaan, Ph.D.
OGD, DC II**

Table of Contents

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Chemistry Review Data Sheet

1. **ANDA 200812**
2. **REVIEW #1**
3. **REVIEW DATE:** 15-Jul-2010
4. **REVIEWER:** Nashed I. Samaan, Ph.D.
5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
N/A	

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	16-Dec-09

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Watson Laboratories, Inc.- Florida
Address:	4955 Orange Drive, Ft. Lauderdale, FL 33314
Representative:	Janet Vaughn, Regulatory Affairs
Telephone:	(954) 358-6125
Fax	(954) 358-6350

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: Not Applicable

Non-Proprietary Name (USAN): Morphine Sulfate Extended-release Capsules

9. **LEGAL BASIS FOR SUBMISSION:**

The reference product is Kadian® (Morphine Sulfate Extended-release) Capsules, 80 mg and 100 mg manufactured by Actavis Kadian LLC, under NDA # 020616. There are two (2) unexpired patent listed in FDA's electronic "Orange Book" for Kadian® (Morphine Sulfate Extended-release) Capsules. In addition, Kadian® has no unexpired exclusivity

Executive Summary Section

10. PHARMACOL. CATEGORY:

Narcotic Analgesic. Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

11. DOSAGE FORM:

Extended-release Capsules

12. STRENGTH/POTENCY:

80 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral**14. Rx/OTC DISPENSED: X Rx OTC****15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

 SPOTS product – Form Completed

 X Not a SPOTS product

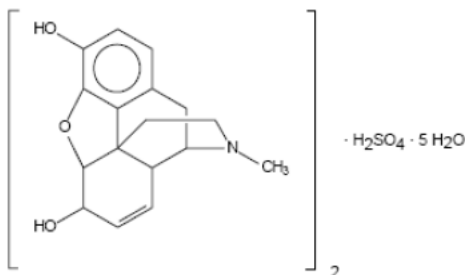
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Morphinan-3,6-diol,7,8-didehydro-4,5-epoxy-17-methyl, (5 α , 6 α)-, sulfate (2:1) (salt), pentahydrate; or 7,8-Didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1) (salt), pentahydrate

Molecular Formula: (C₁₇H₁₉NO₃)₂ • H₂SO₄ • 5H₂O

Molecular Weight: 758.83

CAS No.: 6211-15-0



Executive Summary Section

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	LOA page #
(b) (4)	II		(b) (4)	1	Adequate	B. Scott on 1-Jul-10	
	III			4			
				4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

* No CMC submission is provided after this revision up to July, 2010.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF;

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application;

5 – Authority to reference not granted

6 – DMF not available; 7 – Other (explain under "Comments")

Executive Summary Section

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Not Satisfactory	30-Jun-10	N. Samaan
Labeling	Not Satisfactory	14-Jul-10	Park Chan
Bioequivalence	Pending		P. Kaur
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		
Methods Validation	USP		
EA	Categorical Exclusion claimed		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

Chemistry Review for ANDA 200-812

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not recommended for approval. CMC is not satisfactory, and Bio is pending. Labeling is deficient (fax 7/14/10 to firm). EES is satisfactory (5/3/10).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

i. Drug Substance:

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether.

ii. Drug Product: Morphine sulfate extended -release capsule 80 mg and 100 mg

a. Product Description:

80 mg: Size “0” CS, Hard Gelatin Capsules, Flesh Opaque Cap Printed with “WATSON/3576” and White Opaque Body Printed with “80 mg”, containing white to off-white pellets.

100 mg: Size “0” CS, Hard Gelatin Capsules, Blue-Green Opaque Cap Printed with “WATSON/3453” and White Opaque Body Printed with “100 mg”, containing white to off-white pellets.

Each morphine sulfate extended -release capsule contains either 80 mg or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: diethyl phthalate, ethylcellulose, hypromellose 2910,

Executive Summary Section

methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30, and talc.

The capsule shells contain black iron oxide, gelatin, propylene glycol and titanium dioxide, D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C red #40, FD&C yellow #6 (80 mg), D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C green #3, FD&C red #40 (100 mg).

The formulation involves (b) (4)

and each strength is packaged in HDPE bottles of 30, and 100 counts.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The maximum recommended daily dose is 400 mg.

Storage conditions: Store at 20 to 25°C (68° -77°F); (See USP Controlled Room Temperature). Protect from light and moisture.

Tentative expiration dating: 24 months based on 3 months accelerated data.

C. Basis for Approvability or Not-Approval Recommendation**Recommend Approval.**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Not Satisfactory	30-Jun-10	N. Samaan
Labeling	Deficient	14-Jul-10	Park Chan
Bioequivalence	Pending		P. Kaur
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		

Following this page, 44 pages withheld in full - (b)(4)

Chemistry Assessment Section

Capsules, USP” as the established name. Please revise and correct the CMC part as needed.

B. Bioequivalence: Pending

C. Environmental Assessment Or Claim Of Categorical Exclusion

Reviewer’s Comment: Under 21 CFR 25.31(a) the applicant requests a categorical exclusion from the preparation of an environmental analysis. Acceptable

III. List Of Deficiencies To Be Communicated

See Attached

Chemistry Assessment Section

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Morphine Sulfate Extended-Release Capsules USP, 80 mg and 100mg

A. Chemistry Deficiencies:

1. You have submitted your ANDA 200812 for Morphine Sulfate Extended-Release Capsules, USP 80 mg and 100 mg strengths. However, in the introduction to the Quality Overall Summary you reported strengths 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100mg. Please clarify and/or correct.

2. Regarding your manufacturing process:

- a.

(b) (4)

- b.

- c.

- d.

3. Regarding your in-process controls:

- a.

(b) (4)

Chemistry Assessment Section

- c. We will defer the acceptance of the dissolution specifications until the DBE completes its review. We may request additional information based on DBE review.

9. [REDACTED] (b) (4)
[REDACTED] Please justify the employment of alternative methods. In the event of dispute, only the results obtained by the official methods in the USP will be considered conclusive.

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

1. Your Product Development Report includes information on lots that have similar dissolution profiles, yet did not pass the in-vivo criteria. Please discuss whether the in-vitro dissolution method is discriminating in identifying lots that are not in-vivo equivalent.
2. You have submitted long term stability data up to three months for the 80 mg strength only. Please provide available long-term stability data for both 80 mg and 100 mg strengths lots # 3576R0013 and 3453R0001.
3. In the description section of the package insert you have stated that “Each morphine sulfate extended -release capsule contains either 80 mg or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: corn starch, diethyl phthalate, -----“. The corn starch is not used as ingredient in this formula. Please address.
4. We refer you to the labeling comment on July 14, 2010 stated “Please note that the term “extended-released capsules” is not an official USP dosage form. Please revise the name of the drug product to read “Morphine Sulfate Extended-Released Capsules, USP” in all labeling pieces. Please also be advised that the reference listed drug, Kadian® Capsules, uses “Morphine Sulfate Extended-Released Capsules, USP” as the established name. Please revise and correct the CMC part as needed.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200812

Endorsements:

HFD-647/Nashed I. Samaan Ph.D./15-Jul-10 (Revised 29-Jul-2010)

HFD-647/U.V. Venkataram Ph.D./29-Jul-2010

HFD-617/ Simon Eng/04-Aug-2010

F/T by

V:\Division of Chemistry II/Team 8/Final Version for DARRTS\200812N01_RNS.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-200812	ORIG-1	WATSON LABORATORIES INC	MORPHINE SULFATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NASHED I SAMAN
08/04/2010

UBRANI V VENKATARAM
08/04/2010

SIMON S ENG
08/04/2010

ANDA 200-812

**Morphine Sulfate Extended-Release Capsules USP
(20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg)**

Watson Laboratories, Inc.

**Nashed I. Samaan, Ph.D.
OGD, DC II**

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Chemistry Review Data Sheet

1. **ANDA** 200-812
2. **REVIEW #2**
3. **REVIEW DATE:** 9-Mar-2011; 15-Mar-2011
4. **REVIEWER:** Nashed I. Samaan, Ph.D.
5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	16-Dec-2009
CMC Deficiency Letter (Review # 1)	04-Aug-2010

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (New strengths) *	30-Sep-2010
Amendment (response to Deficiency letter review #1)	16-Feb-2011

* Watson Laboratories, Inc.-Florida (WLF) is submitting this amendment to market four (4) additional strengths of Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg and 60 mg strengths. The reference-listed drug (RLD) is Kadian® (Morphine Sulfate Extended-release) Capsules, manufactured by Actavis Kadian LLC, under NDA # 020616.

The review is updated to reflect the addition of new strengths and to add the firm's response to our deficiency letter dated August 4, 2010. For the ease of review, all updated information will be in blue until we finalize this review cycle.

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Watson Laboratories, Inc.- Florida
Address:	4955 Orange Drive, Ft. Lauderdale, FL 33314
Representative:	Alberto Rivalta, Manager, Regulatory Affairs
Telephone:	(954) 358-6109
Fax	(954) 358-6350

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Not Applicable

Non-Proprietary Name (USAN): Morphine Sulfate Extended-release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The reference product is Kadian® (Morphine Sulfate Extended-release) Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg manufactured by Actavis Kadian LLC, under NDA # 020616. There are two (2) unexpired patent listed in FDA's electronic "Orange Book" for Kadian® (Morphine Sulfate Extended-release) Capsules. In addition, Kadian® has no unexpired exclusivity

10. PHARMACOL. CATEGORY:

Narcotic Analgesic. Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

11. DOSAGE FORM:

Extended-release Capsules

12. STRENGTH/POTENCY:

20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral**14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC****15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**☐ SPOTS product – Form Completed☒ Not a SPOTS product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

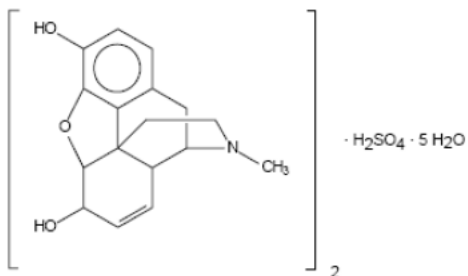
Chemical Name: Morphinan-3,6-diol,7,8-didehydro-4,5-epoxy-17-methyl, (5 α , 6 α)-, sulfate (2:1) (salt), pentahydrate; or 7,8-Didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1) (salt), pentahydrate

Molecular Formula: (C₁₇H₁₉NO₃)₂• H₂SO₄• 5H₂O

Molecular Weight: 758.83

CAS No.: 6211-15-0

Executive Summary Section



A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	LOA page #
(b) (4)	II		(b) (4)	1	Adequate (IR)	N. Samaan on 24-Jan-11	
	III			4			
				4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

Executive Summary Section

* No CMC submission is provided after this revision up to March 9, 2011.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF;

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application;

5 – Authority to reference not granted

6 – DMF not available; 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Not Satisfactory	09-Mar-11	N. Samaan
Labeling	Not Satisfactory	08-Dec-10	Park Chan
Bioequivalence	Not Satisfactory	29-Sep-10	P. Kaur
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		
Methods Validation	USP		
EA	Categorical Exclusion claimed		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 200-812

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not recommended for approval. CMC, Bio and labeling are not satisfactory. EES is satisfactory.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

i. Drug Substance:

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether.

ii. Drug Product: Morphine sulfate Extended -release capsule 80 mg and 100 mg

a. Product Description:

20 mg: Size “4” CS, hard gelatin capsules, yellow opaque cap printed with “WATSON/3449” and white opaque body printed with “20 mg” containing white to off-white pellets

30 mg: Size “3” CS, hard gelatin capsules, blue-violet opaque cap printed with “WATSON/3450” and white opaque body printed with “30 mg” containing white to off-white pellets

50 mg: Size “2” CS, hard gelatin capsules, light blue opaque cap printed with “WATSON/3451” and white opaque body printed with “50 mg”

Executive Summary Section

60 mg: Size “1” CS, hard gelatin capsules, pink opaque cap printed with “WATSON/3452” and white opaque body printed with “60 mg” containing white to off-white pellets.

80 mg: Size “0” CS, Hard Gelatin Capsules, Flesh Opaque Cap Printed with “WATSON/3576” and White Opaque Body Printed with “80 mg”, containing white to off-white pellets.

100 mg: Size “0” CS, Hard Gelatin Capsules, Blue-Green Opaque Cap Printed with “WATSON/3453” and White Opaque Body Printed with “100 mg”, containing white to off-white pellets.

Each morphine sulfate Extended -release capsule contains 20 mg, 30 mg, 50 mg, 60 mg, 80 mg or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: diethyl phthalate, ethylcellulose, hypromellose 2910, methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30, and talc.

The capsule shells contain black iron oxide, gelatin, propylene glycol and titanium dioxide. In addition, the 20 mg capsule shell contains D&C yellow #10, the 30 mg capsule shell contains FD&C blue #1 and FD&C red #3, the 50 mg capsule shell contains FD&C blue #1, the 60 mg capsule shell contains D&C red #28, FD&C blue #1 and FD&C red #40, the 80 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C red #40 and FD&C yellow #6 and the 100 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C green # 3 and FD&C red #40 .

The formulation involves

(b) (4)

and each strength is packaged in HDPE bottles of 30, and 100 counts.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The maximum recommended daily dose is 400 mg.

Storage conditions: Store at 20 to 25°C (68° -77°F); (See USP Controlled Room Temperature). Protect from light and moisture.

Tentative expiration dating: 24 months based on 3 months accelerated data.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Recommend Approval.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Not Satisfactory	15-Mar-11	N. Samaan
Labeling	Not Satisfactory	08-Dec-10	Park Chan
Bioequivalence	Not Satisfactory	29-Sep-10	P. Kaur
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		

Following this page, 61 pages withheld in full - (b)(4)

Chemistry Assessment Section

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc. Florida.

DRUG PRODUCT: Morphine Sulfate Extended-Release Capsules USP, 80 mg and 100mg

A. Chemistry Deficiencies:

1. It is noted that the DMF holder establishes (b) (4)
(b) (4) Please consult with the drug substance manufacturer and update your specifications.
2. We acknowledge that you have provided dissolution data for (b) (4)
(b) (4)
3. We acknowledge that you have (b) (4)
(b) (4) Please discuss.
4. The dissolution test results of batches # 3576P0008 and batch # 3576P0011 that (b) (4)
(b) (4) In this regard:
 - a. You have determined an optimum (b) (4)
(b) (4). What is the process (b) (4)?
 - b. Please establish (b) (4) limit and justify the limit with data.
5. You have used (b) (4)
(b) (4) on drug product quality? Please submit results of your studies.

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

1. In table #1 "Composition of Morphine Sulfate Extended-release Capsules" you have reported the size of all hard gelatin capsules for all strengths as "Size "0"

Chemistry Assessment Section

CS, hard gelatin capsules”. However, you have used hard gelatin capsules sizes of 4, 3, 2 and 1 for the strengths 20mg, 30mg, 50mg and 60mg respectively. Please fix the table and submit.

2. Please provide available long-term stability data for all strengths.
3. We refer you to the labeling question regarding listing of corn starch in the inactive ingredients and "propylene glycol" as a component of capsule shell, which are not included in your "Description and Composition" section. Please harmonize your CMC response with labeling response. You may need to update the component/composition section based on your response

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200-812

Endorsements:

HFD-647/Nashed I. Samaan Ph.D./09-Mar-1; Revised 15-Mar-11 and 17-Mar-11

HFD-647/U.V. Venkataram Ph.D./10-Mar-2011; 15-Mar-2011

HFD-617/ T. Nhu/18-March-2011

F/T by

V:\Division of Chemistry II\Team 8\Final Version for DARRTS\200812N02_RNS.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NASHED I SAMAN
03/18/2011

UBRANI V VENKATARAM
03/18/2011

TINA T NHU
03/18/2011

ANDA 200-812

**Morphine Sulfate Extended-Release Capsules USP
(20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg)**

Watson Laboratories, Inc.

**Nashed I. Samaan, Ph.D.
OGD, DC II**

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Chemistry Review Data Sheet

1. **ANDA** 200-812
2. **REVIEW #3**
3. **REVIEW DATE:** 20-Jul-2011
4. **REVIEWER:** Nashed I. Samaan, Ph.D.
5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	16-Dec-2009
CMC Deficiency Letter (Review # 1)	04-Aug-2010
Amendment (New strengths) *	30-Sep-2010
Amendment (response to Deficiency letter review #1)	16-Feb-2011
CMC Deficiency Letter (Review # 2)	18-Mar-2011

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (response to Deficiency letter review #2)	18-May-2011
Gratuitous Amendment*	28-Jun-2011

*Review of this amendment is located separately at the end of this document.

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Watson Laboratories, Inc.- Florida
Address:	4955 Orange Drive, Ft. Lauderdale, FL 33314
Representative:	Alberto Rivalta, Manager, Regulatory Affairs
Telephone:	(954) 358-6109
Fax	(954) 358-6350

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: Not Applicable

Non-Proprietary Name (USAN): Morphine Sulfate Extended-release Capsules

9. **LEGAL BASIS FOR SUBMISSION:**

Executive Summary Section

The reference product is Kadian® (Morphine Sulfate Extended-release) Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg manufactured by Actavis Kadian LLC, under NDA # 020616. There are two (2) unexpired patent listed in FDA's electronic "Orange Book" for Kadian® (Morphine Sulfate Extended-release) Capsules. In addition, Kadian® has no unexpired exclusivity.

10. PHARMACOL. CATEGORY:

Narcotic Analgesic. Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

11. DOSAGE FORM:

Extended-release Capsules

12. STRENGTH/POTENCY:

20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral**14. Rx/OTC DISPENSED: X Rx OTC****15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

 SPOTS product – Form Completed

 X Not a SPOTS product

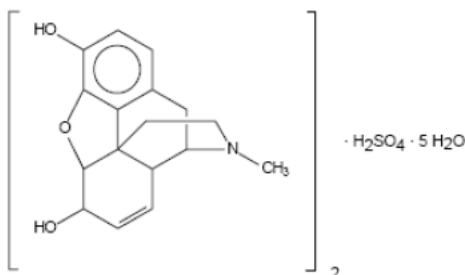
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, (5 α , 6 α)-, sulfate (2:1) (salt), pentahydrate; or 7,8-Didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1) (salt), pentahydrate

Molecular Formula: (C₁₇H₁₉NO₃)₂ • H₂SO₄ • 5H₂O

Molecular Weight: 758.83

CAS No.: 6211-15-0



Executive Summary Section

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	LOA page #
(b) (4)	II		(b) (4)	3	Adequate	N. Samaan on 11-Jul-11	
	III			4			
				4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

* No CMC submission is provided after this revision up to July 19, 2011.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF;

3 – Reviewed previously and no revision since last review

Executive Summary Section

- 4 – Sufficient information in application;
- 5 – Authority to reference not granted
- 6 – DMF not available; 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Satisfactory	20-Jul-11	N. Samaan
Labeling	Satisfactory	12-May-11	A. Vezza
Bioequivalence	Incomplete	15-Mar-11	C. Chaurasia
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		
Methods Validation	USP		
EA	Categorical Exclusion claimed		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

Chemistry Review for ANDA 200-812

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable contingent Bio review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

i. Drug Substance:

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether.

ii. Drug Product: Morphine sulfate Extended -release Capsule

a. Product Description:

20 mg: Size “4” CS, hard gelatin capsules, yellow opaque cap printed with “WATSON/3449” and white opaque body printed with “20 mg” containing white to off-white pellets

30 mg: Size “3” CS, hard gelatin capsules, blue-violet opaque cap printed with “WATSON/3450” and white opaque body printed with “30 mg” containing white to off-white pellets

50 mg: Size “2” CS, hard gelatin capsules, light blue opaque cap printed with “WATSON/3451” and white opaque body printed with “50 mg”

60 mg: Size “1” CS, hard gelatin capsules, pink opaque cap printed with “WATSON/3452” and white opaque body printed with “60 mg” containing white to off-white pellets.

Executive Summary Section

80 mg: Size “0” CS, Hard Gelatin Capsules, Flesh Opaque Cap Printed with “WATSON/3576” and White Opaque Body Printed with “80 mg”, containing white to off-white pellets.

100 mg: Size “0” CS, Hard Gelatin Capsules, Blue-Green Opaque Cap Printed with “WATSON/3453” and White Opaque Body Printed with “100 mg”, containing white to off-white pellets.

Each morphine sulfate Extended -release capsule contains 20 mg, 30 mg, 50 mg, 60 mg, 80 mg or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: diethyl phthalate, ethylcellulose, hypromellose 2910, methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30, and talc.

The capsule shells contain black iron oxide, gelatin, propylene glycol and titanium dioxide. In addition, the 20 mg capsule shell contains D&C yellow #10, the 30 mg capsule shell contains FD&C blue #1 and FD&C red #3, the 50 mg capsule shell contains FD&C blue #1, the 60 mg capsule shell contains D&C red #28, FD&C blue #1 and FD&C red #40, the 80 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C red #40 and FD&C yellow #6 and the 100 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C green # 3 and FD&C red #40 .

The formulation involves

(b) (4)

and each strength is packaged in HDPE bottles of 30, and 100 counts.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The maximum recommended daily dose is 400 mg.

Packaging: Morphine sulfate Extended -release capsule 20mg, 30mg, 50mg; 60mg; 80mg and 100 mg are packaged in HDPE bottles of 30, and 100 counts.

Storage conditions: Store at 20 to 25°C (68° -77°F); (See USP Controlled Room Temperature). Protect from light and moisture.

Tentative expiration dating: 24 months based on the twelve weeks accelerated stability data.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Recommend Approval.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Satisfactory	20-Jul-11	N. Samaan
Labeling	Satisfactory	12-May-11	A. Vezza
Bioequivalence	Incomplete	15-Mar-11	C. Chaurasia
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		

Following this page, 66 pages withheld in full - (b)(4)

Chemistry Assessment Section

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc. Florida.

DRUG PRODUCT: Morphine Sulfate Extended-Release Capsules USP, 80 mg and 100mg

A. Chemistry Deficiencies:

The application is approvable contingent Bio review.

Sincerely yours,

Glen J. Smith
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200-812

Endorsements:

HFD-647/Nashed I. Samaan Ph.D./ 20-Jul-2011

HFD-647/U.V. Venkataram Ph.D./20-Jul-2011

HFD-617/ T. Nhu Pharm.D/25-Jul-2011

F/T by

V:\Division of Chemistry II/Team 8/Final Version for DARRTS\200812N03_RNS.doc

TYPE OF LETTER: The application is approvable contingent Bio review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NASHED I SAMAAAN
07/25/2011

UBRANI V VENKATARAM
07/25/2011

TINA T NHU
07/26/2011

ANDA 200-812

**Morphine Sulfate Extended-Release Capsules USP
(20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg)**

Watson Laboratories, Inc.

**Nashed I. Samaan, Ph.D.
OGD, DC II**

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Chemistry Review Data Sheet

1. **ANDA** 200-812
2. **REVIEW # 4** Addendum
3. **REVIEW DATE:** 09-Nov-2011
4. **REVIEWER:** Nashed I. Samaan, Ph.D.
5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	16-Dec-2009
CMC Deficiency Letter (Review # 1)	04-Aug-2010
Amendment (New strengths)	30-Sep-2010
Amendment (response to Deficiency letter review #1)	16-Feb-2011
CMC Deficiency Letter (Review # 2)	18-Mar-2011
Amendment (response to Deficiency letter review #2)	18-May-2011
Gratuitous Amendment	28-Jun-2011
CMC (Review # 3) Satisfactory contingent Bio	18-Mar-2011

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Gratuitous Amendment	13-Sep-2011
Telecom	24-Oct-2011
Telephone amendment	07-Nov-2011

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Watson Laboratories, Inc.- Florida
Address:	4955 Orange Drive, Ft. Lauderdale, FL 33314
Representative:	Alberto Rivalta, Manager, Regulatory Affairs
Telephone:	(954) 358-6109
Fax	(954) 358-6350

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Not Applicable

Non-Proprietary Name (USAN): Morphine Sulfate Extended-release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The reference product is Kadian® (Morphine Sulfate Extended-release) Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg manufactured by Actavis Kadian LLC, under NDA # 020616. There are two (2) unexpired patent listed in FDA's electronic "Orange Book" for Kadian® (Morphine Sulfate Extended-release) Capsules. In addition, Kadian® has no unexpired exclusivity.

10. PHARMACOL. CATEGORY:

Narcotic Analgesic. Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

11. DOSAGE FORM:

Extended-release Capsules

12. STRENGTH/POTENCY:

20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral**14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC****15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**☐ SPOTS product – Form Completed☒ Not a SPOTS product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

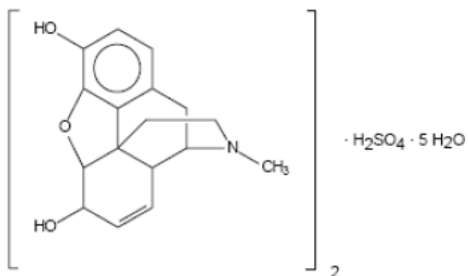
Chemical Name: Morphinan-3,6-diol,7,8-didehydro-4,5-epoxy-17-methyl, (5 α , 6 α)-, sulfate (2:1) (salt), pentahydrate; or 7,8-Didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1) (salt), pentahydrate

Molecular Formula: (C₁₇H₁₉NO₃)₂• H₂SO₄ • 5H₂O

Molecular Weight: 758.83

CAS No.: 6211-15-0

Executive Summary Section



A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ₁	STATUS ²	DATE REVIEW COMPLETED	LOA page #
(b) (4)	II		(b) (4)	3	Adequate	N. Samaan on 11-Jul-11	
	III			4			
				4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

Executive Summary Section

* No CMC submission is provided after this revision up to July 19, 2011.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF;

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application;

5 – Authority to reference not granted

6 – DMF not available; 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Satisfactory	09-Nov-11	N. Samaan
Labeling	Satisfactory	12-May-11	A. Vezza
Bioequivalence	Satisfactory	10-Oct-11	C. Chaurasia
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		
Methods Validation	USP		
EA	Categorical Exclusion claimed		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 200-812

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

i. Drug Substance:

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether.

ii. Drug Product: Morphine sulfate Extended -release Capsule

a. Product Description:

20 mg: Size “4” CS, hard gelatin capsules, yellow opaque cap printed with “WATSON/3449” and white opaque body printed with “20 mg” containing white to off-white pellets

30 mg: Size “3” CS, hard gelatin capsules, blue-violet opaque cap printed with “WATSON/3450” and white opaque body printed with “30 mg” containing white to off-white pellets

50 mg: Size “2” CS, hard gelatin capsules, light blue opaque cap printed with “WATSON/3451” and white opaque body printed with “50 mg”

60 mg: Size “1” CS, hard gelatin capsules, pink opaque cap printed with “WATSON/3452” and white opaque body printed with “60 mg” containing white to off-white pellets.

Executive Summary Section

80 mg: Size “0” CS, Hard Gelatin Capsules, Flesh Opaque Cap Printed with “WATSON/3576” and White Opaque Body Printed with “80 mg”, containing white to off-white pellets.

100 mg: Size “0” CS, Hard Gelatin Capsules, Blue-Green Opaque Cap Printed with “WATSON/3453” and White Opaque Body Printed with “100 mg”, containing white to off-white pellets.

Each morphine sulfate Extended -release capsule contains 20 mg, 30 mg, 50 mg, 60 mg, 80 mg or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: diethyl phthalate, ethylcellulose, hypromellose 2910, methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30, and talc.

The capsule shells contain black iron oxide, gelatin, propylene glycol and titanium dioxide. In addition, the 20 mg capsule shell contains D&C yellow #10, the 30 mg capsule shell contains FD&C blue #1 and FD&C red #3, the 50 mg capsule shell contains FD&C blue #1, the 60 mg capsule shell contains D&C red #28, FD&C blue #1 and FD&C red #40, the 80 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C red #40 and FD&C yellow #6 and the 100 mg capsule shell contains D&C yellow #10, FD&C blue #1, FD&C blue #2, FD&C green # 3 and FD&C red #40 .

The formulation involves

(b) (4)

and each strength is packaged in HDPE bottles of 30, and 100 counts.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The maximum recommended daily dose is 400 mg.

Packaging: Morphine sulfate Extended -release capsule 20mg, 30mg, 50mg; 60mg; 80mg and 100 mg are packaged in HDPE bottles of 30, and 100 counts.

Storage conditions: Store at 20 to 25°C (68° -77°F); (See USP Controlled Room Temperature). Protect from light and moisture.

Tentative expiration dating: 24 months based on the twelve weeks accelerated stability data.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Recommend Approval.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Satisfactory	09-Nov-11	N. Samaan
Labeling	Satisfactory	12-May-11	A. Vezza
Bioequivalence	Satisfactory	10-Oct-11	C. Chaurasia
EES	Acceptable	03-May-10	A. Inyard
Microbiology	N/A		

Following this page, 8 pages withheld in full - (b)(4)



CHEMISTRY REVIEW



Chemistry Assessment Section

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc. Florida.

DRUG PRODUCT: Morphine Sulfate Extended-Release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

A. Chemistry Deficiencies:

The application is approvable.

Sincerely yours,

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200-812

Endorsements:

HFD-647/Nashed I. Samaan Ph.D./ 09-Nov-2011

HFD-647/U.V. Venkataram Ph.D./09-Nov-2011

HFD-617/ T. Nhu Pharm.D/9-Nov-2011

F/T by

V:\Division of Chemistry II/Team 22/Final Version for DARRTS\200812N04
Addendum_NS.doc

TYPE OF LETTER: The application is approvable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NASHED I SAMAN
11/09/2011

UBRANI V VENKATARAM
11/09/2011

TINA T NHU
11/09/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 200812

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200812			
Drug Product Name	Morphine Sulfate Sustained-release Capsules ¹ , USP			
Strength(s)	80 mg and 100 mg			
Applicant Name	Watson Laboratories Inc.			
Address	4955 Orange Drive Ft. Lauderdale, FL 33314			
Applicant's Point of Contact	Alberto E. Rivalta, Manager Regulatory Affairs			
Contact's Telephone Number	(954) 358-6109			
Contact's Fax Number	(954) 358-6350			
Original Submission Date(s)	December 16, 2009			
Submission Date(s) of Amendment(s) Under Review				
Reviewer	Paramjeet Kaur, Ph.D.			
Study Number (s)	R09-0072	R09-0073	R09-0074	R09-0905
Study Type (s)	Fasting	Fed	Fasting sprinkle-in-applesauce	Fed
Strength (s)	80 mg	80 mg	80 mg	100 mg
Clinical Site	Cetero Research			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	(b) (4)			
Analytical Site Address				
OUTCOME DECISION	INADEQUATE			

OVERALL REVIEW RESULT	INADEQUATE		
WAIVER REQUEST RESULT	N/A		
DSI REPORT RESULT	ADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	FASTING STUDY	80 MG	INADEQUATE
1	FED STUDY	80 MG	INADEQUATE
1	FASTING SPRINKLE STUDY	80 MG	INADEQUATE
1	FED STUDY	100 MG	INADEQUATE
1	DISSOLUTION	80 MG and 100 MG	INADEQUATE

¹ In the labeling deficiency letter sent to the firm on 7/14/2010 (DARRTS, ANDA 200812, COR-ANDADE-03(Labeling Deficiencies)) the firm was informed that, "the term "(b) (4)" is not an official USP dosage form. Please revise the name of the drug product to read "Morphine Sulfate Extended-Released Capsules, USP" in all labeling pieces. Please also be advised that the reference listed drug, Kadian® Capsules, uses " "Morphine Sulfate Extended-Released Capsules, USP" as the established name".

1 EXECUTIVE SUMMARY

This application contains the results of fasting, fed and fasting sprinkle bioequivalence (BE) studies comparing Watson Laboratories' test product, Morphine Sulfate Extended Release Capsules, 80 mg, to the corresponding Actavis Elizabeth's reference product, Kadian® (Morphine Sulfate) Extended Release Capsules, 80 mg strength. In addition, the firm submitted a fed study comparing Watson Laboratories' test product, Morphine Sulfate Sustained Release Capsules, 100 mg, to the corresponding Actavis Elizabeth's reference product, Kadian® (Morphine Sulfate) Extended Release Capsules, 100 mg strength. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. Results of the PK statistical analyses of the fasting, fed and fasting sprinkle studies are summarized in the tables below:

Morphine Sulfate Extended Release Capsules, Dose (1 x 80 mg) Fasting Bioequivalence Study, Study No. R09-0072; N =44 (M=27; F=17)					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	284622.0	280541.7	1.01	94.09	109.40
AUC _∞ (hr *pg/ml)	295662.4	288060.3	1.03	95.21	110.65
C _{max} (pg/ml)	14727.61	13164.33	1.12	104.72	119.52

Morphine Sulfate Extended Release Capsules, Dose (1 x 80 mg) Fed Bioequivalence Study, Study No. R09-0073; N =42 (M=30; F=12)					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	330011.2	342341.7	0.96	93.51	99.37
AUC _∞ (hr *pg/ml)	341069.7	352369.5	0.97	94.30	99.35
C _{max} (pg/ml)	13451.47	15253.25	0.88	82.38	94.41

Morphine Sulfate Extended Release Capsules, Dose (1 x 80 mg) Fasting Sprinkle Bioequivalence Study, Study No. R09-0074; N =40 (M=25; F=15)					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	295013.7	305678.9	0.97	92.72	100.46
AUC _∞ (hr *pg/ml)	304091.0	313310.2	0.97	93.11	101.17
C _{max} (pg/ml)	13605.21	13060.75	1.04	98.04	110.68

Morphine Sulfate Extended Release Capsules, Dose (1 x 100 mg) Fed Bioequivalence Study, Study No. R09-0905; N=37 (M=23; F=14)					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	398224.9	401341.1	0.99	97.00	101.50
AUC _∞ (hr *pg/ml)	406874.6	410567.7	0.99	96.84	101.41
C _{max} (pg/ml)	18335.42	19827.43	0.92	86.35	99.04

The results of fasting, fed and fasting sprinkle studies are incomplete due to bioanalytical method validation and formulation deficiencies.

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, morphine-6-glucuronide (morphine-6G), were comparable. However, the metabolite data is incomplete due to issues concerning the specificity of the morphine-6G assay.

Firm has conducted comparative dissolution testing on 80 mg and 100 mg strengths using the USP dissolution method, but has not submitted the individual dissolution data. In addition, dissolution testing has been conducted at sampling points different from that of USP method.

The firm has also conducted dissolution testing under different pH conditions (pH 1.2, pH 4.5 buffer and pH 6.8 buffer). In addition, the firm's *in vitro* alcohol dose-dumping testing using the FDA-recommended method suggests that the risk of alcohol- dose dumping for the generic product is no more than that for the reference product.

The formulation of morphine sulfate extended release (ER) capsules, 80 mg and 100 mg is incomplete pending firm's submission of actual amount of (b) (4) and (b) (4) and total amount of elemental iron per capsule. Firm has not requested waiver for other strengths of morphine sulfate ER capsules².

The Division of Scientific Investigation (DSI) routine inspection was completed for the clinical site (previously also know as PRACS) on 5/15/2009 for NDA 022418 and outcome was VAI (Voluntary Action Indicated). The analytical site was inspected as routine inspection on (b) (4) for NDA (b) (4) and outcome was VAI (Voluntary Action Indicated).

The application is incomplete pending firm's response to deficiencies cited above.

² As per orange book, morphine sulfate extended release capsules are available in 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg and 200 mg strengths. For OGD recommendations on this drug product please refer to section 3.3 of this review.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Morphine Sulfate Sustained-Release Capsules ¹ , USP, 80 mg and 100 mg
Reference Product	Kadian [®] (Morphine Sulfate) Extended-Release Capsules, 10 mg, 80 mg, and 100 mg are the RLDs, also available in 20 mg, 30 mg, 50 mg, 60 mg and 200 mg strengths ³ .
RLD Manufacturer	Actavis Elizabeth
NDA No.	N020616
RLD Approval Date	July 3, 1996 (20 mg, 50 mg and 100 mg) March 9, 2001 (30 mg and 60 mg) October 27, 2006 (80 mg) February 27, 2007 (200 mg) April 20, 2007 (10 mg)
Indication	Kadian [®] extended-release capsules are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

3.2 PK/PD Information⁴

Bioavailability	Because of pre-systemic elimination, only about 20 - 40% of the administered dose reaches the systemic circulation. The single-dose pharmacokinetics of Kadian [®] are linear over the dosage range of 30-100 mg.
Food Effect	The extent of absorption is not affected by food, however, food slows the rate of absorption of Kadian [®] .
Tmax	In single-dose studies (parameter normalized to 100 mg), Kadian [®] capsules had t _{max} of 8.6 hours (%CV of 41%)
Metabolism	The major pathway of the detoxification of morphine is conjugation, either with D-glucuronic acid in the liver to produce glucuronides or with sulfuric acid to give morphine-3-etheral sulfate. Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide, M3G (about 50%), and morphine-6-glucuronide, M6G (about 5 to 15%). M3G has no significant analgesic activity. M6G has been shown to have opioid agonist and analgesic activity in humans.
Excretion	The elimination of morphine is primarily via hepatic metabolism to glucuronide metabolites (55 - 65%) which are then renally excreted. Approximately 10% of morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. A small amount of the glucuronide metabolites is excreted in the bile and there is

³ As per Orange Book (last accessed June 29, 2010)

⁴ Most recent labeling of Kadian[®] as approved on 4/20/2007 from drugs@fda (last accessed: June 29, 2010)

	some minor enterohepatic cycling. 7 - 10% of administered morphine is excreted in the feces. The mean adult plasma clearance is about 20-30 mL/minute/kg.
Half-life	The terminal $t_{1/2}$ of morphine is 2-4 hours, however, a longer $t_{1/2}$ of about 15 hours has been reported in studies where blood has been sampled up to 48 hours.
Dosage and Administration	Kadian[®] may be administered once or twice daily without regard to meals. Kadian[®] capsules should be swallowed whole. Kadian[®] capsules may be administered as a sprinkle on apple sauce or through a 16 French gastrostomy tube. The 100 mg and 200 mg capsules are for use only in opioid-tolerant patients.
Black Box Warning:	Kadian[®] contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Kadian[®] can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Kadian[®] in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Kadian[®] capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Kadian[®] capsules are NOT for use as a pm analgesic. KADIAN[®] 100 mg and 200 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsule may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN[®] CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE PELLETS IN THE CAPSULES ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	6, 3 fasting, 2 fed, 1 fasting sprinkle in applesauce*
---------------------------------------	--

1.	Type of study:	Fasting
	Design:	Single-dose, two-way crossover in-vivo
	Strength:	100 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	A naltrexone blockade should be used to remove the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid

		receptors. A common approach is to administer 50 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug. Please consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.
2.	Type of study:	Fed
	Design:	Single-dose, two-way crossover in-vivo
	Strength:	100 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Please see comments above
3.	Type of study:	Fasting Sprinkle in applesauce
	Design:	Single-dose, two-way crossover in-vivo
	Strength:	100 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Please see comments above
4.	Type of study:	Fasting
	Design:	Single-dose, two-way crossover in-vivo
	Strength:	200 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Please see comments above
5.	Type of study:	Fed
	Design:	Single-dose, two-way crossover in-vivo
	Strength:	200 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Please see comments above
6.	Type of study:	Fasting
	Design:	Single-dose, two-way crossover in-vivo
	Strength:	10 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Please see comments above

**Note: The firm submitted fasting (80 mg), fed (80 mg and 100 mg) and fasting sprinkle-in-applesauce BE studies (80 mg) on 12/16/09 before posting of current revised individual product recommendations for this drug product in May 2010.*

Analytes to measure (in plasma/serum/blood):	Morphine and Morphine-6-glucuronide in plasma
Bioequivalence based on (90% CI):	Morphine
Waiver request of in-vivo testing:	20 mg, 30 mg, 50 mg, 60 mg and 80 mg strengths based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) acceptable in vitro dissolution testing for the 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg strengths, and (iii) proportional similarity of formulations across 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg strengths.

Dissolution test method and sampling times

The FDA-recommended method for morphine sulfate extended release capsules is provided below (FDA Website, Dissolution Methods:

<http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>):

Morphine Sulfate	Capsule (Extended Release)			Refer to USP	08/11/2008
------------------	----------------------------	--	--	--------------	------------

USP Dissolution Method for Morphine Sulfate ER Capsules (USP 32-NF 27)

Medium	0.1 N HCl for 1 hr & followed by pH 7.5 phosphate buffer for 8 hrs
Volume	500 mL
USP Apparatus	Type I
Speed	100 rpm
Specifications	1 hr: NMT 10% 4 hr: 25-50% 6 hr: 50-90% 9 hr: NLT 85%

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2 and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Dissolution test method and sampling times	Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.
Source of most recent recommendations:	Individual Product Bioequivalence Recommendations for Morphine Sulfate Extended Release Tablets available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm088709.pdf
Summary of OGD or DBE History (for details, see Appendix 4.4):	

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fasting, sprinkle	Yes	1
Single-dose fed	Yes	2
Steady-state	No	-
In vitro dissolution	No	-
In vitro alcohol dose-dumping	Yes	2
Waiver requests	No	-
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	No	-

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Morphine	Morphine-6-Glucuronide
Bioanalytical method validation report location	Module 5.3.1.2.3	Module 5.3.1.2.3
Study Report Number	064.3, 064.3 Amendment 1 and 064.3 Amendment 2	064.3, 064.3 Amendment 1 and 064.3 Amendment 2
Analyte	Morphine	Morphine-6G
Internal standard (IS)	(b) (4)	(b) (4)
Method description	Solid Phase Extraction/ LC-MS/MS	Solid Phase Extraction/ LC-MS/MS
Limit of quantitation (pg/mL)	250	250
% recovery (and %CV) at each concentration tested	92.94%	91.48%
Average recovery of IS (%)	80.26%	76.37%
Standard curve concentrations (pg/mL)	250, 500, 1000, 5000, 10,000, 50,000, 100,000, 170,000, and 200,000	250, 500, 1000, 5000, 10,000, 50,000, 100,000, 170,000, and 200,000
QC concentrations (pg/mL)	750, 4000, 40,000 160,000	750, 4000, 40,000 160,000
QC Intraday precision range (%)	1.65% - 2.91%	1.66% - 6.40%
QC Intraday accuracy range (%)	97.45% - 110.28%	96.89% - 103.18%
QC Interday precision range (%)	3.02% - 4.92%	3.80% - 13.43%
QC Interday accuracy range (%)	95.30% - 108.55%	96.22% -107.67%
Bench-top stability (hrs)	19:52 hours-minutes @ room temperature	19:52 hours-minutes @ room temperature
Stock stability (days)	238:50 hours-minutes @ 4°C 238:50 hours-minutes @ RT ⁵	238:50 hours-minutes @ 4°C 238:50 hours-minutes @ RT
Processed stability (hrs)	#118:37 hours-minutes @ 4°C	72:28 hours-minutes @ 4°C
Freeze-thaw stability (cycles)	4 cycles	4 cycles
Long-term storage stability (days)#	145 days @ -20°C	145 days @ -20°C
Dilution integrity	240,000 pg/mL 3:1 / 1:9 (sample :blank)	240,000 pg/mL 3:1 / 1:9 (sample :blank)
Selectivity	No interfering peaks noted blank plasma samples	No interfering peaks noted blank plasma samples

#Long term stability and processed stability was carried out as per Amendment I of Method Validation No. 064.3

⁵ RT: Room temperature

Pre-Study Partial Bioanalytical Method Validation:

Information Requested	Morphine	Morphine-6-Glucuronide
Bioanalytical Partial Method Validation Report location	Module 5.3.1.2.3	Module 5.3.1.2.3
Study No.	064.4 and 064.4 Amendment I	064.4 and 064.4 Amendment I
Analyte	Morphine	Morphine-6G
Internal Standard (IS)	(b) (4)	(b) (4)
Method Description	LC-MS/MS/ Solid Phase Extraction	
Limit of quantitation (pg/ml)	250	250
Standard curve concentrations (pg/mL)	250, 500, 1000, 5000, 10000, 50000, 100000, 170000, 200,000	250, 500, 1000, 5000, 10000, 50000, 100000, 170000, 200000
QC concentrations (pg/mL)	LLOQ QC: 250.0; LQC: 750.0; MQC: 40000; HQC: 160000; ULQ QC: 200000	LLOQ QC: 250.0; LQC: 750.0; MQC: 40000; HQC: 160000; ULQ QC: 200000
QC Intrabatch precision range (%)	1.6% - 10.0%	1.7% - 14.2%
QC Intrabatch accuracy range (%)	-3.9% - 14.7%	-15.5% ⁶ - 13.9%
QC Interday precision range (%)	2.8% - 9.8%	4.7% - 17.0% ⁶
QC Interday accuracy range (%)	-0.7% - 7.1%	-1.0% - 4.1%
Freeze-thaw stability (cycles) [^]	6 cycles	4 cycles ^{&}

[^]Done as a part of method validation report 064.4 Amendment I[&]Three attempts at extending the freeze-thaw stability to six cycles for morphine-6G failed due to standards or QCs not meeting the acceptance criteria.**Pre-Study Partial Bioanalytical Method Validation:**

Information Requested	Morphine	Morphine-6-Glucuronide
Bioanalytical method validation report location	Module 5.3.1.2.3	Module 5.3.1.2.3
Study Report Number	064.5	064.5
Analyte	Morphine	Morphine-6G
Internal standard (IS)	(b) (4)	(b) (4)
Method description	Solid Phase Extraction/ LC-MS/MS	Solid Phase Extraction/ LC-MS/MS
Limit of quantitation (pg/mL)	250	250
Standard curve concentrations (pg/mL)	250, 500, 1000, 5000, 10000, 50000, 100000, 170000, 200,000	250, 500, 1000, 5000, 10000, 50000, 100000, 170000, 200000
QC concentrations (pg/mL)	250, 750, 40000, 160000, 200000	250, 750, 40000, 160000, 200000
QC Intraday precision range (%)	1.1% - 5.5%	#
QC Intraday accuracy range (%)	-3.2% -12.4%	#

⁶ Only LOQ QC samples are above 15% (meet the criteria of CV ≤ 20% at LOQQC as per the FDA's Guidance for Industry: Bioanalytical Method Validation (May 2001)).

Processed stability (hrs)	94:39 hours-minutes @ RT 98:19 hours-minutes @ 4°C	94:39 hours-minutes @ RT 98:19 hours-minutes @ 4°C
Selectivity	No interfering peaks noted in blank plasma samples	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes
Bioanalytical method is acceptable	Pending firm's response to bioanalytical method validation deficiencies

Please refer to Comments on the Pre-Study Method Validation

Comments on the Pre-Study Method Validation:

During cross validation of bioanalytical method (# 064.3, Amendment 2) from the LC/MS/MS API 5000 to LC/MS/MS API 3000; QCs and standards did not meet the acceptance criteria, therefore partial validation was carried out under bioanalytical method# 064.4.

Partial method validation (064.5) was carried out to support the main validation (bioanalytical method# 064.4) due to change in chromatography column.

Deficiencies related to pre-study method validation are as follow:

- The firm has not provided 1) the solid phase extraction procedure used to extract morphine and morphine-6G from the plasma samples, and 2) the concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples for analysis of morphine and morphine-6G in human plasma. Firm will be asked to provide this information.
- The study report (bioanalytical method# 064.5) mentions that precision and accuracy run of QCs samples for morphine-6G can be seen in Tables 12 and 14. However, the table titles are for the parent compound, morphine (Title for Tables# 12 and 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine in Human Plasma). Firm will be asked to clarify the reason for this discrepancy and submit the intraday accuracy and precision data for the QC samples for morphine-6G.
- The effect of naltrexone on the measurement of morphine and morphine-6G was not investigated. Since the naltrexone was administered pre-, post- and during dosing of the study drugs, the firm should investigate the possible effect of naltrexone on the extraction and detection of morphine and morphine-6G.

The pre-study method validation is incomplete pending firm's response to deficiencies cited above.

3.6 In Vivo Studies

**Table 1. Summary of all in vivo Bioequivalence Studies
For Parent Compound: Morphine**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters Median (Range) for T _{max}						Study Report Location
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-inf} (pg-hr/mL)	T _{1/2} (hr)	Kel (1/hr)	
R09-0072	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules Under Fasting Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 80 mg, Oral [Lot No. 3576R0013B]	44 (27/17) Healthy Subjects 24.8 (18-45)	15479.16 (31.44)	11.06 (5.00 – 24.00)	300156.30 (31.07)	310436.67 (30.15)	8.48 (26.00)	0.0872 (26.40)	Module 5.3.1.2
			Reference: KADIAN® Extended-Release Capsules 80 mg, Oral [Lot No. 510M81]		13925.66 (33.47)	10.00 (5.00 – 20.00)	296449.85 (31.99)	304315.53 (32.39)	8.80 (32.85)	0.0864 (29.78)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters Median (Range) for T _{max}						Study Report Location
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-inf} (pg-hr/mL)	T _{1/2} (hr)	Kel (1/hr)	
R09-0073	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules Under Fed Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 80 mg, Oral [Lot No. 3576R0013B] Reference: KADIAN® Extended-Release Capsules 80 mg, Oral [Lot No. 510M81]	42 (30/12) Healthy Subjects 26.3 (19-45)	14388.57 (53.61)	16.00 (8.00 – 30.00)	343282.66 (35.62)	353414.06 (35.39)	9.70 (27.18)	0.0772 (31.09)	Module 5.3.1.2
					16121.93 (38.15)	13.00 (6.00 - 24.00)	354546.73 (36.97)	363965.28 (36.53)	9.47 (31.77)	0.0811 (33.37)	
R09-0074	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules, Sprinkled on Applesauce, Under Fasting Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 80 mg, Oral [Lot No. 3576R0013B] Reference: KADIAN® Extended-Release Capsules 80 mg, Oral [Lot No. 510M81]	40 (25/15) Healthy Subjects 28.6 (20-44)	14325.28 (31.48)	14.00 (5.00 – 24.00)	307054.10 (29.93)	315183.52 (28.69)	10.37 (22.35)	0.0707 (26.85)	Module 5.3.1.2
					13822.50 (35.47)	13.03 (5.00 – 36.00)	319626.98 (33.19)	327452.78 (33.10)	9.80 (24.03)	0.0755 (28.41)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects ¹ No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters Median (Range) for T _{max}						Study Report Location
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-inf} (pg-hr/mL)	T _{1/2} (hr)	Kel (1/hr)	
R09-0905	A Relative Bioavailability Study of 100 mg Morphine Sulfate Extended-Release Capsules Versus 100 mg KADIAN® Capsules Under Fed Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 100 mg, Oral [Lot No. 3453R0001B]	37 (23/14) Healthy Subjects 25.7 (18-45)	19182.84 (33.37)	14.00 (8.00 – 24.00)	417846.97 (31.00)	427726.02 (31.44)	9.73 (36.06)	0.0817 (42.16)	Module 5.3.1.2
			Reference: KADIAN® Extended-Release Capsules 100 mg, Oral [Lot No. 320E71]		20771.62 (34.19)	14.00 (8.00 – 30.00)	421715.32 (32.65)	432078.20 (32.77)	9.71 (30.68)	0.0795 (36.38)	

For Metabolite of Morphine: Morphine-6-Glucuronide

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters Median (Range) for T _{max}						Study Report Location
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-inf} (pg-hr/mL)	T _{1/2} (hr)	Kel (1/hr)	
R09-0072	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules Under Fasting Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 80 mg, Oral [Lot No. 3576R0013B]	44 (27/17) Healthy Subjects 24.8 (18-45)	83406.36 (26.17)	12.00 (5.00 – 20.00)	1655027.79 (22.15)	1671631.90 (22.73)	8.72 (28.89)	0.0870 (35.23)	Module 5.3.1.2
			Reference: KADIAN® Extended-Release Capsules 80 mg, Oral [Lot No. 510M81]		77548.86 (24.09)	11.00 (5.00 – 20.00)	1661641.88 (21.70)	1683250.72 (22.06)	9.23 (35.75)	0.0850 (39.74)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters Median (Range) for T _{max}						Study Report Location
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-inf} (pg-hr/mL)	T _{1/2} (hr)	Kel (1/hr)	
R09-0073	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules Under Fed Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 80 mg, Oral [Lot No. 3576R0013B]	42 (30/12) Healthy Subjects 26.3 (19-45)	70570.48 (20.01)	16.00 (8.00 – 24.00)	1685934.54 (18.64)	1716975.81 (18.89)	9.90 (28.98)	0.0759 (28.71)	Module 5.3.1.2
			Reference: KADIAN® Extended-Release Capsules 80 mg, Oral [Lot No. 510M81]		79685.80 (28.52)	14.00 (8.00 – 24.00)	1662525.75 (17.32)	1691051.48 (17.76)	9.92 (22.61)	0.0736 (23.64)	
R09-0074	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules, Sprinkled on Applesauce, Under Fasting Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 80 mg, Oral [Lot No. 3576R0013B]	40 (25/15) Healthy Subjects 28.6 (20-44)	76066.50 (22.11)	12.00 (5.00 – 24.00)	1607019.60 (18.45)	1635851.94 (18.70)	10.72 (36.47)	0.0728 (39.03)	Module 5.3.1.2
			Reference: KADIAN® Extended-Release Capsules 80 mg, Oral [Lot No. 510M81]		74455.00 (24.92)	12.00 (5.00 – 36.00)	1701752.41 (15.54)	1724024.06 (16.01)	10.67 (24.07)	0.0684 (22.83)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects ¹ No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters ¹ Median (Range) for T _{max}						Study Report Location
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-inf} (pg-hr/mL)	T _{1/2} (hr)	Kel (1/hr)	
R09-0905	A Relative Bioavailability Study of 100 mg Morphine Sulfate Extended-Release Capsules Versus 100 mg KADIAN® Capsules Under Fed Conditions	Randomized, single-dose, two-way open-label crossover study	Test: Morphine Sulfate Sustained-Release Capsules 100 mg, Oral [Lot No. 3453R0001B]	37 (23/14) Healthy Subjects 25.7 (18-45)	95656.22 (21.71)	14.00 (9.00 – 20.00)	2114008.26 (20.83)	2151139.53 (21.47)	9.71 (31.70)	0.0799 (37.77)	Module 5.3.1.2
			Reference: KADIAN® Extended-Release Capsules 100 mg, Oral [Lot No. 320E71]		107898.38 (27.93)	14 (9.00 – 30.00)	2109221.30 (18.37)	2150482.94 (19.06)	10.11 (33.41)	0.0770 (39.11)	

Table 2.

Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Morphine Sulfate Extended Release Capsules, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. R09-0072; N =44					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	284622.0	280541.7	1.01	94.09	109.40
AUC _∞ (hr *pg/ml)	295662.4	288060.3	1.03	95.21	110.65
C _{max} (pg/ml)	14727.61	13164.33	1.12	104.72	119.52

Morphine Sulfate Extended Release Capsules, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. R09-0073; N=42 (M=30; F=12)					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	330011.2	342341.7	0.96	93.51	99.37
AUC _∞ (hr *pg/ml)	341069.7	352369.5	0.97	94.30	99.35
C _{max} (pg/ml)	13451.47	15253.25	0.88	82.38	94.41

Morphine Sulfate Extended Release Capsules, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Sprinkle Bioequivalence Study, Study No. R09-0074; N=40					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	295013.7	305678.9	0.97	92.72	100.46
AUC _∞ (hr *pg/ml)	304091.0	313310.2	0.97	93.11	101.17
C _{max} (pg/ml)	13605.21	13060.75	1.04	98.04	110.68

Morphine Sulfate Extended Release Capsules, Dose (1 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. R09-0905; N=37					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	398224.9	401341.1	0.99	97.00	101.50
AUC _∞ (hr *pg/ml)	406874.6	410567.7	0.99	96.84	101.41
C _{max} (pg/ml)	18335.42	19827.43	0.92	86.35	99.04

Table 3. Reanalysis of Study Samples***For Parent Compound: Morphine***

Fasted Study, Study No. R09-0072								
Module 5.3.1.2, R09-072, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 44-47								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=920 ²	Reference N=922 ²	Test N=920 ²	Reference N=922 ²	Test N=920 ²	Reference N=922 ²	Test N=920 ²	Reference N=922 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Poor Chromatography	5	4	0.5	0.4	5	3	0.5	0.3
Low Internal Standard	7	9	0.8	1.0	6	9	0.7	1.0
Adjusted Lower Limit of Quantitation	3	2	0.3	0.2	3	2	0.3	0.2
Inadvertent Repeat	21	21*	2.3	2.2	19	19*	2.1	2.1
Retention Time Shift	2	1	0.2	0.1	1	1	0.1	0.1
High Internal Standard	1	0	0.1	0.0	-	-	-	-
Total Number of Samples Reanalyzed	39	36	4.2	3.9	34	33	3.7	3.7

*corrected by reviewer

Fed Study, Study No. R09-0073								
Module 5.3.1.2, R09-073, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 44-45								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=877 ²	Reference N=877 ²	Test N=877 ²	Reference N=877 ²	Test N=877 ²	Reference N=877 ²	Test N=877 ²	Reference N=877 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Poor Chromatography	2	1	0.2	0.1	2	1	0.2	0.1
Low Internal Standard	6	5	0.7	0.6	5	4	0.6	0.5
Adjusted Lower Limit of Quantitation	2	2	0.2	0.2	2	2	0.2	0.2
Retention Time Shift	1	1	0.1	0.1	1	-	0.1	-
High Internal Standard	0	1	0.0	0.1	-	1	-	0.1
Total Number of Samples Reanalyzed	11	10	1.3	1.1	10	8	1.1	0.9

Sprinkle Fasted Study, Study No. R09-0074								
Module 5.3.1.2, R09-074, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 45-47								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=837 ²	Reference N=835 ²	Test N=837 ²	Reference N=835 ²	Test N=837 ²	Reference N=835 ²	Test N=837 ²	Reference N=835 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Low Internal Standard	17	19	2.0	2.3	15	19	1.8	2.3
Possible Extraction Error	2	0	0.2	0.0	2	-	0.2	-
Poor Chromatography	5	7	0.6	0.8	4	7	0.5	0.8
Poor Chromatography, Low Internal Standard	1	0	0.1	0.0	1	-	0.1	-
High Internal Standard	3	4	0.4	0.5	3	4	0.4	0.5
Total Number of Samples Reanalyzed	28	30	3.3	3.6	25	30	3.0	3.6
Fed Study, Study No. R09-0905								
Module 5.3.1.2, R09-905, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 51-54								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=777 ²	Reference N=777 ²	Test N=777 ²	Reference N=777 ²	Test N=777 ²	Reference N=777 ²	Test N=777 ²	Reference N=777 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Low Internal Standard	23	29	3.0	3.7	21	27	2.7	3.5
Peak In Pre-Dose*	0	1	0.0	0.1	-	1	-	0.1
Poor Chromatography	2	3	0.3	0.4	1	3	0.1	0.4
Retention Time Shift	1	1	0.1	0.1	-	1	-	0.1
High Internal Standard	7	2	0.9	0.3	5	-	0.6	-
Low Internal Standard, Low Internal Standard	0	1	0.0	0.1	-	-	-	-
Adjusted Lower Limit of Quantitation, Low Internal Standard	0	1	0.0	0.1	-	1	-	0.1
Adjusted Lower Limit of Quantitation	4	2	0.5	0.3	4	2	0.5	0.3
Total Number of Samples Reanalyzed	37	40	4.8	5.1	31	35	4.0	4.5

* Peak in pre-dose sample for subject# 12 was observed after administration of reference product (original concentration: (b) (4) pg/mL; repeated and used concentration for PK analysis is below the LLQ (250 pg/mL)).

For Metabolite of Morphine: Morphine-6-Glucoronide

Fasted Study, Study No. R09-0072								
Module 5.3.1.2, R09-072, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 77-78								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=920 ²	Reference N=922 ²	Test N=920 ²	Reference N=922 ²	Test N=920 ²	Reference N=922 ²	Test N=920 ²	Reference N=922 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
High Internal Standard	9	6	1.0	0.7	9	5	1.0	0.5
Low Internal Standard	4	2	0.4	0.2	4	2	0.4	0.2
Poor Chromatography	5	6	0.5	0.7	4	6	0.4	0.7
Adjusted Lower Limit of Quantitation	4	2	0.4	0.2	4	2	0.4	0.2
Adjusted Lower Limit of Quantitation, Poor Chromatography	1	0	0.1	0.0	1	-	0.1	-
Total Number of Samples Reanalyzed	23	16	2.5	1.7	22	15	2.4	1.6

Fed Study, Study No. R09-0073								
Module 5.3.1.2, R09-073, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 73-74								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=877 ²	Reference N=877 ²	Test N=877 ²	Reference N=877 ²	Test N=877 ²	Reference N=877 ²	Test N=877 ²	Reference N=877 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Adjusted Lower Limit of Quantitation	4	2	0.5	0.2	4	2	0.5	0.2
Poor Chromatography	4	2	0.5	0.2	4	1	0.5	0.1
High Internal Standard	11	11	1.3	1.3	7	9	0.8	1.0
Peak In Pre-Dose*	0	1	0.0	0.1	-	1	-	0.1
Low Internal Standard	0	1	0.0	0.1	-	1	-	0.1
Total Number of Samples Reanalyzed	19	17	2.2	1.9	15	14	1.7	1.6

*Peak in pre-dose sample for subject# 22 was observed after administration of reference product (original concentration: (b) (4) pg/mL; repeated and used concentration for PK analysis (b) (4) pg/mL).

Sprinkle Fasted Study, Study No. R09-0074								
Module 5.3.1.2, R09-074, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 70-71								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=837 ²	Reference N=835 ²	Test N=837 ²	Reference N=835 ²	Test N=837 ²	Reference N=835 ²	Test N=837 ²	Reference N=835 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
High Internal Standard	11	11	1.3	1.3	11	10	1.3	1.2
Possible Extraction Error	2	0	0.2	0.0	2	-	0.2	-
Low Internal Standard	4	2	0.5	0.2	4	2	0.5	0.2
Poor Chromatography	4	3	0.5	0.4	3	3	0.4	0.4
Adjusted Lower Limit of Quantitation	0	2	0.0	0.2	-	2	-	0.2
Total Number of Samples Reanalyzed	21	18	2.5	2.2	20	17	2.4	2.0

Fasted Study, Study No. R09-0905								
Module 5.3.1.2, R09-905, Reports of Bioanalytical and Analytical Methods for Human Studies, Pages: 82-86								
Reason for Reanalysis	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis ⁵			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=777 ²	Reference N=777 ²	Test N=777 ²	Reference N=777 ²	Test N=777 ²	Reference N=777 ²	Test N=777 ²	Reference N=777 ²
	n ³	n ³	% ⁴	% ⁴	n ³	n ³	% ⁴	% ⁴
Pharmacokinetic ¹	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Low Internal Standard	3	2	0.4	0.3	2	2	0.3	0.3
High Internal Standard	13	12	1.7	1.5	11	11	1.4	1.4
Inadvertent Repeat	42	42	5.4	5.4	38	38	4.9	4.9
Total Number of Samples Reanalyzed	58	56	7.5	7.2	51	51	6.6	6.6

¹ If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table

² N = Number of samples analyzed for each treatment

³ n = Number of samples repeated

⁴ % = percentage of assays repeated (i.e. 100*(n/N)%)

⁵ Reported values that are different from the original value

Did use of recalculated plasma concentration data change study outcome? All reassays were performed for analytical reasons; there were no pharmacokinetic repeats and no recalculations were performed.

Comments from the Reviewer:

The firm's reanalysis SOP ((b)(4)_SOP_04_LBP_006) did not define "Adjusted lower limit of quantitation (ALLQ) and retention time shift (RTS) or identify the criteria for selecting samples with ALLQ and RTS.

The available data indicates that ALLQ were identified as samples where original concentrations < 500 pg/mL were coded as below the lower limit of quantitation (BLQ) (Note: the bioanalytical method results indicate that LOQ is 250 pg/mL).

Comments on reanalysis of samples for fasting study #R09-0072:

1. The reanalysis of the study samples included a total of 3.9% - 4.2% and 1.7% - 2.5% reassay repeats for morphine and morphine-6G, respectively.
2. For morphine analysis, samples from two subjects (# 8 and 19) were rejected due to failed runs (standards failed to meet the acceptance criteria) and repeated. One subject (# 12) was repeated and inadvertently regressed for morphine when acceptable results had already been obtained, for pharmacokinetic calculations the mean of original and repeat values was used as per SOP.
3. The reanalysis SOP does not define inadvertent repeats. Since the repeat concentrations were within $\pm 30\%$, firm used the mean of original and repeat values to calculate the PK parameters as per the SOP. Reviewer recalculated the PK parameters using the original values for the inadvertent repeat sample, as shown in the table below, the 90% CIs for LAUC_{0-t}, LAUC_{0-∞} and LC_{max} are within the acceptable limits of 80%-125%.

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
LAUCT	284622.0	280541.7	1.01	94.09	109.40
LAUCI	295662.4	288060.3	1.03	95.21	110.65
LCMAX	14727.61	13164.33	1.12	104.72	119.52

4. For morphine-6G analysis, samples from five subjects (# 4, 12 (QCs failed to meet the acceptance criteria), #19, 23, 35 (x2) (standards failed to meet the acceptance criteria) were rejected and repeated.
5. SOP deviation: Due to the repeating of some samples for morphine-6G, the validated freeze/thaw stability was extended beyond established 4 cycles. The

samples that exceeded freeze/thaw stability were for reproducibility of incurred samples and showed that the results were reproducible.

6. To evaluate reproducibility for morphine and morphine-6G, incurred sample analysis was carried out by analyzing 143 samples for morphine and morphine-6G. The results of incurred sample analysis revealed that bioanalytical assay is reproducible and met the acceptance criteria of at least 2/3 of the incurred samples concentrations being within $\pm 20\%$ of each other.

Comments on reanalysis of samples for fed study #R09-0073:

1. The reanalysis of the study samples included a total of 1.1% - 1.3 % and 1.9% - 2.2% reassay repeats for morphine and morphine-6G, respectively.
2. For morphine analysis, samples from 2 subjects (#8, 42; QCs failed to meet the acceptance criteria) were repeated due to failed runs. In addition, samples from 2 subjects (# 4 (poor chromatography) and #40 (instrument malfunction)) were re-injected due to failed runs.
3. For morphine-6G analysis, samples from 6 subject (# 5, 28 (x2), 38 (QCs failed to meet the acceptance criteria), # 7, 26 and 48 (standards failed to meet the acceptance criteria) were rejected due to failed runs and repeated.
4. The established freeze/thaw stability for morphine-6G is 4 cycles. Due to the repeating of some samples for morphine-6G, the validated freeze/thaw stability was exceeded.
5. To evaluate reproducibility for morphine and morphine-6G, incurred sample analysis was carried out by analyzing 138 samples for morphine and morphine-6G. The results of incurred sample analysis revealed that bioanalytical assay is reproducible and met the acceptance criteria of at least 2/3 of the incurred samples concentrations being within $\pm 20\%$ of each other.

Comments on reanalysis of samples for fasting sprinkle study #R09-0074:

1. The reanalysis of the study samples included a total of 3.3% - 3.6 % and 2.2% - 2.5% reassay repeats for morphine and morphine-6G, respectively.
2. For morphine analysis, samples from 4 subjects (# 6 (QCs failed to meet the acceptance criteria); # 13, 35 and 39 (standards failed to meet the acceptance criteria)) were repeated due to rejected runs.
3. For morphine-6G analysis, samples from 5 subject (# 30 (QCs failed to meet the acceptance criteria); # 3, 13, 21, and 39 (standards failed to meet the acceptance criteria)) were repeated due to rejected runs

4. To evaluate reproducibility for morphine and morphine-6G, incurred sample analysis was carried out by analyzing 134 samples for morphine and morphine-6G. The results of incurred sample analysis revealed that bioanalytical assay is reproducible and met the acceptance criteria of at least 2/3 of the incurred samples concentrations being within $\pm 20\%$ of each other.

Comments on reanalysis of samples for fed study #R09-0905:

1. The reanalysis of the study samples included a total of 4.8% - 5.5 % and 7.2% - 7.5% reassay repeats for morphine and morphine-6G, respectively.
2. For morphine analysis, samples from 3 subjects (#2, 13, 28; due to unacceptable standards, poor chromatography and QCs, respectively) were rejected due to failed runs and repeated. In addition, samples from 2 subjects (#37 and 38, poor chromatography) were re-injected due to failed runs.
3. For morphine-6G analysis, samples from 13 runs, 8 subjects (# 2, 34, 42 (x2), 28, 7 unacceptable standards; # 4, 7, 10 (x2), 28, 32, 42 unacceptable QCs) were repeated due to failed runs. In addition, 2 runs were re-injected (subjects# 37 and 38) and inadvertently regressed when acceptable results had previously been obtained.
4. The reanalysis SOP does not define inadvertent repeats. Since the repeat concentrations were within $\pm 30\%$, firm used the mean of original and repeat values to calculate the morphine-6G PK parameters as per the SOP. Reviewer recalculated the PK parameters using the original values for the inadvertent repeat sample, as shown in the table below, the 90% CIs for LAUC_{0-t}, LAUC_{0-∞} and LC_{max} are within the acceptable limits of 80%-125%.

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
LAUCT	2067089	2069764	1.00	97.66	102.13
LAUCI	2099795	2105920	1.00	97.56	101.91
LCMAX	93840.04	105274.2	0.89	83.33	95.35

5. The established freeze/thaw stability for morphine-6G is 4 cycles. Due to the repeating of some samples for morphine-6G, the validated freeze/thaw stability was exceeded. Firm has mentioned that freeze-thaw stability will be extended
6. To evaluate reproducibility for morphine and morphine-6G, incurred sample analysis was carried out by analyzing 128 samples for morphine and morphine-6G. The results of incurred sample analysis revealed that bioanalytical assay is reproducible and met the acceptance criteria of at least 2/3 of the incurred samples concentrations being within $\pm 20\%$ of each other.

Comments to be communicated to the firm:

1. Firm will be asked to provide the supporting data to show that naltrexone does not affect the extraction and measurement of morphine and morphine-6G in human plasma samples.
2. Please confirm whether selection of samples with adjusted lower limit of quantitation and retention time shift was based on established procedures. The analytical site's Standard Operating Procedure (b) (4) _SOP_04_LBP_006 does not define adjusted lower limit of quantitation and retention time shift and fails to provide the criteria for selecting samples with adjusted lower limit of quantitation and retention time shift.
3. For fed studies #R09-0073 and #R09-0905, the freeze-thaw stability of morphine-6G samples exceeded beyond the established 4 freeze-thaw cycle stability. Please provide the freeze-thaw stability to cover the stability of samples during bioanalytical study conduct.

3.7 Formulation

Location in appendix	Section 4.2, Page 81
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	FORMULATION UNACCEPTABLE
If not acceptable, why?	Firm did not provide the actual amount of (b) (4) (b) (4) and (b) (4) and total amount of elemental iron per capsule.

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	N/A
Source of Method (USP, FDA or Firm)	USP
Medium	0.1 N HCl for 1 hour, followed by replacing with pH 7.5 Phosphate buffer for 8 hours
Volume (mL)	500 mL
USP Apparatus type	Type I (Basket)
Rotation (rpm)	100 rpm
DBE-recommended specifications	1 hr: NMT 10%; 4 hr: 25-50%; 6 hr: 50-90%; 9 hr: NLT 85%
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	N/A
Is method acceptable?	INCOMPLETE

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If not then why?	Firm has not submitted the dissolution testing data on 80 mg and 100 mg strengths using the USP-recommended method (specifically, sampling points). Firm is proposing to use the USP method for morphine sulfate extended release capsules, 80 mg and 100 mg with the following specifications: 1 hr: NMT 10%; 5 hr: (b) (4) %; 7 hr: (b) (4) %; 10 hr: NLT 85%. Firm will be asked to submit the comparative dissolution data using the USP method.
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Multimedia Dissolution Testing: The firm has conducted dissolution testing in three different pH media (pH 1.2, pH 4.5 and pH 6.8). The f2 values indicate that the release of drug from the test formulations is comparable to RLD products under three different pH conditions.

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	Test 80 mg vs. Test 100 mg	Test 80 mg vs. Reference 80 mg	Test 100 mg vs. Reference 100 mg
pH 1.2			
Whole capsule	75.22	73.20	59.44
pH 4.5 Buffer			
Whole capsule	83.43	66.39	80.19
pH 6.8 Buffer			
Whole capsule	72.24	61.21	56.10

In Vitro Alcohol Dose Dumping Study: The firm has conducted in vitro alcohol dose-dumping study on all strengths using FDA recommended alcohol dose-dumping conditions.

F2 metric, biostudy strengths compared to other strength(s)				
Biostudy Strength	Test 80 mg vs. Reference 80 mg			
Dissolution Media	0.1 N HCl	0.1 N HCl/5% Ethanol	0.1 N HCl/20% Ethanol	0.1 N HCl/40% Ethanol
Whole capsule	73.02	71.52	50.28	26.72*
Test 100 mg vs. Reference 100 mg				
Whole capsule	88.48	82.05	54.40	29.27*

**Please refer to Reviewer's Comment in Section 4.3*

It is noted that mean % of morphine dissolved at 2 hours in 40% alcohols is 39-44% lower for test products than the reference products. This data suggests that the risk of

dose-dumping from the generic product is no more than that of reference product, which, is further supported by the f2 values presented in the above table.

3.9 Waiver Request(s)

Strengths for which waivers are requested	None
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	No
Waivers granted?	No - Firm has not requested waiver for 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, and 200 mg strengths
If not then why?	

3.10 Deficiency Comments

1. Pre-study bioanalytical method validation report no. 064.5 does not contain the description of solid phase extraction procedure used to extract morphine and morphine-6G from human plasma samples, concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples for analysis of morphine and morphine-6G in human plasma.
2. Pre-study bioanalytical method validation report no. 064.5 mentions that precision and accuracy run of QC samples for morphine-6G can be seen in Tables 12 and 14. However, the table titles are for the parent compound, morphine (Title for Tables# 12 and 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine in Human Plasma). Firm will be asked to clarify the reason for this discrepancy and submit the intraday accuracy and precision data for the QC samples for morphine-6G.
3. The effect of naltrexone on the estimation of morphine and morphine-6G was not investigated. Naltrexone was administered pre-, post- and during dosing of the study drugs. The firm will be requested to investigate the effect of naltrexone on the extraction and detection of morphine and morphine-6G.
4. The firm should confirm whether selection of samples with adjusted lower limit of quantitation and retention time shift was based on established procedures. The analytical site's Standard Operating Procedure ^{(b) (4)} SOP_04_LBP_006 does not define adjusted lower limit of quantitation (ALLQ) and retention time shift (RTS) and fails to provide the criteria for selecting samples with ALLQ and RTS.
5. For fed studies# R09-0073 and R09-0905, the freeze-thaw stability of morphine-6G samples exceeded beyond the established 4 freeze-thaw cycle stability. Firm will be asked to provide the freeze-thaw stability data to cover the stability of morphine-6G during bioanalytical study conduct.

6. Firm did not provide the actual amount of (b) (4) and (b) (4) used in morphine sulfate extended release capsules, 80 mg and 100 mg. Firm will be asked to submit the actual amount of (b) (4) and (b) (4) including the total amount of elemental iron per capsule.
7. Firm did not provide the comparative dissolution testing on 12 dosage units each of the test and reference 80 mg and 100 mg formulations using the USP method. Firm will be asked to provide this information.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study R09-0072 incomplete due to the deficiency comments # 1-4 and 6-7. The Watson Laboratories conducted the fasting BE study on its Morphine Sulfate Extended Release Capsules, 80 mg, lot# 3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
2. The Division of Bioequivalence finds the fed BE study R09-0073 incomplete due to the deficiency comments # 1-7. The Watson Laboratories conducted the fed BE study on its Morphine Sulfate Extended Release Capsules, 80 mg, lot# 3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
3. The Division of Bioequivalence finds the fasting sprinkle BE study R09-0074 incomplete due to the deficiency comments # 1-4 and 6-7. The Watson Laboratories conducted the fasting sprinkle BE study on its Morphine Sulfate Extended Release Capsules, 80 mg, lot# 3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
4. The Division of Bioequivalence finds the fed BE study R09-0905 incomplete due to the deficiency comments # 1-7. The Watson Laboratories conducted the fed BE study on its Morphine Sulfate Extended Release Capsules, 100 mg, lot# 3453R0001B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 100 mg, lot #320E71.
5. The firm should conduct dissolution testing according to the current USP monograph for morphine sulfate extended release capsules.
6. The application is incomplete due to deficiencies cited above.

3.12 Comments for Other OGD Disciplines

Discipline	Comment

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4. Study Information

Study Number	R09-0072
Study Title	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules Under Fasting Conditions
Clinical Site (Name & Address)	Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 29 August 2009 Period II: 12 September 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	22 September 2009 – 03 November 2009
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	66 days (29 August 2009 – 03 November 2009)

Table 5. Product information

Product	Test	Reference	Treatment
Treatment ID	A	B	N/A
Product Name	Morphine Sulfate Sustained-Release Capsules ¹ , USP, 80 mg	KADIAN® Extended-Release Capsules 80 mg	NALTREXONE HYDROCHLORIDE TABLETS, USP 50 mg
Manufacturer	Watson Laboratories—Florida	Actavis Elizabeth LLC	Mallinckrodt Inc.
Batch/Lot No.	3576R0013B	510M81	1170N69101
Manufacture Date	06/09/09		
Expiration Date		12/2010	12/2010
Strength	80 mg	80 mg	50 mg
Dosage Form	Capsule	Capsule	Tablet

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Bio-Batch Size	(b) (4) apstules		
Production Batch Size	Capsules		
Potency (Assay)	101.8% label claim	103.3%	N/A
Content Uniformity (mean, %CV)	Mean#: 103.5% %RSD: 1.7 *AV: 6.1		
Dose Administered	80 mg	80 mg	50 mg
Route of Administration	Oral	Oral	Oral

#As provided in module 2.3 quality overall summary *AV = Acceptance value

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	48 enrolled; 44 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 2, 4, 6, 8, 10, 11, 14, 15, 17, 19, 21, 22, 27, 28, 31, 32, 34, 35, 39, 40, 42, 43, 45, 46 BA: 1, 3, 5, 7, 9, 12, 13, 16, 18, 20, 23, 24, 25, 26, 29, 30, 33, 36, 37, 38, 41, 44, 47, 48 To remove the risk of any opioid-related adverse events, subjects were administered naltrexone (1 × 50 mg tablet) with 240 mL of water at approximately 12 hours prior to morphine administration, concurrent with morphine administration, and 12 hours after morphine administration⁷.
Blood Sampling Times	Pre-dose and 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 30, 36, 48, 60 and 72 hours post-dose
Blood Volume Collected/Sample*	1 x 6 mL of blood in K ₂ EDTA vacutainers
Blood Sample Processing/Storage	-20 °C (range -10 °C to -30 °C)
IRB Approval	August 26, 2009
Informed Consent	Yes
Length of Fasting	10 hrs
Length of Confinement	14 hrs prior to dosing until 36 hrs after dosing
Safety Monitoring	Blood pressure, heart rate, and respiratory rate were to be measured at screening, prior to dosing and at approximately 1, 2, 4, 6, 8, 12, 24 and 36 hours (± 60 minutes) after each dose and at study exit. Blood pressure, heart rate, and respiratory rate measurements prior to dose administration (0 hour) were to be collected within 90 minutes prior to the scheduled dose administration.

*As specified in fasting study protocol# R09-0072

⁷ The naltrexone regimen is similar as recommended by OGD for this drug product (posted on FDA's website: 5/2010)

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. R09-0072			
		Treatment Groups	
		Test Product N = 44	Reference Product N = 44
Age (years)	Mean ± SD Range	24.8 ± 6.6 18 - 45	24.8 ± 6.6 18 - 45
Age Groups	< 18 18 – 40 40 – 64 65 – 75 > 75	- 41 (93.2%) 3 (6.8%) - -	- 41 (93.2%) 3 (6.8%) - -
Sex	Male Female	27 (61.4%) 17 (38.6%)	27 (61.4%) 17 (38.6%)
Race	American Indian or Alaskan Native (N) Asian (A) Black or African American Native Hawaiian or Other Pacific Islander White (W) WN WA	1 (2.3%) 2 (4.5%) 3 (6.8%) - 36 (81.8%) 1 (2.3%) 1 (2.3%)	1 (2.3%) 2 (4.5%) 3 (6.8%) - 36 (81.8%) 1 (2.3%) 1 (2.3%)
BMI	Mean ± SD Range	25.4 ± 2.0 21.9 - 29.9	25.4 ± 2.0 21.9 - 29.9
Other Factors			

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
21	Dropped by the investigator in Period I prior to study hour 2.00 activity due to adverse event (emesis)	I	No
22	Withdrew consent prior to Period II check-in due to family emergency	II	No
28	Dropped by the sponsor prior to Period II study hour -13.50 activities due to adverse event (urinary tract infection)	II	No
48	Dropped by the investigator prior to Period II study hour -12.00 activities due to positive drug screen at check-in	II	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event ¹	Reported Incidence by Treatment Groups	
	Study No. R09-0072	
	Test N=47 ²	Reference N=45 ²
	n (%) ³	n (%) ³
Gastrointestinal disorders		
Diarrhoea	1 (2.13%)	-
Nausea	4 (8.51%)	4 (8.89%)
Vomiting	1 (2.13%)	-
General disorders and administration site conditions		
Chills	1 (2.13%)	-
Venipuncture site inflammation	1 (2.13%)	-
Infections and infestations		
Hepatitis infectious mononucleosis	1 (2.13%)	-
Infectious mononucleosis	-	1 (2.22%)
Urinary tract infection	1 (2.13%)	-
Nervous system disorders		
Dizziness	1 (2.13%)	3 (6.67%)
Headache	5 (10.64%)	2 (4.44%)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	-	1 (2.22%)
Total	9 (19.15%)	9 (20.00%)

¹ MedDRA Version 12; ² N = Number of subjects dosed for each treatment

³ n = Number of subjects reporting at least one incidence of respective adverse event;

(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Concomitant medications	26, 28	N/A
Blood Sample Collection Deviations During Study Period I	19 (x5), 31 (x2), 45, 15	12 (x2), 13 (x4), 22, 23 (x3), 29, 33 (x2), 38, 41, 48 (x3), 20 (x2)
Blood Sample Collection Deviations During Study Period II	12 (x2), 13 (x2), 33, 9, 16 (x2), 20 (x2), 23 (x2), 29 (x2)	10, 31, 15, 39, 17 (x2), 31, 32, 45
Period I study hour 72, no query or blood sample collected	N/A	03, 18
Period I study hour 12.00, no blood sample collected	19	N/A
Period I study hour 16.00, no blood sample collected	19	N/A
Period I study hour 72, no centrifuge or freezer date and time for blood sample was documented	15	N/A
Period II study hour 72, no query or blood sample collected	03	N/A
Period II study hour 20, no blood sample collected	16	N/A
Period II check-in, positive drug screen	N/A	48
Exit procedures were completed more than 14 days from last blood draw	22	N/A

Comments on Dropouts/Adverse Events/Protocol Deviations:

A total of 48 subjects were enrolled in the study with 44 subjects completing both study periods. Subject# 21 and 28 were dropped due to their adverse events, emesis and urinary tract infection, respectively. Subject# 22 withdrew consent prior to Period II check-in due to a family emergency, and subject# 48 was dropped due to positive drug screen at check-in.

During the course of study protocol deviations occurred in the following areas:

- Use of concomitant medications. Subjects# 26 and 28 were given Sucrets Complete lozenges (as needed on 9/13/09) and 500 mg Cipro tablets (2 times daily from 9/10/2009 to 9/12/09), respectively to treat their adverse events. Subject# 28 was dropped from the study. Considering that Sucrets Complete lozenges (subject# 26) are used to treat sore throat locally, the use of concomitant medications is unlikely to have an impact on the outcome of the study.
- Female subjects taking birth control pills were included into the study by principal Investigator and judged to have no effect on the study results.
- Missing blood sample collection at 12 hr and thereafter post-dose.
- Deviation in blood sampling time collections occurred by 1-13 mins. These deviations are not going to have an impact on the results of study because pharmacokinetic parameters were calculated by using the actual sample collection times by the firm.

These protocol deviations are unlikely to have an impact on the results of study.

There were 29 adverse events involving 15 subjects in the study. Out of 29 adverse events, 18 (12 related, 6 unrelated) were reported for the test and 11 (6 related, 5 unrelated) were reported for the reference. The adverse events were mild (13 for test and 8 for reference) to moderate (5 for test and 3 for reference) in severity. Overall, the most common adverse events were dizziness, nausea and headache.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Analyte: Morphine									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250.0	500.0	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	8.4	7.0	6.2	5.8	5.0	3.9	4.0	4.9	5.0
Interday Accuracy (%Actual)	-1.4	0.2	-0.3	-0.1	1.1	0.6	0.4	-2.2	1.6
Linearity	0.9920 – 0.9996								
Linearity Range (pg/mL)	250.0 – 200,000								
Sensitivity/LOQ (pg/mL)	250.0								
Parameter	Quality Control Samples								
Concentration (pg/mL)	750.0		4000		40,000		160,000		
Interday Precision (%CV)	9.0		4.7		4.7		4.6		
Interday Accuracy (%Actual)	0.7		-0.7		-0.6		1.7		

Analyte: Morphine-6G									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250.0	500.0	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	11.1	6.0	6.0	5.7	5.5	4.9	3.9	5.1	4.5
Interday Accuracy (%Actual)	-2.0	-0.6	1.6	0.1	0.4	0.1	0.8	-1.9	1.3
Linearity	0.9952 – 0.9994								
Linearity Range (pg/mL)	250.0 – 200000								
Sensitivity/LOQ (pg/mL)	250.0								
Parameter	Quality Control Samples								
Concentration (pg/mL)	750.0		4000		40,000		160,000		
Interday Precision (%CV)	20.4*		6.7		6.4		5.7		
Interday Accuracy (%Actual)	4.1		0.7		-0.5		0.9		

**Please refer to comments on Study Assay Validation*

Comments on Study Assay Validation:

Of the 376 QC samples analyzed for morphine-6G with the subject samples in acceptable batch runs, 27 QCs (7.2%) failed the acceptance criteria. As shown in the above table, the inter-run %Bias of the QCs ranged from -0.5% - 4.1% and the inter-run CV ranged from 5.7% - 20.4%. Since the % CV for the LQC level did not meet acceptance requirements ($\pm 15\%$), firm recalculated the %CV by excluding all of the failed QCs

from that level. The recalculated results shows the inter-run %Bias of the QCs ranged from -0.5% to 1.5% and the inter-run CV ranged from 5.7% to 8.7%.

As per the FDA's Guidance for Industry: Bioanalytical Method Validation (May 2001), at least 67% of the QC samples should be within 15% of their respective nominal values; 33% of the QC samples (not all replicates at the same concentration) can be outside the $\pm 15\%$ of the nominal value. Since, at low LQC, only 20 out of 94 (21.3%) QC failed the acceptance criteria, the results of study assay validation are acceptable.

Any interfering peaks in chromatograms?	Yes
Were 20% of chromatograms included?	Yes (Subjects# 36, 37, 38, 39, 40, 41, 42, 43, 44)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4) _SOP_04_LBP_006	18 March 2009	Sample Reanalysis and Reporting Criteria
_SOP_04_LBP_002	3 February 2009	Sample Analysis (Chromatographic)

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	See comments below
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	Pending firm's response to ALLQ and RTS criteria for repeat analysis

The analytical site's Standard Operating Procedure (b) (4) _SOP_04_LBP_006 does not define adjusted lower limit of quantitation and retention time shift and fails to provide the criteria for selecting samples with adjusted lower limit of quantitation and retention time shift.

Summary/Conclusions, Study Assays:

The firm submitted the SOPs for analytical run acceptance and repeat analysis. The long term stability data of 145 days cover the entire duration of study sample.

The results of bioanalytical study are incomplete pending firm's response to bioanalytical deficiencies.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 18](#) and [Figure 2](#)

Fasting Bioequivalence Study, Study No. R09-0072; N=44 Analyte: Morphine									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *pg/ml)	300156.3	31.07	108747.5	503369.3	296449.8	31.99	105938.9	535550.1	1.01
AUC _∞ (hr *pg/ml)	310436.7	30.15	115740.6	533232.7	304315.5	32.39	108655.3	560790.1	1.02
C _{max} (pg/ml)	15479.16	31.44	6606.00	26770.00	13925.66	33.47	5768.00	25580.00	1.11
T _{max} * (hr)	11.060	.	5.00	24.00	10.000	.	5.00	20.00	1.11
K _{el} (hr ⁻¹)	0.087	26.40	0.04	0.15	0.086	29.78	0.04	0.15	1.01
T _{1/2} (hr)	8.476	26.00	4.50	15.63	8.801	32.85	4.53	16.95	0.96
Analyte: Morphine-6-glucuronide									
AUC _{0-t} (hr *pg/ml)	1655028	22.15	757265.2	2559115	1661642	21.70	782167.1	2739135	1.00
AUC _∞ (hr *pg/ml)	1671632	22.73	765108.1	2681072	1683251	22.06	787574.6	2818734	0.99
C _{max} (pg/ml)	83406.36	26.17	52720.00	146700.0	77548.86	24.09	49640.00	126200.0	1.08
T _{max} * (hr)	12.000	.	5.00	20.00	11.000	.	5.00	20.00	1.09
K _{el} (hr ⁻¹)	0.087	35.23	0.04	0.20	0.085	39.74	0.03	0.22	1.02
T _{1/2} (hr)	8.725	28.89	3.44	15.85	9.234	35.75	3.13	20.08	0.94

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Morphine, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. R09-0072; N =44				
Analyte: Morphine				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (hr *pg/ml)	284622.03	280541.66	101.45	(94.09, 109.40)
AUC _∞ (hr *pg/ml)	295662.42	288060.32	102.64	(95.29, 110.56)
C _{max} (pg/ml)	14727.61	13164.33	111.88	(104.72, 119.52)
Analyte: Morphine-6-glucuronide				
AUC _{0-t} (hr *pg/ml)	1610433.05	1620050.60	99.41	(93.50, 105.69)
AUC _∞ (hr *pg/ml)	1624837.50	1640398.05	99.05	(93.14, 105.34)
C _{max} (pg/ml)	80929.37	75420.33	107.30	(101.05, 113.94)

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Morphine, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. R09-0072; N =44					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	284622.0	280541.7	1.01	94.09	109.40
AUC _∞ (hr *pg/ml)	295662.4	288060.3	1.03	95.21	110.65
C _{max} (pg/ml)	14727.61	13164.33	1.12	104.72	119.52
Analyte: Morphine-6-glucuronide					
AUC _{0-t} (hr *pg/ml)	1610433	1620051	0.99	93.50	105.69
AUC _∞ (hr *pg/ml)	1624837	1640398	0.99	93.14	105.34
C _{max} (pg/ml)	80929.37	75420.33	1.07	101.05	113.94

Table 17. Additional Study Information, Fasting Study No. R09-0072

Root mean square error, AUC _{0-t}	0.2101	
Root mean square error, AUC _∞	0.2069	
Root mean square error, C _{max}	0.1842	
	Test	Reference
Kel and AUC _∞ determined for how many subjects?	43	43
Do you agree or disagree with firm's decision?*	Disagree	Disagree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	No	No

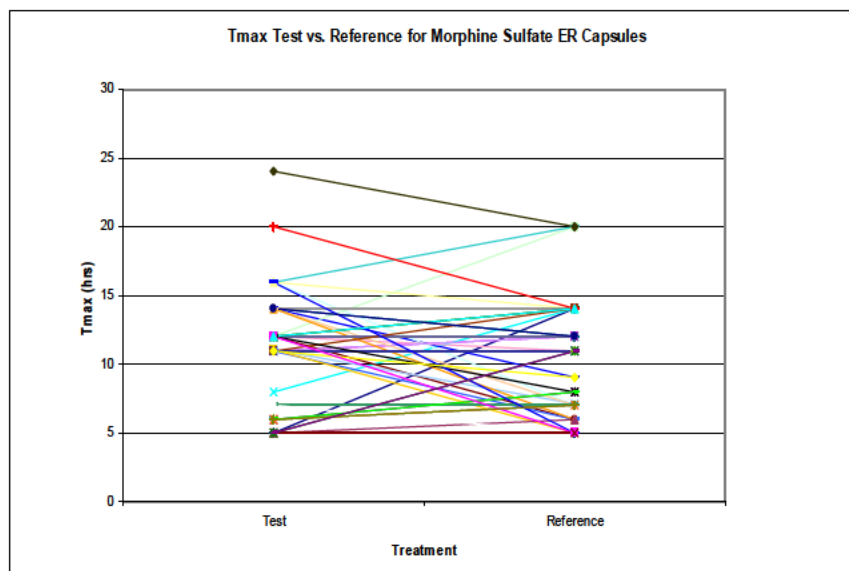
*Please refer to Comments on Pharmacokinetic and Statistical Analysis.

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	43	0.97	0.89	0.99
Reference	43	0.98	0.94	0.99

Comments on Pharmacokinetic and Statistical Analysis:

1. The median t_{max} value (range) for parent compound, morphine for the test and reference products were 11.06 hr (5.0-24.0 hrs), and 10 hr (5.0–20.0 hrs) respectively. The t_{max} range for the test product (5.0-20.0 hrs) is within that of the reference product for all subjects (5.0–20.0 hrs) as shown in the **Figure 1** below, except subject# 31 (24 hrs)

Figure 1: Stick plot for Morphine T_{max} (Fasting Study No: R09-0072)



2. The firm did not calculate the K_{el} and $AUC_{0-\infty}$ for subject# 18 after administration of test and reference products. Reviewer calculated the K_{el} and $AUC_{0-\infty}$ values using the last 3 measureable concentration time points (WinNonlin Software). The k_{el} and AUC values for subject# 18 are listed in the table below:

Parameter	Test	Reference
K_{el}	0.125	0.174
$AUC_{0-\infty}$	248192.41	268547.5
AUC_{0-t}	235141.5	261833.0

As shown in the table below, the calculation of BE statistics for $AUC_{0-\infty}$ including subject# 18 did not have an impact on the results of study

Dependent	RefGeoLSM	TestGeoLSM	Ratio__Ref__	CI_90_Lower	CI_90_Upper
$\ln(AUC_{last})$	280561.04	284647.56	101.46	94.08	109.41
$\ln(AUC_{INF_obs})$	287278.33	294201.46	102.41	95.15	110.22
$\ln(C_{max})$	13164.33	14727.61	111.88	104.72	119.52

3. The reviewer calculated 90% confidence intervals for T/R ratios for $LAUC_{0-t}$, $LAUC_{0-\infty}$ and LC_{max} morphine were within the acceptable limits (80% -125%) and similar to those reported by the firm.

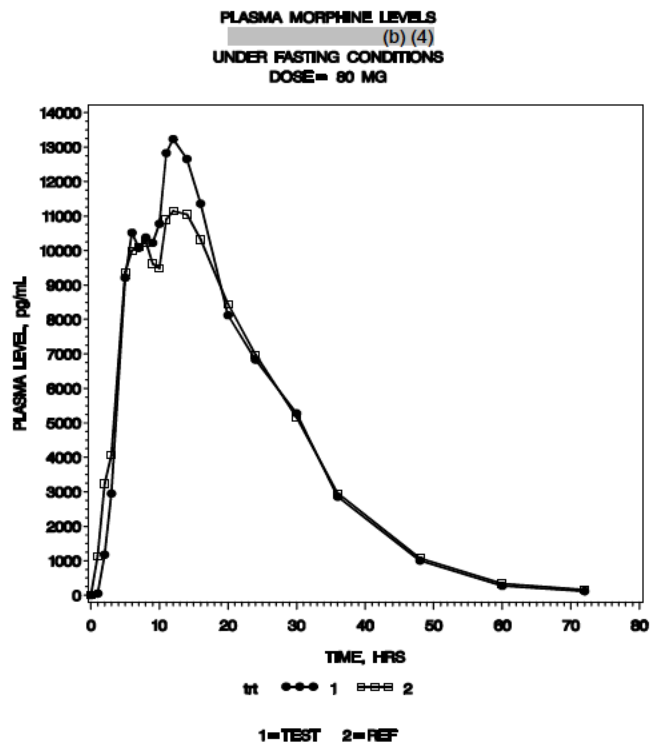
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study is incomplete, pending firm's response to bioanalytical deficiencies.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Analyte: Morphine					
Time (hr)	Test (n=44)		Reference (n=44)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.00	.	.
1.00	48.77	371.33	1137.06	82.71	0.04
2.00	1176.14	54.16	3236.22	42.86	0.36
3.00	2950.45	46.97	4063.77	49.88	0.73
5.00	9211.91	42.51	9379.59	49.03	0.98
6.00	10516.70	45.32	10002.45	45.68	1.05
7.00	10076.95	38.93	10114.98	43.37	1.00
8.00	10375.11	34.83	10244.93	39.14	1.01
9.00	10223.05	36.89	9620.84	39.52	1.06
10.00	10777.50	38.28	9488.25	40.90	1.14
11.00	12829.75	36.76	10905.05	38.97	1.18
12.00	13233.67	38.71	11141.09	34.36	1.19
14.00	12656.20	38.99	11051.27	35.45	1.15
16.00	11358.98	37.35	10320.00	34.22	1.10
20.00	8124.42	35.39	8446.95	39.53	0.96
24.00	6833.73	37.00	6987.64	36.83	0.98
30.00	5276.33	39.35	5157.52	40.02	1.02
36.00	2854.47	44.92	2956.36	44.37	0.97
48.00	1006.61	79.53	1072.62	64.18	0.94
60.00	273.02	148.14	336.57	110.17	0.81
72.00	116.72	233.84	167.76	197.42	0.70

Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	R09-0073
Study Title	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules Under Fed Conditions
Clinical Site (Name & Address)	Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 12 September 2009 Period II: 26 September 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	13 October 2009 – 06 November 2009
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	55 days (12 September 2009 - 06 November 2009)

Table 20. Product Information

Product	Test	Reference	Treatment
Treatment ID	A	B	N/A
Product Name	Morphine Sulfate Sustained-Release Capsules ¹ , USP, 80 mg	KADIAN® Extended-Release Capsules 80 mg	NALTREXONE HYDROCHLORIDE TABLETS, USP 50 mg
Manufacturer	Watson Laboratories—Florida	Actavis Elizabeth LLC	Mallinckrodt Inc.
Batch/Lot No.	3576R0013B	510M81	1170N71851
Manufacture Date	06/09/09		
Expiration Date		12/2010	06/2011
Strength	80 mg	80 mg	50 mg
Dosage Form	Capsule	Capsule	Tablet
Bio-Batch Size	(b) (4) Capsules		
Production Batch Size	(b) (4) Capsules		

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Potency (Assay)	101.8% label claim (LC)	103.3%	N/A
Content Uniformity (mean, %CV)	Mean: 103.5% %RSD: 1.7 AV: 6.1		
Dose Administered	80 mg	80 mg	50 mg
Route of Administration	Oral	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	48 enrolled 42 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 4, 6, 8, 10, 11, 13, 14, 17, 18, 22, 24, 26, 28, 29, 30, 33, 36, 37, 38, 41, 44, 47, 48 BA: 2, 3, 5, 7, 9, 12, 15, 16, 19, 20, 21, 23, 25, 27, 31, 32, 34, 35, 39, 40, 42, 43, 45, 46 To remove the risk of any opioid-related adverse events, subjects were administered naltrexone (1 × 50 mg tablet) with 240 mL of water at approximately 12 hours prior to morphine administration, concurrent with morphine administration, and 12 hours after morphine administration
Blood Sampling Times	Pre-dose and 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 30, 36, 48, 60 and 72 hours post-dose
Blood Volume Collected/Sample*	1 x 6 mL of blood in K ₂ EDTA vacutainers
Blood Sample Processing/Storage	-20 °C (range -10 °C to -30 °C)
IRB Approval	26 August 2009
Informed Consent	Yes
Length of Fasting Before Meal	10 hrs
Length of Confinement	14 hrs prior to dosing until 36 hrs after dosing
Safety Monitoring	Blood pressure, heart rate, and respiratory rate were to be measured at screening, prior to dosing and at approximately 1, 2, 4, 6, 8, 12, 24 and 36 hours (± 60 minutes) after each dose and at study exit. Blood pressure, heart rate, and respiratory rate measurements prior to dose administration (0 hour) were to be collected within 90 minutes prior to the scheduled dose administration.

*As provided in fed study protocol# R09-0073

Standard FDA Meal Used?	Yes
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Comments on Study Design: The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. R09-0073			
		Treatment Groups	
		Test Product N = 42	Reference Product N = 42
Age (years)	Mean $\pm$ SD	26.3 $\pm$ 6.5	26.3 $\pm$ 6.5
	Range	19 - 45	19 - 45
Age Groups	< 18	-	-
	18 - 40	39 (92.9%)	39 (92.9%)
	40 - 64	3 (7.1%)	3 (7.1%)
	65 - 75	-	-
	> 75	-	-
Sex	Male	30 (71.4%)	30 (71.4%)
	Female	12 (28.6%)	12 (28.6%)
Race	American Indian or Alaskan Native (N)	-	-
	Asian (A)	1 (2.4%)	1 (2.4%)
	Black or African American	1 (2.4%)	1 (2.4%)
	Native Hawaiian or Other Pacific Islander	-	-
	White (W)	39 (92.9%)	39 (92.9%)
	WN	1 (2.4%)	1 (2.4%)
	WA	-	-
BMI	Mean $\pm$ SD	25.6 $\pm$ 3.2	25.6 $\pm$ 3.2
	Range	19.1 - 32.0	19.1 - 32.0
Other Factors			

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
06	Withdrew consent prior to Period II check-in due to family emergency	II	No
14	Dropped by the investigator prior to Period II dosing due to inability to finish breakfast	II	No
24	Dropped by the investigator prior to Period I study hour 2.00 activities due to an adverse event (vomiting)	I	No
33	Dropped by the investigator prior to Period II dosing due to inability to finish breakfast	II	No
35	Dropped by the investigator prior to Period I study hour 2.00 activities due to an adverse event (vomiting)	I	No
37	Dropped by the investigator prior to Period I study hour 2.00 activities due to an adverse event (vomiting)	I	No

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event ¹	Reported Incidence by Treatment Groups	
	Study No. R09-0073	
	Test N=47 ²	Reference N=43 ²
	n (%) ³	n (%) ³
Gastrointestinal disorders		
Nausea	3 (6.38%)	2 (4.65%)
Vomiting	2 (4.26%)	1 (2.33%)
General disorders and administration site conditions		
Loss of control of legs	1 (2.13%)	-
Injury, poisoning and procedural complications		
Confusion	1 (2.13%)	-
Musculoskeletal and connective tissue disorders		
Pain in extremity	1 (2.13%)	-
Nervous system disorders		
Dizziness	2 (4.26%)	1 (2.33%)
Tremor	1 (2.13%)	-
Skin and subcutaneous tissue disorders		
Hyperhidrosis	1 (2.13%)	-
Total	8*(17.02%)	2* (4.65%)

¹ MedDRA Version 12; ² N = Number of subjects dosed for each treatment

³ n = Number of subjects reporting at least one incidence of respective adverse event;

(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

*Number of subjects. *In clinical studies in patients with chronic cancer pain after administration of KADIAN, the most common adverse events reported were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%) and anxiety (6%)⁴.*

Table 25. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood Sample Collection Deviations During Study Period I	14, 22 (x2), 28(x2), 38, 44	5 (x8), 19, 21, 23
Blood Sample Collection Deviations During Study Period II	5 (x3), 7, 42, 45(x2)	22, 48
Period I study hour 48, no query or blood sample collected for return blood draw	22	42
Period I study hour 60, no query or blood sample collected for return blood draw	13	N/A
Period I study hour 72, no query or blood sample collected for return blood draw	08	19, 42
Period II study hour 48, no query or blood sample collected for return blood draw	34	08, 22
Period II study hour 72, no query, blood sample, or vital signs collected for return blood draw	34	N/A
Period II, subjects did not finish breakfast prior to dosing	14, 33	N/A
Early termination query not collected	06, 24, 37	33, 35
Early termination vital signs not collected	37	N/A

Comments on Adverse Events/Protocol Deviations:

A total of 48 subjects were enrolled in the study with 22 subjects completing both study periods. Subjects# 24, 35 and 37 were dropped by the investigator prior to study period I study hour 2 due to their adverse event, vomiting. Subject# 14 and 33 were dropped due to their inability to finish breakfast. Subject# 6 withdrew the consent.

During the course of study protocol deviations occurred in the following areas:

- Missing adverse event query.
- Missing blood sample collection at 48 hr and thereafter.
- Deviation in blood sampling time collections occurred by 1-9 mins. These deviations did not have an impact on the results of study as pharmacokinetic parameters were calculated by using the actual sample collection times by the firm.

These protocol deviations are unlikely to have an impact on the results of study.

There were 17 adverse events involving 10 subjects in the study. Out of 17 adverse events, 13 (8 related, 5 unrelated) were reported for the test and 4 (4 related, 0 unrelated) were reported for the reference. The adverse events were considered mild (9 for test and 3 for reference) to moderate (4 for test and 1 for reference) in severity. Overall, the most common adverse events were nausea, vomiting and dizziness.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Analyte: Morphine									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250	500	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	8.9	6.1	5.4	5.9	5.0	3.8	4.4	4.8	4.3
Interday Accuracy (%Actual)	-1.7	-0.9	0.7	0.8	0.4	0.4	1.9	-5.1	3.3
Linearity	0.9928 – 0.9993								
Linearity Range (pg/mL)	250.0 – 200,000								
Sensitivity/LOQ (pg/mL)	250.0								
Parameter	Quality Control Samples								
Concentration (pg/mL)	750.0				4000				160,000
Interday Precision (%CV)	8.4				6.5				5.9
Interday Accuracy (%Actual)	-1.7				1.1				2.2

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Analyte: Morphine-6G									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250	500	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	9.6	6.9	6.4	6.0	5.6	4.7	4.4	5.5	4.7
Interday Accuracy (%Actual)	-3.8	0.1	0.1	1.4	1.7	-0.8	2.2	-4.5	2.8
Linearity	0.9901 – 0.9992								
Linearity Range (pg/mL)	250.0 – 200,000								
Sensitivity/LOQ (pg/mL)	250.0								
Parameter	Quality Control Samples								
Concentration (pg/mL)	750.0		4000		40,000		160,000		
Interday Precision (%CV)	12.9		8.2		6.4		7.6		
Interday Accuracy (%Actual)	0.9		1.7		1.1		1.9		

Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms?	Yes
Were 20% of chromatograms included?	Yes (subject# 16, 17, 18, 19, 20, 21, 22, 23 and 24)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4) _SOP_04_LBP_006	18 March 2009	Sample Reanalysis and Reporting Criteria
(b) (4) _SOP_04_LBP_002	3 February 2009	Sample Analysis (Chromatographic)

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	See comments below
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	Pending firm's response to ALLQ and RTS criteria for repeat analysis.

The Standard Operating Procedure (b) (4) _SOP_04_LBP_006 does not define adjusted lower limit of quantitation (ALLQ) and retention time shift (RTS) and fails to provide the criteria for selecting samples with ALLQ and RTS.

Summary/Conclusions, Study Assays:

The firm submitted the SOPs for analytical run acceptance and repeat analysis. The long term stability data of 145 days cover the entire duration of study sample.

The results of bioanalytical study are incomplete pending firm's response to bioanalytical deficiencies.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 33](#) and [Figure 4](#)

Fasting Bioequivalence Study, Study No. R09-0073; N=42 Analyte: Morphine									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *pg/ml)	343282.7	35.62	176745.9	765355.0	356023.1*	37.18	177868.4	846330.6	0.96
AUC _∞ (hr *pg/ml)	353414.1	35.39	180486.2	769364.4	365168.7*	36.80	180824.3	852969.8	0.97
C _{max} (pg/ml)	14388.57	53.61	7077.00	56950.00	16121.93	38.15	7148.00	37290.00	0.89
T _{max} * (hr)	16.000	.	8.00	30.00	13.000	.	6.00	24.00	1.23
K _{el} (hr ⁻¹)	0.077	31.09	0.04	0.18	0.082	32.81	0.04	0.15	0.94
T _{1/2} (hr)	9.702	27.18	3.87	16.03	9.353	31.46	4.78	15.49	1.04

**Please refer to Comments on Pharmacokinetic and Statistical Analysis*

Fasting Bioequivalence Study, Study No. R09-0073; N=42 Analyte: Morphine-6- glucuronide									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *pg/ml)	1685935	18.64	1161530	2488584	1662526	17.32	1183280	2273505	1.01
AUC _∞ (hr *pg/ml)	1716976	18.89	1238815	2556560	1691051	17.76	1199628	2353719	1.02
C _{max} (pg/ml)	70570.48	20.01	44050.00	115400.0	79685.80	28.52	41750.00	141600.0	0.89
T _{max} * (hr)	16.000	.	8.00	24.00	14.000	.	8.00	24.00	1.14
K _{el} (hr ⁻¹)	0.076	28.71	0.04	0.13	0.074	23.64	0.05	0.12	1.03
T _{1/2} (hr)	9.900	28.98	5.32	17.07	9.925	22.61	5.95	13.79	1.00

*T_{max} values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Morphine, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. R09-0073; N =42				
Analyte: Morphine				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (hr *pg/ml)	330011.15	342341.68	96.40	(93.57, 99.31)
AUC _∞ (hr *pg/ml)	341069.67	352369.51	96.79	(94.32, 99.33)
C _{max} (pg/ml)	13451.47	15253.25	88.19	(82.34, 94.45)
Analyte: Morphine-6-glucuronide				
AUC _{0-t} (hr *pg/ml)	1664487.31	1644690.00	101.20	(99.20, 103.25)
AUC _∞ (hr *pg/ml)	1695349.08	1672188.10	101.39	(99.34, 103.47)
C _{max} (pg/ml)	69350.80	76601.67	90.53	(84.70, 96.77)

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Morphine, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. R09-0073; N =42					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	330011.2	342341.7	0.96	93.51	99.37
AUC _∞ (hr *pg/ml)	341069.7	352369.5	0.97	94.30	99.35
C _{max} (pg/ml)	13451.47	15253.25	0.88	82.38	94.41
Analyte: Morphine-6-glucuronide					
AUC _{0-t} (hr *pg/ml)	1664487	1644690	1.01	99.20	103.25
AUC _∞ (hr *pg/ml)	1695349	1672188	1.01	99.34	103.47
C _{max} (pg/ml)	69350.80	76601.67	0.91	84.70	96.77

Table 32. Additional Study Information

Root mean square error, AUC _{0-t}	0.0799	
Root mean square error, AUC _∞	0.0696	
Root mean square error, C _{max}	0.1846	
	Test	Reference
Kel and AUC _∞ determined for how many subjects?	41	41
Do you agree or disagree with firm's decision?*	Disagree	Disagree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	No	No

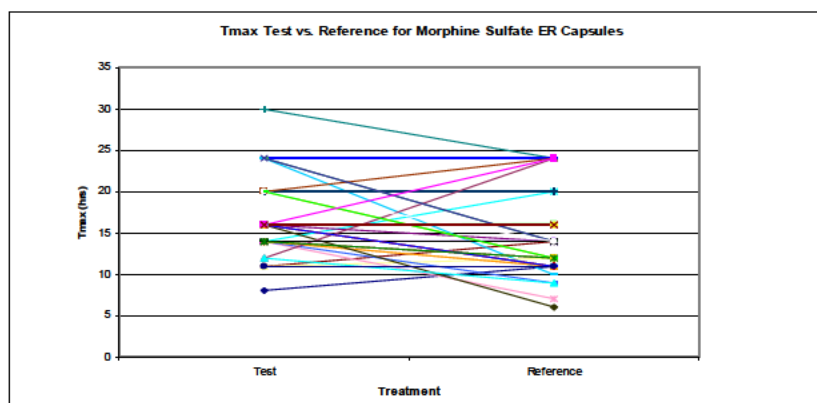
*Please refer to Comments on Pharmacokinetic and Statistical Analysis.

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	41	0.97	0.81	0.99
Reference	41	0.97	0.92	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The median $t_{\max}$ value (range) for parent compound, morphine after administration of the test and reference products were 16.0 hr (8.0-30.0 hrs), and 13.0 hr (6.0–24.0 hrs) respectively. The $t_{\max}$ range for the test product (8.0-24.0 hrs) is within that of the reference product for all subjects (6.0–24.0 hrs) as shown in **Figure 3** below, except subject# 8 (30 hrs).

Figure 3: Stick plot for Morphine $T_{\max}$ (Fed Study No: R09-0073)



- Mean AUC_{0-t} and AUC_{0-∞} values for the reference product (**Table 29** above) are slightly higher than those reported by the firm in **Table 1**, page# 15 of this

review. Firm reported values for AUC_{0-t} and $AUC_{0-\infty}$ are 354546.73 and 363965.28 pg.hr/mL. This discrepancy is due to 1) lack of submission of the AUC values for subject#8 for the reference product in the SAS data, however, during calculation of mean AUC values (Appendix 16.1.9, documentation of statistical methods of study report# R09-0073) firm utilized the AUC values for subject#8. The reviewer calculated AUC parameters for subject#8 are comparable to as reported by firm.

3. The firm did not calculate the K_{el} and AUC values for subject# 8 after administration of test and reference product. Reviewer calculated the K_{el} and $AUC_{0-\infty}$ using the last 3 and 5 measureable concentration time points for test and reference products respectively (WinNonlin Software). The k_{el} and AUC values for subject# 8 are shown in the table below:

Parameter	Test	Reference
$K_{el} (hr^{-1})$	0.06838	0.04803
$AUC_{0-t} (hr * pg/ml)$	332314.45	294058.8
$AUC_{0-\infty} (hr * pg/ml)$	349188.54	314671.12

As shown in the table below, the calculation of BE statistics for $AUC_{0-\infty}$ including subject# 8 did not have an impact on the results of study

Dependent	RefGLSM	TestGLSM	Ratio_ Ref_	CI_90_ Lower	CI_90_ Upper
$\ln(AUC_{INF_obs})$	351253.39	340112.59	96.83	94.31	99.42
$\ln(AUC_{last})$	342035.34	330080.06	96.50	93.66	99.43
$\ln(C_{max})$	15253.25	13451.47	88.19	82.38	94.41

4. Subject# 22 had a measureable metabolite concentration (329.7 pg/mL) at 0 hr following the administration of reference product. According to FDA's Guidance for Industry - Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations (March 2003), if the pre-dose concentration is ≤ 5 percent of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. The reviewer agrees with the action taken by the investigator not to exclude subject# 22 from statistical analysis.
5. The reviewer calculated 90% confidence intervals for T/R ratios for $LAUC_{0-t}$, $LAUC_{0-\infty}$ and LC_{max} morphine were within the acceptable limits (80% -125%) and similar to those reported by the firm.

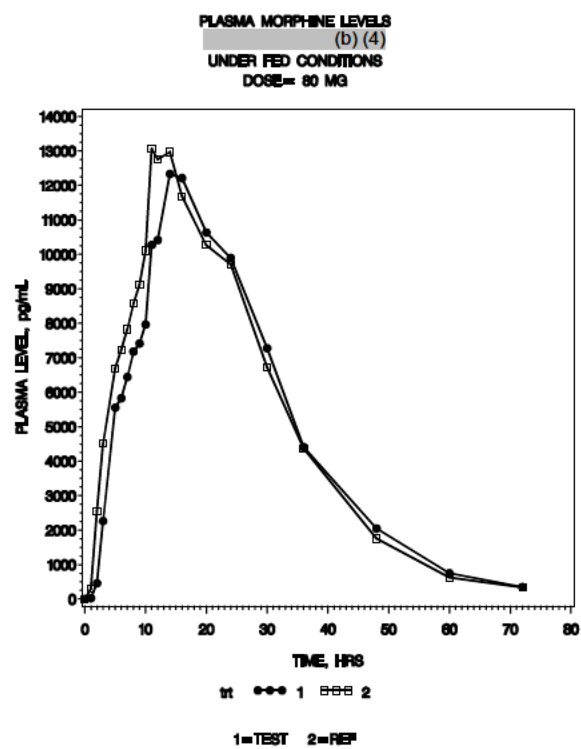
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is incomplete, pending firm's response to bioanalytical deficiencies.

Table 33. Mean Plasma Concentrations, Single-Dose Fasting Sprinkle Bioequivalence Study

Analyte: Morphine					
Time (hr)	Test (n=42)		Reference (n=42)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.00	.	.
1.00	24.22	489.84	297.14	153.42	0.08
2.00	456.67	82.67	2555.72	52.49	0.18
3.00	2261.78	52.21	4511.64	36.44	0.50
5.00	5554.33	31.30	6698.95	33.05	0.83
6.00	5826.86	31.31	7228.57	41.14	0.81
7.00	6439.50	43.09	7833.83	47.20	0.82
8.00	7178.79	39.87	8579.38	49.01	0.84
9.00	7414.67	39.56	9117.43	48.79	0.81
10.00	7963.67	35.83	10099.62	49.32	0.79
11.00	10270.29	34.50	13064.83	44.16	0.79
12.00	10417.26	40.67	12757.45	39.75	0.82
14.00	12332.60	65.10	12969.93	46.85	0.95
16.00	12212.95	50.37	11682.05	43.62	1.05
20.00	10634.64	43.56	10267.12	49.26	1.04
24.00	9894.33	40.94	9713.24	56.91	1.02
30.00	7276.10	37.75	6720.24	44.66	1.08
36.00	4409.60	44.31	4365.57	45.18	1.01
48.00	2046.67	55.65	1759.35	66.22	1.16
60.00	748.94	96.54	625.81	90.65	1.20
72.00	345.60	107.91	335.30	129.64	1.03

Figure 4. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.1.3 Single-dose Fasting Sprinkle Bioequivalence Study

4.1.3.1 Study Design

Table 34. Study Information

Study Number	R09-0074
Study Title	A Relative Bioavailability Study of 80 mg Morphine Sulfate Extended-Release Capsules Versus 80 mg KADIAN® Capsules, Sprinkled on Applesauce, Under Fasting Conditions
Clinical Site (Name & Address)	Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 29 August 2009 Period II: 12 September 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	29 September 2009 – 23 October 2009
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	55 days (29 August 2009 - 23 October 2009)

Table 35. Product Information

Product	Test	Reference	Treatment
Treatment ID	A	B	N/A
Product Name	Morphine Sulfate Sustained-Release Capsules ¹ , USP, 80 mg	KADIAN® Extended-Release Capsules 80 mg	NALTREXONE HYDROCHLORIDE TABLETS, USP 50 mg
Manufacturer	Watson Laboratories—Florida	Actavis Elizabeth LLC	Mallinckrodt Inc.
Batch/Lot No.	3576R0013B	510M81	1170N69101
Manufacture Date	06/09/09		
Expiration Date		12/2010	12/2010
Strength	80 mg	80 mg	50 mg
Dosage Form	Capsule	Capsule	Tablet
Bio-Batch Size	(b) (4) Capsules		
Production Batch Size	(b) (4) Capsules		
Potency (Assay)	101.8% label claim (LC)	103.3%	N/A

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Content Uniformity (mean, %CV)	Mean: 103.5% %RSD: 1.7 AV: 6.1		
Dose Administered	80 mg	80 mg	50 mg
Route of Administration	Oral	Oral	Oral

Table 36. Study Design, Single-Dose Fasting Sprinkle Bioequivalence Study

No. of Subjects	48 enrolled; 40 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 2, 5, 8, 9, 10, 13, 14, 17, 19, 23, 24, 26, 27, 30, 31, 34, 35, 37, 40, 43, 44, 45, 46 BA: 3, 4, 6, 7, 11, 12, 15, 16, 18, 20, 21, 22, 25, 28, 29, 32, 33, 36, 38, 39, 41, 42, 47, 48 To remove the risk of any opioid-related adverse events, subjects were administered naltrexone (1 × 50 mg tablet) with 240 mL of water at approximately 12 hours prior to morphine administration, concurrent with morphine administration, and 12 hours after morphine administration.
Blood Sampling Times	Pre-dose and 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 30, 36, 48, 60 and 72 hours post-dose
Blood Volume Collected/Sample	1 x 6 mL of blood collected in K ₂ EDTA vacutainers
Blood Sample Processing/Storage	-20 °C (range -10 °C to -30 °C)
IRB Approval	21 August 2009
Informed Consent	Yes
Length of Fasting Before Meal	10 hrs
Length of Confinement	14 hrs prior to dosing until 36 hrs after dosing
Safety Monitoring	Blood pressure, heart rate, and respiratory rate were to be measured at screening, prior to dosing and at approximately 1, 2, 4, 6, 8, 12, 24 and 36 hours (± 60 minutes) after each dose and at study exit. Blood pressure, heart rate, and respiratory rate measurements prior to dose administration (0 hour) were to be collected within 90 minutes prior to the scheduled dose administration.

*As provided in fasting sprinkle study protocol# R09-0074

Comments on Study Design:

The study design is acceptable.

4.1.3.2 Clinical Results

Table 37. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Sprinkle Bioequivalence Study No. R09-0074			
		Treatment Groups	
		Test Product N = 40	Reference Product N = 40
Age (years)	Mean ± SD	28.6 ± 7.4	28.6 ± 7.4
	Range	20 - 44	20 - 44
Age Groups	< 18	-	-
	18 - 40	35 (87.5%)	35 (87.5%)
	40 - 64	5 (12.5%)	5 (12.5%)
	65 - 75	-	-
	> 75	-	-
Sex	Male	25 (62.5%)	25 (62.5%)
	Female	15 (37.5%)	15 (37.5%)
Race	American Indian or Alaskan Native (N)	2 (5.0%)	2 (5.0%)
	Asian (A)	1 (2.5%)	1 (2.5%)
	Black or African American (B)	2 (5.0%)	2 (5.0%)
	Native Hawaiian or Other Pacific Islander (I)	-	-
	White (W)	34 (85.0%)	34 (85.0%)
	WN	1 (2.5%)	1 (2.5%)
	WA		
BMI	Mean ± SD	26.1 ± 2.9	26.1 ± 2.9
	Range	21.2-31.8	21.2-31.8
Other Factors			

Table 38. Dropout Information, Fasting Sprinkle Bioequivalence Study

Subject No.	Reason	Period	Replaced?
05	Dropped by the investigator prior to Period II dosing due to an adverse event (vomiting)	II	No
09	Withdrew consent prior to Period I study hour 60.00 due to adverse events (racing heart, dizziness, and nausea)	I	No
20	Dropped by the investigator prior to Period II study hour 3.0 activities due to an adverse event (vomiting)	II	No
27	Dropped by the investigator prior to Period I study hour 4.00 activities due to an adverse event (vomiting)	I	No
31	Withdrew consent prior to Period II dosing due to an adverse event (nausea).	II	No
33	Withdrew consent after completion of Period I study hour 72.00 activities due to schedule conflict	II	No
37	Dropped by the investigator prior to Period I study hour 2.00 activity due to an adverse event (vomiting)	I	No
46	Dropped by the investigator prior to Period II study hour 1.25 activity due to an adverse event (vomiting)	II	No

Table 39. Study Adverse Events, Fasting Sprinkle Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No: R09-0074	
	Test N=47 ²	Reference N=43 ²
	n (%) ³	n (%) ³
Cardiac disorders		
Palpitations	1 (2.13%)	-
Eye disorders		
Blepharospasm	1 (2.13%)	-
Eye pruritus	-	1 (2.33%)
Lacrimation increased	1 (2.13%)	-
Gastrointestinal disorders		
Abdominal discomfort	3 (6.38%)	1 (2.33%)
Abdominal pain	-	1 (2.33%)
Abdominal pain upper	1 (2.13%)	-
Nausea	9 (19.15%)	7 (16.28%)
Vomiting	5 (10.64%)	1 (2.33%)
General disorders and administration site conditions		
Fatigue	-	1 (2.33%)
Irritability	1 (2.13%)	-
Oedema peripheral	-	1 (2.33%)
Pain	-	1 (2.33%)
Musculoskeletal and connective tissue disorders		
Muscle twitching	1 (2.13%)	-
Muscular weakness	2 (4.26%)	-
Nervous system disorders		
Dizziness	3 (6.38%)	1 (2.33%)
Dysgeusia	1 (2.13%)	-
Headache	5 (10.64%)	3 (6.98%)
Sinus headache	1 (2.13%)	-
Tremor	2 (4.26%)	-
Psychiatric disorders		
Anxiety	1 (2.13%)	-
Skin and subcutaneous tissue disorders		
Hyperhidrosis	1 (2.13%)	-
Urticarias	-	1 (2.33%)
Total	16 (34.04%)	13 (30.23%)

Table 40. Protocol Deviations, Fasting Sprinkle Bioequivalence Study

Type	Subject# (Test)	Subject # (Reference)
Concomitant medications	20	N/A
Blood Sample Collection Deviations During Study Period I	17, 30, 46, 24	3 (x2), 12, 18, 33 (x2)
Blood Sample Collection Deviations During Study Period II	15, 3	26
Period I study hour 48, no query or blood sample collected for return blood draw	09, 45	48
Period I study hour 72, no query or blood sample collected for return blood draw	N/A	48
Period II study hour 48, no query or blood sample collected for return blood draw	25	17, 45
Period II study hour 60, no query or blood sample collected for return blood draw	48	N/A
Period II study hour 72, no query or blood sample collected for return blood draw	N/A	45
Early termination procedures were completed more than 14 days from last blood draw	09	N/A

Comments on Adverse Events/Protocol Deviations:

A total of 48 subjects were enrolled in the study with 40 subjects completing both study periods. Subjects# 5, 20, 27, 37 and 46 were dropped by the investigator due to their adverse event (vomiting); subject# 31 was dropped due nausea. Subjects# 9 and 33 withdrew the consent due to adverse events (racing heart, dizziness and nausea), and schedule conflict, respectively.

During the course of study protocol deviations occurred in the following areas:

- Concomitant medications: subject# 20 was given 2 x 325 mg tablets of acetaminophen on 9/12/09 to treat his adverse event. The subject# 20 was dropped from the study and was not used in statistical calculations; therefore, this deviation is not going to have any impact on the study results.
- Missing blood sample collection at 48 hr and thereafter.
- Deviation in blood sampling collection times occurred by 1-8 mins. These deviations did not have an impact on the results of study as pharmacokinetic parameters were calculated by using the actual sample collection times by the firm.
- Missing adverse event query.
- Exit termination procedure completed more than 14 days from the last blood draw. As per protocol, exit/early termination procedures were to be completed within 14 days after the last blood sample collection.

These protocol deviations are unlikely to have an impact on the results of study.

There were 64 adverse events involving 23 subjects in the study. Out of 64 adverse events, 43 (31 related, 12 unrelated) were reported for the test and 21 (17 related, 4 unrelated) were reported for the reference. The adverse events were considered mild (33 for test and 18 for reference) to moderate (10 for test and 3 for reference) in severity. Overall, the most common adverse events were abdominal discomfort, dizziness, headache, muscular weakness, nausea, tremor, and vomiting.

As shown in Table 39 above, the incidence of vomiting is considerably higher after administration of test product (10.64%; 5 subjects) as compared to reference product (2.33%; 1 subject). The vomiting was considered to be probably related to the treatment by the investigator. In the opinion of clinical investigators study was completed without any significant sequelae attributable to the investigational drug.

The higher incidence of vomiting observed after administration test product might not be formulation issue because in fed study (100 mg dose), the incidence of vomiting is higher after administration of reference product (8.89%, 4 subjects) than test product (2.5%; 1 subject)(please refer to Table 54). In addition, as shown in Figure 6, mean plasma concentration profile for test product is comparable to that of the reference product.

4.1.3.3 Bioanalytical Results

Table 41. Assay Validation – Within the Fed Bioequivalence Study

Analyte: Morphine									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250	500	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	9.7	6.9	6.9	7.3	5.4	5.0	5.4	5.4	5.6
Interday Accuracy (%Actual)	0.6	1.4	0.3	-2.4	-0.2	0.3	0.5	-0.9	0.5
Linearity	0.9931 – 0.9997								
Linearity Range (pg/mL)	250.0 – 200000								
Sensitivity/LOQ (pg/mL)	250.0								
Parameter	Quality Control Samples								
Concentration (pg/mL)	750		4000		40,000		160,000		
Interday Precision (%CV)	8.5		5.5		5.1		5.5		
Interday Accuracy (%Actual)	0.5		0.2		-0.3		0.9		

Analyte: Morphine-6G									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250	500	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	10.3	8.4	6.9	7.1	4.8	4.3	4.4	5.7	4.8
Interday Accuracy (%Actual)	-0.7	0.3	1.1	-1.9	0.7	0.6	0.2	-1.3	0.9

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Linearity	0.9936 – 0.9996			
Linearity Range (pg/mL)	250.0 – 200000			
Sensitivity/LOQ (pg/mL)	250.0			
Parameter	Quality Control Samples			
Concentration (pg/mL)	750	4000	40,000	160,000
Interday Precision (%CV)	12.4	8.0	6.3	6.1
Interday Accuracy (%Actual)	0.8	1.1	0.4	-0.1

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	Yes
Were 20% of chromatograms included?	Yes (subjects# 40, 41, 42, 43, 44, 45, 47, 48)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 42. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4) SOP_04_LBP_006	18 March 2009	Sample Reanalysis and Reporting Criteria
SOP_04_LBP_002	3 February 2009	Sample Analysis (Chromatographic)

Table 43. Additional Comments on Repeat Assays

Were all SOPs followed?	See comments below
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	Pending firm's response to ALLQ criteria for repeat analysis.

The Standard Operating Procedure (b) (4) SOP_04_LBP_006 does not define adjusted lower limit of quantitation (ALLQ) and fails to provide the criteria for selecting samples with ALLQ.

Summary/Conclusions, Study Assays:

The firm submitted the SOPs for analytical run acceptance and repeat analysis. The long term stability data of 145 days cover the entire duration of study sample.

The results of bioanalytical study are incomplete pending firm's response to bioanalytical deficiencies.

4.1.3.4 Pharmacokinetic Results

Table 44. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 48](#) and [Figure 6](#)

Fasting Sprinkle Bioequivalence Study, Study No. R09-0074; N=40 Analyte: Morphine									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *pg/ml)	307054.1	29.93	166722.6	677556.6	319627.0	33.19	172029.3	801809.7	0.96
AUC _∞ (hr *pg/ml)	315183.5	28.69	180672.7	682650.3	327452.8	33.10	182863.4	819396.8	0.96
C _{max} (pg/ml)	14325.28	31.48	7402.00	25380.00	13822.50	35.47	7903.00	30810.00	1.04
T _{max} * (hr)	14.000	.	5.00	24.00	13.025	.	5.00	36.00	1.07
K _{el} (hr ⁻¹)	0.071	26.85	0.05	0.14	0.076	28.41	0.05	0.15	0.94
T _{1/2} (hr)	10.373	22.35	4.92	15.23	9.796	24.03	4.68	14.94	1.06
Analyte: Morphine-6-glucuronide									
AUC _{0-t} (hr *pg/ml)	1607020	18.45	947533.9	2374244	1701752	15.54	1253413	2258127	0.94
AUC _∞ (hr *pg/ml)	1635852	18.70	949727.0	2414900	1724024	16.01	1266528	2347685	0.95
C _{max} (pg/ml)	76066.50	22.11	51930.00	133900.0	74455.00	24.92	50910.00	131900.0	1.02
T _{max} * (hr)	12.000	.	5.00	24.00	12.000	.	5.00	36.00	1.00
K _{el} (hr ⁻¹)	0.073	39.03	0.03	0.19	0.068	22.83	0.04	0.11	1.06
T _{1/2} (hr)	10.724	36.47	3.59	26.59	10.675	24.07	6.43	18.99	1.00

* T_{max} values are presented as median, range

Table 45. Geometric Means and 90% Confidence Intervals - Firm Calculated

Morphine, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. R09-0074; N =40				
Analyte: Morphine				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (hr *pg/ml)	295013.73	305678.91	96.51	(92.72, 100.46)
AUC _∞ (hr *pg/ml)	304091.00	313310.16	97.06	(93.11, 101.17)
C _{max} (pg/ml)	13605.21	13060.75	104.17	(98.04, 110.68)
Analyte: Morphine-6-glucuronide				
AUC _{0-t} (hr *pg/ml)	1580408.64	1684019.42	93.85	(89.96, 97.90)
AUC _∞ (hr *pg/ml)	1608222.68	1710902.92	94.00	(90.02, 98.15)
C _{max} (pg/ml)	74411.59	72648.37	102.43	(97.63, 107.47)

Table 46. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Morphine, Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. R09-0072; N =40					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	295013.7	305678.9	0.97	92.72	100.46
AUC _∞ (hr *pg/ml)	304091.0	313310.2	0.97	93.11	101.17
C _{max} (pg/ml)	13605.21	13060.75	1.04	98.04	110.68
Analyte: Morphine-6-glucuronide					
AUC _{0-t} (hr *pg/ml)	1580409	1684019	0.94	89.96	97.90
AUC _∞ (hr *pg/ml)	1608223	1710903	0.94	89.90	98.28
C _{max} (pg/ml)	74411.59	72648.37	1.02	97.63	107.47

Table 47. Additional Study Information

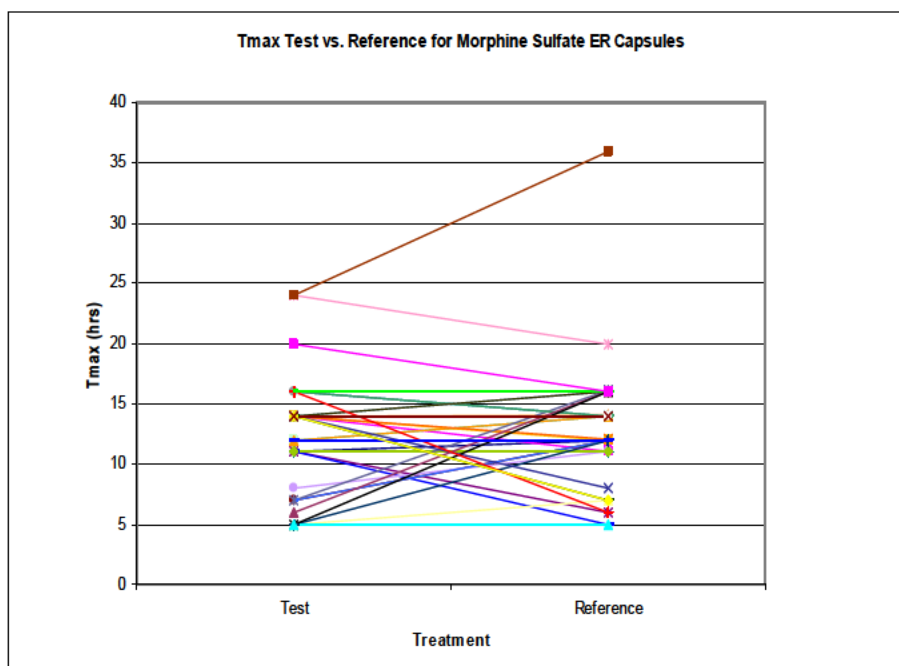
Root mean square error, AUC _{0-t}	0.1059	
Root mean square error, AUC _∞	0.1096	
Root mean square error, C _{max}	0.1600	
	Test	Reference
Kel and AUC _∞ determined for how many subjects?	40	40
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?		

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	40	0.97	0.81	0.99
Reference	40	0.98	0.94	0.99

Comments on Pharmacokinetic and Statistical Analysis:

The median $t_{\max}$ value (range) for parent compound, morphine for the test and reference products were 14.0 hr (5.0-24.0 hrs), and 13.025 hr (5.0–36.0 hrs) respectively. The $t_{\max}$ range for the test product (5.0-24.0 hrs) is within that of the reference product for all subjects (5.0–36.0 hrs) as shown in **Figure 5** below. The observed $t_{\max}$ of 36 hrs in subject# 35 after administration of reference product is apparently an aberrant.

Figure 5: Stick plot for Morphine $T_{\max}$ (Fasting Sprinkle Study No: R09-0074)



The reviewer calculated 90% confidence intervals for T/R ratios for LAUC_{0-t}, LAUC_{0-∞} and LC_{max} morphine were within the acceptable limits (80% -125%) and similar to those reported by the firm.

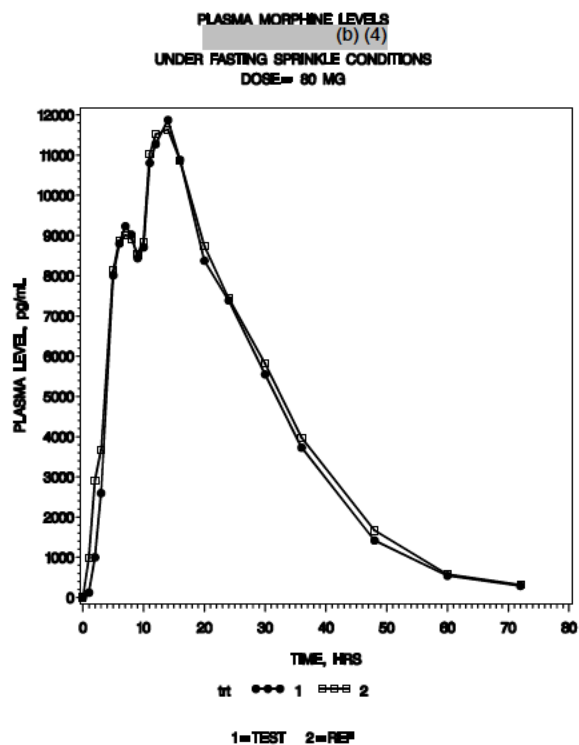
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fasting sprinkle bioequivalence study is incomplete, pending firm's response to bioanalytical deficiencies.

Table 48. Mean Plasma Concentrations, Single-Dose Fasting Sprinkle Bioequivalence Study

Analyte: Morphine					
Time (hr)	Test (n=40)		Reference (n=40)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.00	.	.
1.00	120.93	239.96	979.30	58.80	0.12
2.00	996.80	68.96	2911.96	37.00	0.34
3.00	2592.34	66.44	3670.93	39.82	0.71
5.00	8008.10	47.93	8126.58	41.90	0.99
6.00	8796.43	43.17	8858.58	34.30	0.99
7.00	9229.00	42.22	9012.88	34.29	1.02
8.00	9021.73	35.34	8911.13	34.87	1.01
9.00	8435.70	32.60	8532.43	38.05	0.99
10.00	8705.65	32.46	8854.15	36.51	0.98
11.00	10802.38	33.85	11038.15	35.35	0.98
12.00	11275.88	34.05	11516.93	37.20	0.98
14.00	11871.98	32.71	11639.35	36.34	1.02
16.00	10879.55	33.00	10873.35	33.76	1.00
20.00	8372.38	36.11	8739.28	48.74	0.96
24.00	7384.58	61.21	7440.93	50.82	0.99
30.00	5545.86	48.75	5810.68	45.44	0.95
36.00	3725.74	50.52	3971.30	57.48	0.94
48.00	1417.40	56.04	1667.26	66.58	0.85
60.00	540.32	64.91	575.07	85.27	0.94
72.00	288.69	91.83	312.47	100.56	0.92

Figure 6. Mean Plasma Concentrations, Single-Dose Fasting Sprinkle Bioequivalence Study



4.1.4 Single-dose Fed Bioequivalence Study

4.1.4.1 Study Design

Table 49. Study Information

Study Number	R09-0905
Study Title	A Relative Bioavailability Study of 100 mg Morphine Sulfate Extended-Release Capsules Versus 100 mg KADIAN® Capsules Under Fed Conditions
Clinical Site (Name & Address)	Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I (Subject 01-47): 19 September 2009 Period IA (Subject 48): 19 September 2009 Period II (Subject 01-47): 03 October 2009 Period IIA (Subject 48): 03 October 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates*	27 October 2009 – 13 November 2009
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	56 days (19 September 2009 - 13 November 2009)

*Corrected by reviewer based on bioanalytical study report

Table 50. Product Information

Product	Test	Reference	Treatment
Treatment ID	A	B	N/A
Product Name	Morphine Sulfate Sustained-Release Capsules ¹ , USP, 100 mg	KADIAN® Extended-Release Capsules 100 mg	NALTREXONE HYDROCHLORIDE TABLETS, USP 50 mg
Manufacturer	Watson Laboratories-Florida	Actavis Elizabeth LLC	Mallinckrodt Inc.
Batch/Lot No.	3453R0001B	320E71	1170N71851
Manufacture Date	08/26/09		
Expiration Date		05/2010	06/2011
Strength	100 mg	100 mg	50 mg
Dosage Form	Capsule	Capsule	Tablet
Bio-Batch Size	(b) (4) Capsules		

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Production Batch Size	(b) (4) Capsules		
Potency (Assay)	100.1% label claim (LC)	100.0%	N/A
Content Uniformity (mean, %CV)	Mean: 100.7 % %RSD: 1.6, AV: 3.8		
Dose Administered	1 x 100 mg	1 x 100 mg	1 x 50 mg
Route of Administration	Oral	Oral	Oral

Table 51. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	48 enrolled; 37 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups#	2
Washout Period	14 days
Randomization Scheme	AB: 2, 3, 7, 8, 9, 10, 13, 16, 19, 20, 22, 23, 27, 28, 29, 30, 33, 34, 37, 38, 41, 42, 45, 47 BA: 1, 4, 5, 6, 11, 12, 14, 15, 17, 18, 21, 24, 25, 26, 31, 32, 35, 36, 39, 40, 43, 44, 46, 48 To remove the risk of any opioid-related adverse event, subjects were administered naltrexone (1 x 50 mg tablet) with 240 mL of water at approximately 12 hours prior to morphine administration, concurrent with morphine administration, and 12 hours after morphine administration.
Blood Sampling Times	Pre-dose and 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 30, 36, 48, 60 and 72 hours post-dose
Blood Volume Collected/Sample*	1 x 6 mL of blood was collected in K ₂ EDTA vacutainers
Blood Sample Processing/Storage	-20°C (range -10°C to -30°C)
IRB Approval	August 26, 2009
Informed Consent	Yes
Length of Fasting Before Meal	10 hrs
Length of Confinement	14 hrs prior to dosing until 36 hrs after dosing
Safety Monitoring	Blood pressure, heart rate, and respiratory rate were to be measured at screening, prior to dosing and at approximately 1, 2, 4, 6, 8, 12, 24 and 36 hours (± 60 minutes) after each dose and at study exit. Blood pressure, heart rate, and respiratory rate measurements prior to dose administration (0 hour) were to be collected within 90 minutes prior to the scheduled dose administration.

*As specified in protocol# R90-0905 for fed study. #Please refer to Comments on Pharmacokinetic and Statistical Analysis

Standard FDA Meal Used?	Yes
--------------------------------	-----

Comments on Study Design: The study design is acceptable.

4.1.4.2 Clinical Results

Table 52. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. R09-0905			
		Treatment Groups	
		Test Product N = 37	Reference Product N = 37
Age (years)	Mean $\pm$ SD Range	25.7 $\pm$ 7.9 18 - 45	25.7 $\pm$ 7.9 18 - 45
Age Groups	< 18 18 - 40 40 - 64 65 - 75 > 75	- 33 (89.2%) 4 (10.8%) - -	- 33 (89.2%) 4 (10.8%) - -
Sex	Male Female	23 (62.2%) 14 (37.8%)	23 (62.2%) 14 (37.8%)
Race	American Indian or Alaskan Native (N) Asian (A) Black or African American (B) Native Hawaiian or Other Pacific Islander (I) White (W) WN WA	- - 3 (8.1%) - 33 (89.2%) 1 (2.7%)	- - 3 (8.1%) - 33 (89.2%) 1 (2.7%)
BMI	Mean $\pm$ SD Range	25.3 $\pm$ 3.4 19.8 - 31.7	25.3 $\pm$ 3.4 19.8 - 31.7
Other Factors			

Table 53. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced
01	Subject was dropped prior to Period II dosing due to adverse event (vomiting).	II	No
03	Subject was dropped prior to Period I, study hour 12.00 sample due to adverse event (vomiting).	I	No
05	Subject withdrew consent prior to Period I, study hour 4.00 activities due to adverse event (anxiety).	I	No
11	Subject dropped prior to Period I, study hour 2.00 sample due to adverse event (vomiting).	I	No
18	Subject dropped prior to Period I, study hour 3.00 sample due to adverse event (vomiting).	I	No
19	Subject withdrew consent prior to Period II dosing due to inability to finish breakfast.	II	No
25	Subject dropped prior to Period II check-in due to adverse events (pain, sinus headache)	II	No
33	Subject withdrew consent prior to Period II, study hour -1.50 activities due to adverse event (headache).	II	No
39	Subject dropped at Period II check-in due to positive pregnancy screen.	II	No
40	Subject withdrew consent prior to Period II, study hour -1.50 activities due to family emergency.	II	No
48	Subject dropped prior to Period II dosing due to adverse event (vomiting).	I	No

Table 54. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. R09-0905	
	Test N=40 ²	Reference N=45 ²
	n (%) ³	n (%) ³
Gastrointestinal disorders		
Abdominal discomfort	-	2 (4.44%)
Abdominal pain upper	-	1 (2.22%)
Nausea	1 (2.50%)	7 (15.56%)
Vomiting	1 (2.50%)	4 (8.89%)
General disorders and administration site conditions		
Fatigue	-	1 (2.22%)
Pain	-	1 (2.22%)
Injury, poisoning and procedural complications		
Periorbital haematoma	-	1 (2.22%)
Skin laceration	1 (2.50%)	-
Metabolism and nutrition disorders		
Decreased appetite	-	1 (2.22%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal stiffness	1 (2.50%)	-
Myalgia	-	1 (2.22%)
Pain in extremity	-	1 (2.22%)
Nervous system disorders		
Dizziness	-	2 (4.44%)
Headache	3 (7.50%)	7 (15.56%)
Sinus headache	-	1 (2.22%)
Somnolence	1 (2.50%)	1 (2.22%)
Psychiatric disorders		
Anxiety	-	1 (2.22%)
Respiratory, thoracic and mediastinal disorders		
Cough	-	1 (2.22%)
Oropharyngeal pain	-	1 (2.22%)
Rhinorrhoea	-	1 (2.22%)
Total	6 (15.00%)	20 (44.44%)

¹ MedDRA Version 12; ² N = Number of subjects dosed for each treatment

³ n = Number of subjects reporting at least one incidence of respective adverse event;

(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 55. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Concomitant medications	03, 36, 37, 40	25, 36, 37, 40
Blood sample collection deviations during study Period I	2 (x2), 23	40
Blood sample collection deviations during study Period II	15, 21 (x2),	23, 2 (x3), 16, 28, 29
Period I: Breakfast served 20 minutes prior to dosing	N/A	35
Period I: Breakfast served 21 minutes prior to dosing	N/A	48
Period I: Breakfast served 22 minutes prior to dosing	29	N/A
Period I: Breakfast served 23 minutes prior to dosing	33	N/A
Period I: Breakfast served 24 minutes prior to dosing	37, 45	46
Period I: Breakfast served 25 minutes prior to dosing	38, 42, 47	43, 44
Period I: Breakfast served 26 minutes prior to dosing	30, 34	17, 18, 31, 32, 36, 39, 40
Period I: Breakfast served 27 minutes prior to dosing	19, 20, 22, 27, 28	12, 21, 25, 26
Period I: Breakfast served 28 minutes prior to dosing	09, 10, 13, 16, 23	14, 24
Period I: Breakfast served 29 minutes prior to dosing	02, 03, 41	01, 04, 05, 06, 15
Period I: Breakfast served 31 minutes prior to dosing	N/A	11
Exit procedures completed 34 days after last blood draw	N/A	33
Period II: Subject consumed 50% of breakfast	N/A	19
Period IIA*: Subject consumed 75% of breakfast	48	N/A

Comments on Adverse Events/Protocol Deviations:

A total of 48 subjects were enrolled in the study with 37 subjects completing both study periods. Six subjects were dropped due to their adverse events, vomiting (subjects# 1, 3, 11, 18, and 48), pain, sinus and headache (#25). Four subjects withdrew consent: inability to finish pre-dose meal (# 19), anxiety (# 5), headache (#33), and family emergency (#40). Subject# 39 was dropped by the investigator due to a positive pregnancy screen.

During the course of study protocol deviations occurred in the following areas:

- Deviation in blood sampling time collections occurred by 1-7 mins. These deviations did not have an impact on the results of study as pharmacokinetic parameters were calculated by using the actual sample collection times by the firm.
- Deviation in serving of high-fat and high-calorie breakfast meal by 1-10 minutes prior to study drugs administration.

- Exit procedure completed more than 14 days from the last blood draw. As per protocol, exit/early termination procedures were to be completed within 14 days after the last blood sample collection.
- Subjects# 3, 25 and 40 who took 650 mg acetaminophen, 600 mg ibuprofen + robitussin, and desogen, respectively were not included in the statistical analysis as they were dropped from the study.
- Subjects# 36 and 37 taking birth control pill were included into the study by principal Investigator and judged to have no effect on the study results.

These protocol deviations are unlikely to have an impact on the results of study.

There were 45 adverse events involving 23 subjects in the study. Out of 45 adverse events, 8 (5 related, 3 unrelated) were reported for the test and 37 (16 related, 21 unrelated) were reported for the reference. The adverse events were considered mild (5 for test and 26 for reference) to moderate (3 for test and 11 for reference) in severity. Overall, the most common adverse events were headache and nausea.

4.1.4.3 Bioanalytical Results

Table 56. Assay Validation – Within the Fed Bioequivalence Study

Analyte: Morphine									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250	500	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	9.0	6.4	5.3	5.1	4.7	4.8	4.9	5.6	4.7
Interday Accuracy (%Actual)	-1.3	0.4	-0.3	0.2	0.4	0.5	1.5	-4.3	3.1
Linearity	0.9947 – 0.9995								
Linearity Range (pg/mL)	250.0 – 200,000								
Sensitivity/LOQ (pg/mL)	250.0								
Parameter	Quality Control Samples								
Concentration (pg/mL)	750				4000				160,000
Interday Precision (%CV)	17.3*				5.3				6.9
Interday Accuracy (%Actual)	2.6				0.9				3.3

**Please refer to Comments on Study Assay Validation.*

Analyte: Morphine-6G									
Parameter	Standard Curve Samples								
Concentration (pg/mL)	250	500.0	1000	5000	10,000	50,000	100,000	170,000	200,000
Interday Precision (%CV)	9.6	8.5	6.9	5.4	4.3	4.0	4.0	5.4	4.5
Interday Accuracy (%Actual)	-0.1	0.2	-1.0	0.0	0.6	-0.1	1.8	-4.0	2.6
Linearity	0.9948 – 0.9997								
Linearity Range (pg/mL)	250.0 – 200,000								
Sensitivity/LOQ (pg/mL)	250.0								
Parameter	Quality Control Samples								
Concentration (pg/mL)	750		4000		40,000		160,000		
Interday Precision (%CV)	10.7		5.4		6.5		8.0		
Interday Accuracy (%Actual)	1.8		1.3		0.7		1.9		

Comments on Study Assay Validation:

Of the 320 QC samples analyzed for morphine with the subject samples in acceptable batch runs, 12 QCs (3.8%) failed the acceptance criteria. Firm has stated that, “one LQC for morphine seemed to be an apparent outlier (observed concentration: 1822 pg/mL); therefore a Grubbs’ Outlier test was performed. The result of the test deemed the LQC to be an outlier. Removal of the outlier low QC from the data resulted in % CV of 7.8 and interday accuracy of 0.8%”.

As per the FDA’s Guidance for Industry: Bioanalytical Method Validation (May 2001), at least 67% of the QC samples should be within 15% of their respective nominal values; 33% of the QC samples (not all replicates at the same concentration) can be outside the $\pm 15\%$ of the nominal value. Since, at low LQC, only 7 out of 80 (8.75%) QC failed the acceptance criteria, the study assay validation results are acceptable.

Any interfering peaks in chromatograms?	Yes
Were 20% of chromatograms included?	Yes (subjects#14, 15, 16, 17, 20, 21, 22, 23)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable

Table 57. SOP’s Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4) SOP_04_LBP_006	18 March 2009	Sample Reanalysis and Reporting Criteria
SOP_04_LBP_002	3 February 2009	Sample Analysis (Chromatographic)

Table 58. Additional Comments on Repeat Assays

Were all SOPs followed?	See comments below
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	Pending firm's response to ALLQ criteria for repeat analysis.

The Standard Operating Procedure (b) (4) SOP_04_LBP_006 does not define adjusted lower limit of quantitation (ALLQ) and fails to provide the criteria for selecting samples with ALLQ.

Summary/Conclusions, Study Assays:

The firm submitted the SOPs for analytical run acceptance and repeat analysis. The long term stability data of 145 days cover the entire duration of study sample.

The results of bioanalytical study are incomplete pending firm's response to bioanalytical deficiencies.

4.1.4.4 Pharmacokinetic Results

Table 59. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 63 and Figure 8

Fed Bioequivalence Study, Study No. R09-0905; N=37 Analyte: Morphine									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *pg/ml)	417847.0	31.00	227042.7	690673.3	421715.3	32.65	239649.9	863224.0	0.99
AUC _∞ (hr *pg/ml)	427726.0	31.44	231846.0	695032.5	432078.2	32.77	244600.7	878727.8	0.99
C _{max} (pg/ml)	19182.84	33.37	9105.00	37450.00	20771.62	34.19	10870.00	40390.00	0.92
T _{max} * (hr)	14.000	.	8.00	24.00	14.000	.	8.00	30.00	1.00
K _{el} (hr ⁻¹)	0.082	42.16	0.03	0.20	0.079	36.38	0.05	0.16	1.03
T _{1/2} (hr)	9.729	36.06	3.53	21.49	9.711	30.68	4.47	15.35	1.00

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Fed Bioequivalence Study, Study No. R09-0905; N=37 Analyte: Morphine-6-glucuronide									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *pg/ml)	2114008	20.83	1325589	3144400	2109221	18.37	1459889	2852573	1.00
AUC _∞ (hr *pg/ml)	2151140	21.47	1337042	3244502	2150483	19.06	1466768	2915522	1.00
C _{max} (pg/ml)	95656.22	21.71	58580.00	144200.0	107898.4	27.93	58640.00	183600.0	0.89
T _{max} * (hr)	14.000	.	9.00	20.00	14.000	.	9.00	30.00	1.00
K _{el} (hr ⁻¹)	0.080	37.77	0.04	0.17	0.077	39.11	0.04	0.19	1.04
T _{1/2} (hr)	9.710	31.70	4.01	16.79	10.112	33.41	3.72	19.69	0.96

*T_{max} values are presented as median, range

Table 60. Geometric Means and 90% Confidence Intervals - Firm Calculated

Morphine, Dose (1 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. R09-0905; N=37				
Analyte: Morphine				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (hr *pg/ml)	398224.95	401341.13	99.22	(97.00, 101.50)
AUC _∞ (hr *pg/ml)	406874.65	410567.72	99.10	(96.84, 101.41)
C _{max} (pg/ml)	18335.42	19827.43	92.48	(86.35, 99.04)
Analyte: Morphine-6-glucuronide				
AUC _{0-t} (hr *pg/ml)	2067089.34	2069763.94	99.87	(97.66, 102.13)
AUC _∞ (hr *pg/ml)	2099794.92	2105919.69	99.71	(97.56, 101.91)
C _{max} (pg/ml)	93840.04	105274.24	89.14	(83.33, 95.35)

Table 61. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Morphine, Dose (1 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. R09-0905; N=37					
Analyte: Morphine					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	398224.9	401341.1	0.99	97.00	101.50
AUC _∞ (hr *pg/ml)	406874.6	410567.7	0.99	96.84	101.41
C _{max} (pg/ml)	18335.42	19827.43	0.92	86.35	99.04

Morphine, Dose (1 x 100 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. R09-0905; N=37					
Analyte: Morphine-6-glucuronide					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	2067089	2069764	1.00	97.66	102.13
AUC _∞ (hr *pg/ml)	2099795	2105920	1.00	97.56	101.91
C _{max} (pg/ml)	93840.04	105274.2	0.89	83.33	95.35

Table 62. Additional Study Information

Root mean square error, AUC _{0-t}	0.0572	
Root mean square error, AUC _∞	0.0582	
Root mean square error, C _{max}	0.1729	
	Test	Reference
Kel and AUC _∞ determined for how many subjects?	37	37
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	Yes	Yes

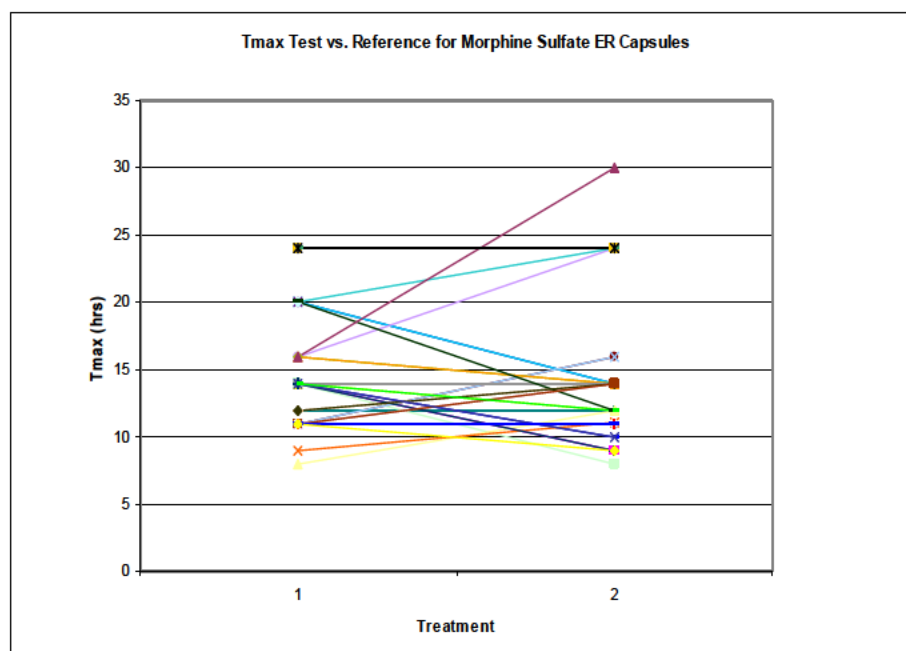
Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	37	0.98	0.91	1.00
Reference	37	0.98	0.93	0.99

Comments on Pharmacokinetic and Statistical Analysis:

1. As per the study design, each group of subjects was to be dosed at one-minute intervals beginning at 0715 (subjects 01-04) and ending at 0726 (subjects 45-48). However, the actual dosing for subject 48 occurred at 0756 hours on days 1 and 15 due to staff oversight. Therefore, periods IA and IIA were added to the study by the investigator to reflect a new schedule of activities for this subject only.
2. As subject# 48 was dropped due to his adverse event (vomiting) prior to study period II, and remaining subjects were administered study drugs in Group I. Therefore no analysis of variance was performed by the reviewer to test for the group by treatment interaction (Group*Treatment).

3. The median $t_{\max}$ value (range) for parent compound, morphine for the test and reference products were 14.0 hr (8.0-24.0 hrs), and 14.0 hr (8.0–30.0 hrs) respectively. The $t_{\max}$ range for the test product (8.0-24.0 hrs) is within that of the reference product for all subjects (8.0–30.0 hrs) as shown in the **Figure 7** below.

Figure 7: Stick plot for Morphine $T_{\max}$ (Fed Study No: R09-0905)



4. The reviewer calculated 90% confidence intervals for T/R ratios for LAUC_{0-t} , $\text{LAUC}_{0-\infty}$ and $\text{LC}_{\max}$ morphine were within the acceptable limits (80% -125%) and similar to those reported by the firm.

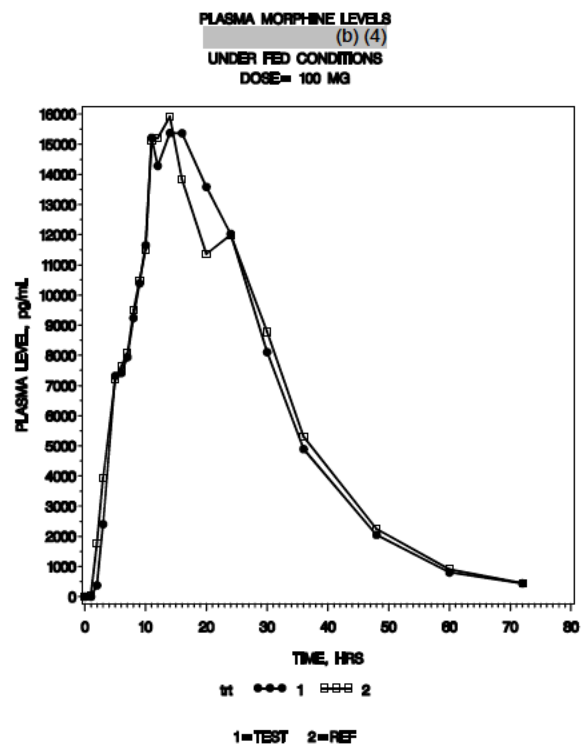
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is incomplete, pending firm's response to bioanalytical deficiencies.

Table 63. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Analyte: Morphine					
Time (hr)	Test (n=37)		Reference (n=37)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0.00	0.00	.	0.00	.	.
1.00	0.00	.	54.99	340.90	0.00
2.00	374.11	129.12	1774.19	81.05	0.21
3.00	2400.79	63.01	3940.95	54.72	0.61
5.00	7316.68	30.97	7192.95	29.80	1.02
6.00	7413.73	35.21	7624.81	36.48	0.97
7.00	7937.97	39.92	8079.95	41.64	0.98
8.00	9237.62	42.74	9506.54	48.41	0.97
9.00	10385.49	46.53	10474.49	50.05	0.99
10.00	11648.84	45.82	11498.38	46.63	1.01
11.00	15214.24	38.48	15124.05	47.11	1.01
12.00	14282.54	33.43	15204.73	41.03	0.94
14.00	15375.16	30.15	15912.22	32.02	0.97
16.00	15365.89	39.78	13828.92	37.99	1.11
20.00	13583.11	36.49	11360.54	38.96	1.20
24.00	12027.32	38.64	11996.19	52.34	1.00
30.00	8104.30	45.80	8779.49	65.91	0.92
36.00	4891.14	57.43	5297.86	68.35	0.92
48.00	2047.24	67.66	2246.43	78.65	0.91
60.00	802.48	89.77	902.02	83.26	0.89
72.00	437.55	109.10	449.68	112.35	0.97

Figure 8. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Ingredients/Grade	mg/capsule		% w/w (per capsule)		IIG limits (mg) (b) (4)
	80 mg	100 mg	80 mg	100 mg	
Size “0” CS, hard gelatin capsules, flesh opaque cap printed with “WATSON/3576” and white opaque body printed with “80 mg”.	(b) (4)	N/A	N/A	N/A	-
Size “0” CS, hard gelatin capsules, blue-green opaque cap printed with “WATSON/3453” and white opaque body printed with “100 mg”.	-	(b) (4)	-	-	-
Total fill weight (with capsule shell)	342.1	403.6	-	-	

(b) (4) [§] Based on average weight of 50 empty capsule shells.

⁸ Retrieved from DPRF database, ANDA (b) (4)

⁹ Retrieved from IIG Max Daily Dose Database, NDA (b) (4)

The quantitative composition for 80 mg and 100 mg capsules is provided in the table below:

	80 mg	100 mg	IIIG limits (mg)
Capsule Components	mg/capsule	mg/capsule	
Titanium Dioxide			(b) (4)
Gelatin			
FD&C Blue # 1			
FD&C Red # 40			
FD&C Yellow # 6			
FD&C Green# 3			
	(b) (4)		
	</		

Note: The firm has mentioned that, “capsules used in the exhibit batch for the 80 mg strength of the drug product used (b) (4) and (b) (4) inks, which are commercially available prepared mixtures of commonly used excipients. For future commercial batches, firm will use (b) (4) (b) (4) and (b) (4).

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	The inactive ingredients are within the acceptable IIG limits. The formulation is incomplete pending firm’s response to actual amount of (b) (4) and (b) (4) and total amount of elemental iron per capsule.

The test product formulations contain (b) (4)

RLD Formulations^{11,12}: In this review, only the composition of reference listed drugs 80 mg and 100 mg is listed in the table below:

Components		Dosage Strength	
(b) (4)		80.0 mg (mg/capsule)	100.0 mg (mg/capsule)
Morphine Sulfate USP,	(b) (4)	80.0	100.0
		(b) (4)	

* (b) (4) is used as (b) (4)

RLD formulations contain the (b) (4)

to achieve the appropriate dosage strengths.

¹⁰ DARRTS, ANDA 200812, supporting document# 1, Module 2.3 and 3.2.P.2

¹¹ V:\FIRMSAM\ACTAVIS PHARMA\100138C0210 DRAF.DOC

¹² The composition for 80 mg and 100 mg strengths is for current approved products as manufactured at (b) (4) manufacturing site.

Reviewer' Comment: Both RLD and test products are designed to release drug over an extended period of time. However, RLD and test products differ with respect to following characteristics: 1) the innovator product contains the (b) (4), where as drug in test product is not (b) (4) and 2) RLD product was manufactured by using only (b) (4), whereas test product formulations were prepared using (b) (4) during (b) (4) with the drug.

4.3 Dissolution Data

Dissolution Review Path	N/A
--------------------------------	-----

Watson is proposing the following dissolution method and specification:

Method: 500 mL of 0.1N HCl for 1 hour and replace with 500 mL of pH 7.5 Phosphate Buffer, USP Apparatus I (Basket), 100 rpm at 37 ± 0.5 °C

Specifications: 1 hr: NMT 10%; 5 hr: (b) (4)%; 7 hr: (b) (4)%; 10 hr: NLT 85%

The firm has not submitted the individual tablet dissolution data in the above mentioned dissolution media. The proposed dissolution media is consistent with USP dissolution method for morphine sulfate extended release capsule; however, dissolution specifications are not in agreement with USP specifications for this drug product.

The following dissolution data on the 80 mg and 100 mg test and reference products is available in the [Module 3.2.P.1, Pharmaceutical Development Report](#)

80 mg strength

Table 56. Dissolution data for 80 mg ANDA batch vs. Kadian®, 80 mg in USP apparatus I @ 100 rpm, 500 mL, 0.1 N HCl for 1 hr, then transferred to pH 7.5 (n=12)

Time (hr.)	0	0.5	1	2	5	7	10	14	f ₂
3576R0013 (80 mg)	0	0	0	4	41	74	102	105	58
510M81 (80 mg)	0	1	3	9	55	89	106	108	

100 mg strength

Table 60. Dissolution data for 100 mg ANDA batch vs. Kadian®, 100 mg in USP apparatus I @ 100 rpm, 500 mL, 0.1 N HCl for 1 hr, then transferred to pH 7.5 (n=12)

Time (hr.)	0	0.5	1	2	5	7	10	14	f ₂
3453R0001 (100 mg)	0	0	0	4	40	74	99	102	64
320E71 (100 mg)	0	0	1	6	52	85	101	103	

Firm will be asked to submit the comparative dissolution testing on 12 dosage units each of the test and reference 80 mg and 100 mg formulations using USP dissolution method

for morphine sulfate extended release capsules. DBE will set the dissolution specification upon review of data.

Multimedia Dissolution Studies:

pH 1.2

Dissolution Conditions			Apparatus:	USP Apparatus 1													
			Speed of Rotation:	100 rpm													
			Medium:	pH 1.2													
			Volume:	900 mL													
			Temperature:	37 ± 0.5 °C													
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location	
						0	1	2	4	6	8	10	12	14	16		
WSR1700, p.75,	11/04/09	Test Product Morphine Sulfate SR capsules Lot # 3576R0013 (Mfg. 06/09/09)	80 mg Capsule	12	Mean	0	0	2	9	15	22	28	34	41	47	Module 2, Section 2.7.1.2	
					Range	(b) (4)											
					% RSD	NA	233.5	13.9	5.7	4.7	5.0	3.8	4.2	4.0	3.9		
	11/05/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	2	6	12	17	21	26	31	36	41		
					Range	(b) (4)											
					% RSD	NA	21.1	15.1	7.1	4.8	3.4	3.4	2.5	2.2	2.2		
WSR1700, p.82	11/07/09	Test Product Morphine Sulfate SR capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	0	2	9	16	23	31	38	46	53	Module 2, Section 2.7.1.2	
					Range	(b) (4)											
					% RSD	NA	NA	0.0	3.2	3.6	2.9	2.3	2.1	2.4	2.3		
	11/07/09	Reference Product Kadian Lot # 320E71 (Exp.05/2010)	100 mg Capsule	12	Mean	0	1	4	11	15	20	25	30	35	40		
					Range	(b) (4)											
					% RSD	NA	0.0	11.4	4.6	3.8	3.0	3.0	3.0	2.8	2.6		

pH 4.5

Dissolution Conditions		Apparatus:		USP Apparatus 1												
		Speed of Rotation:		100 rpm												
		Medium:		pH 4.5												
		Volume:		900 mL												
		Temperature:		37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0	1	2	4	6	8	10	12	14	16	
WSR1700, p.76	11/05/09	Test Product Morphine Sulfate SR capsules Lot # 3576R0013 (Mfg. 06/09/09)	80 mg Capsule	12	Mean	0	0	2	8	13	18	22	26	31	35	Module 2, Section 2.7.1.2
					Range	(b) (4)										
					% RSD	NA	NA	13.9	3.6	5.1	3.0	3.8	2.7	2.8	2.8	
	11/04/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	3	6	13	18	23	27	32	36	40	
					Range	(b) (4)										
					% RSD	NA	25.9	13.5	4.0	2.9	2.6	2.4	2.4	2.0	1.8	
WSR1700, p.83	11/06/09	Test Product Morphine Sulfate SR capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	0	2	8	13	19	23	29	34	39	Module 2, Section 2.7.1.2
					Range	(b) (4)										
					% RSD	NA	346.4	21.3	3.6	3.8	2.8	2.9	2.3	2.3	2.4	
	11/06/09	Reference Product Kadian Lot # 320E71 (Exp.05/2010)	100 mg Capsule	12	Mean	0	0	0	3	12	17	22	27	32	36	
					Range	(b) (4)										
					% RSD	NA	NA	346.4	88.8	3.3	3.0	2.2	2.3	2.6	1.8	

pH 6.8

Dissolution Conditions		Apparatus:		USP Apparatus 1												
		Speed of Rotation:		100 rpm												
		Medium:		pH 6.8												
		Volume:		900 mL												
		Temperature:		37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0	1	2	4	6	8	10	12	14	16	
WSR1700, p.77	11/05/09	Test Product Morphine Sulfate SR capsules Lot # 3576R0013 (Mfg. 06/09/2009)	80 mg Capsule	12	Mean	0	1	9	29	55	80	97	103	104	104	Module 2, Section 2.7.1.2
					Range	(b) (4)										
					% RSD	NA	0.0	5.8	2.1	1.9	1.5	1.9	1.7	1.8	1.9	
	11/05/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	4	12	30	49	68	86	98	103	104	
					Range	(b) (4)										
					% RSD	NA	17.7	5.3	2.6	1.3	1.6	1.5	1.2	1.5	1.5	
WSR1700,p.84	11/09/09	Test Product Morphine Sulfate SR capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	1	11	35	61	86	99	102	103	103	Module 2, Section 2.7.1.2
					Range	(b) (4)										
					% RSD	NA	26.6	5.3	2.5	2.2	1.5	1.1	1.0	0.8	1	
	11/05/09	Reference Product Kadian Lot # 320E71 (Exp.05/2010)	100 mg Capsule	N/A	Mean	0	4	13	32	51	70	87	97	100	101	
					Range	(b) (4)										
					% RSD	NA	14.9	4.5	2.9	3.2	3.1	3.1	3.0	2.9	2.9	

In Vitro Alcohol Dose-dumping

Dissolution Conditions		Apparatus:		USP Apparatus 1											
		Speed of Rotation:		100 rpm											
		Medium:		0.1N HCl											
		Volume:		900 mL											
		Temperature:		37 ± 0.5 °C											
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331													
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)									Study Report Location
						0	15	30	45	60	75	90	105	120	
WSR1700, p.71	11/03/09	Test Product Morphine Sulfate SR capsules Lot # 3576R0013 (Mfg. 06/09/2009)	80 mg Capsule	12	Mean	0	1	0	0	0	0	1	1	2	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	104.4	180.9	147.7	147.7	147.7	60.3	36.9	20.1	
	11/03/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	1	2	2	3	4	5	6	7	
					Range	(b) (4)									
					% RSD	NA	66.6	43.1	32.8	23.2	21.3	17.3	13.7	12.3	
WSR1700, p.78	11/09/09	Test Product Morphine Sulfate SR capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	0	0	0	0	0	1	1	2	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	NA	NA	NA	346.4	233.5	46.7	26.6	13.9	
	11/10/09	Reference Product Kadian Lot # 320E71 (Exp.05/2010)	100 mg Capsule	12	Mean	0	0	0	0	1	2	3	3	4	
					Range	(b) (4)									
					% RSD	NA	NA	NA	NA	0.0	0.0	0.0	12.3	0.0	

Dissolution Conditions		Apparatus:	USP Apparatus 1												
		Speed of Rotation:	100 rpm												
		Medium:	5% Ethanol in 0.1N HCl												
		Volume:	900 mL												
		Temperature:	37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331													
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)									Study Report Location
						0	15	30	45	60	75	90	105	120	
WSR1700 p.72	11/02/09	Test Product Morphine Sulfate SR capsules Lot # 3576R0013 (Mfg. 06/09/2009)	80 mg Capsule	12	Mean	0	0	0	0	0	0	1	2	3	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	346.4	346.4	233.5	180.9	147.7	0.0	21.2	16.4	
	11/02/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	1	1	2	3	5	6	7	8	
					Range	(b) (4)									
					% RSD	NA	80.4	56.0	43.3	29.7	24.2	17.8	13.7	12.0	
WSR1700, p.79	11/13/09	Test Product Morphine Sulfate SR capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	0	0	0	0	0	1	2	3	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	NA	NA	NA	233.5	123.6	0.0	21.2	9.9	
	11/13/09	Reference Product Kadian Lot # 320E71 (Exp.05/2010)	100 mg Capsule	12	Mean	0	0	0	1	1	3	4	5	6	
					Range	(b) (4)									
					% RSD	NA	NA	NA	60.3	36.3	18.5	12.1	9.5	6.7	

Dissolution Conditions			Apparatus:		USP Apparatus 1										
			Speed of Rotation:		100 rpm										
			Medium:		20% Ethanol in 0.1N HCl										
			Volume:		900 mL										
			Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)									Study Report Location
						0	15	30	45	60	75	90	105	120	
WSR1700, p.73	11/11/09	Test Product Morphine Sulfate SR capsules Lot # 3576R0013 (Mfg. 06/09/09)	80 mg Capsule	12	Mean	0	0	0	0	1	2	4	6	8	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	180.9	346.4	180.9	0.0	13.9	10.2	7.9	5.0	
	11/11/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	1	3	6	9	12	16	21	25	
					Range	(b) (4)									
					% RSD	NA	95.3	30.9	23.8	9.9	5.3	5.3	5.5	3.4	
WSR1700, p.80	11/19/09	Test Product Morphine Sulfate SR capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	0	0	1	1	2	4	6	8	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	NA	NA	88.3	31.5	0.0	10.2	6.7	6.5	
	11/19/09	Reference Product Kadian Lot # 320E71 (Exp.05/2010)	100 mg Capsule	12	Mean	0	0	0	2	5	9	14	19	24	
					Range	(b) (4)									
					% RSD	NA	NA	NA	13.9	5.7	3.2	3.6	2.8	3.1	

Dissolution Conditions			Apparatus:		USP Apparatus 1										
			Speed of Rotation:		100 rpm										
			Medium:		40% Ethanol in 0.1N HCl										
			Volume:		900 mL										
			Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)									Study Report Location
						0	15	30	45	60	75	90	105	120	
WSR1700, p.74	11/11/09	Test Product Morphine Sulfate SR capsules Lot # 3576R0013 (Mfg. 06/09/09)	80 mg Capsule	12	Mean	0	0	0	1	1	4	12	22	30	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	NA	346.4	104.4	33.4	15.0	7.9	5.8	3.8	
	11/11/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	1	2	8	24	41	55	66	74	
					Range	(b) (4)									
					% RSD	NA	134.8	15.1	7.4	3.9	2.6	1.9	2.0	2.0	
WSR1700, p.81	11/16/09	Test Product Morphine Sulfate SR capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	0	0	1	3	7	15	23	31	Module 2, Section 2.7.1.2
					Range	(b) (4)									
					% RSD	NA	233.5	123.6	86.1	87.8	81.8	60.5	44.7	35.8	
	11/18/09	Reference Product Kadian Lot # 320E71 (Exp.05/2010)	100 mg Capsule	12	Mean	0	1	3	9	23	39	53	63	70	
					Range	(b) (4)									
					% RSD	NA	85.3	20.1	6.1	3.3	2.7	2.5	1.8	2.0	

Reviewer's Comments

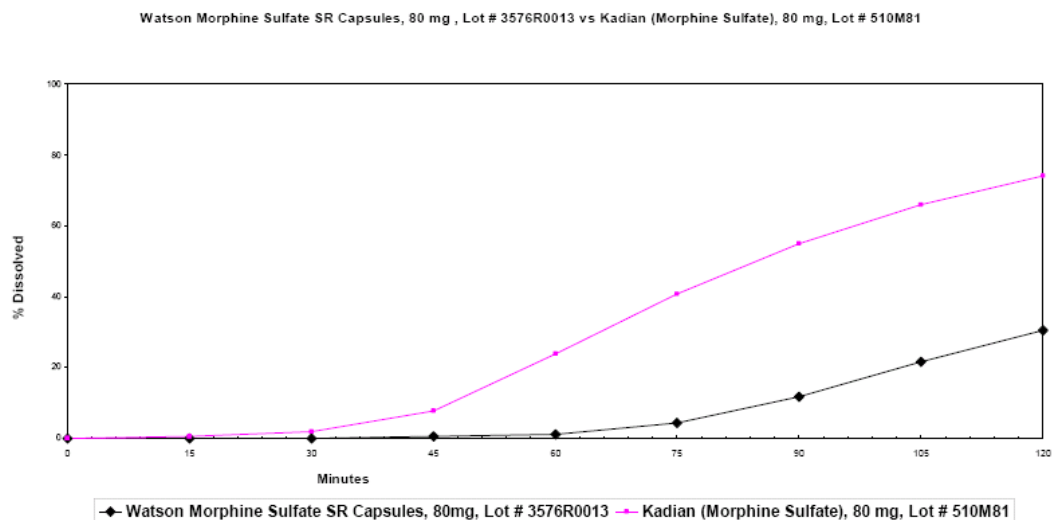
Please refer to below table summarizing mean% (range) drug release at 2 hours in various media for 80 mg and 100 mg strength test product:

	Mean % Drug Released at 2 hours			
	0.1 N HCl	5% EtOH in 0.1 N HCl	20% EtOH in 0.1 N HCl	40% EtOH in 0.1 N HCl
80 mg				
Test	2 (b) (4)	3 (b) (4)	8 (b) (4)	30 (b) (4)
Reference	7	8	25	74
100 mg				
Test	2 (b) (4)	3 (b) (4)	8 (b) (4)	31 (b) (4)
Reference	4	6	24	70

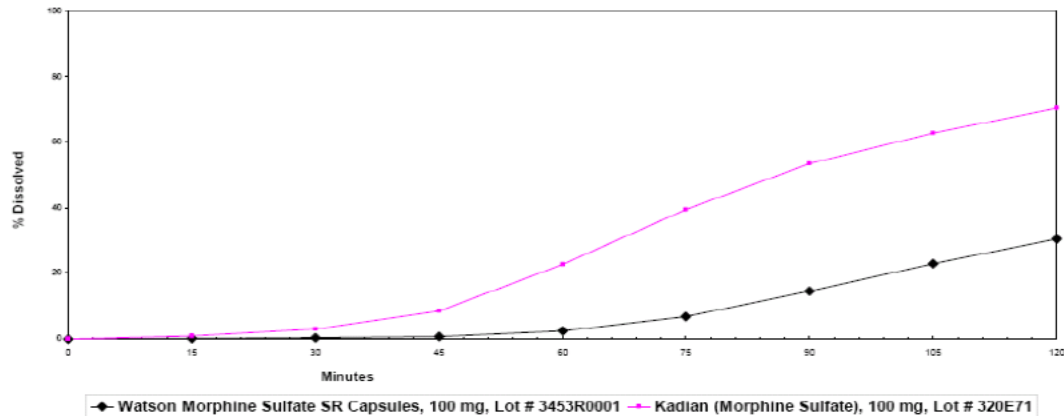
For products that exhibit alcohol dose dumping, the DBE compares the mean percent (%) dissolved at 2 hours in 0.1 N HCl to the % dissolved at 2 hours in 0.1 N HCl/40% alcohol for the test product. Since the mean percent dissolved at 2 hours in 0.1 N HCl/40% alcohol is higher than mean % dissolved in 0.1NHCl for 80 mg (30% vs. 2%) and 100 mg (31% vs. 2%) strengths, further comparisons with the RLD are needed as per OGD policy.¹³

On comparisons with the RLD, reviewer notes that the % dissolved at 2 hours in 40% alcohols is 39-44% lower for test products than the reference products. This data suggests that the risk of dose-dumping from the generic product is no more than that of reference product.

In 0.1 N HCl/40% ethanol dissolution media, the f2 values are less than 50 due to higher release of drug from the reference products as compared to test products as shown in the Figures below:



¹³ OGD Bupropion Memorandum dated 9/12/06 in New Reviewer Handbook



4.4 Detailed Regulatory History (If Applicable)

The Division File contains the review of several relevant documents including

- Control #04-1091, 04-171 and 07-1298 (b) (4)
- Control #04-211 and 04-282 (b) (4)
- Control #04-551, 04-923, 07-0945, and 09-0089 (b) (4)
- Control #05-0257 and 05-0357 (b) (4)
- Control #05-0358 (b) (4)
- Control #05-0963 (b) (4)
- Control #05-1251 and 07-0557 (b) (4)
- Control #05-1261 and 07-1220 (b) (4)
- Control #05-1489 and 05-1505 (b) (4)
- Control #05-1533 (b) (4)
- Control #06-0077 (b) (4)
- Control #07-0976 (b) (4)
- Control #07-1566 (Upsher-Smith)
- Control #08-0315 (b) (4)
- Control #10-0138 (Alston & Bird/Actavis)

The following ANDAs on this drug product are currently under review

- ANDA # (b) (4)
- ANDA #202104 (Upsher Smith Laboratories Inc.)
- ANDA # (b) (4)

Citizen Petition: On February 5, 2010, Alston & Bird LLP submitted the citizen petition (Docket No. FDA-2010-P-0082) on behalf of Actavis Elizabeth LLC requesting the FDA to take following actions with respect to all ANDAs referring Kadian capsules:

1. Imposing additional bioequivalence parameters: partial AUCs from 0-1 hr, 8-12 hr and 8-12 hr.

2. In vitro and in vivo alcohol dose-dumping studies.
3. Demonstration of bioequivalence at three different dosage strengths.

On July 19, 2010, Agency granted the petition in part and denied in part as mentioned below:

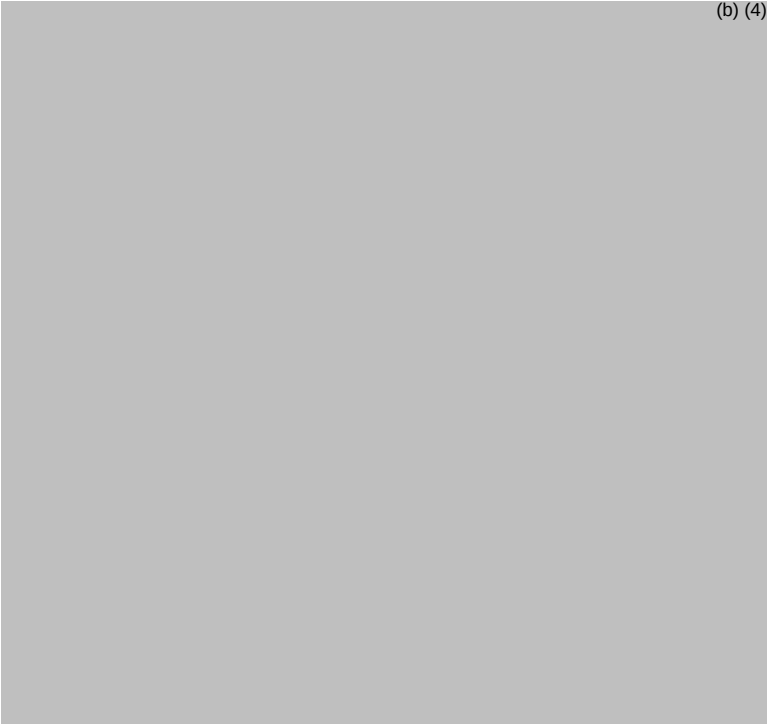
1. Petition to consider partial AUCs was denied based on the following facts:
 - Kadian[®] capsules contain only the extended release pellets.
 - Absence of data showing that $t_{\max}$ differences have caused any difference in clinical drug safety and efficacy of Kadian[®] (contains only ER component) and Avinza[®] (contains both IR and ER components) formulations.
 - Differences in $t_{\max}$ between Kadian[®] and Avinza[®] formulations do not translate into measurable differences in morphine pharmacodynamic effects of pain relief and the incidence and severity of adverse effects.
 - No clear link has been established between the morphine concentration-time profile and efficacy and safety.
 - Kadian is not a drug for which rapid onset is critical for its intended indications.
 - For post approval changes of Kadian[®] formulations only $C_{\max}$ and AUC parameters were used for bioequivalence analysis.
2. Petition to consider in vitro alcohol dose dumping was granted and denied for in vivo alcohol study dumping study. Applicant was informed that FDA will consider in vivo dose dumping study on case-via-case basis depending on the results of in vitro study.
3. Petition to demonstrate bioequivalence at dosage strengths representing each of the three pellet formulations used in Kadian[®] was granted based on the fact that 200 mg and 10 mg strengths used slightly different formulation, and 20 mg to 100 mg use the same pellet formulation with only the amount of fill varying to achieve the appropriate dosage strength. Based on these considerations, FDA recommended six bioequivalence studies (please refer to section 3.3 of this review) and issued revised draft guidance for this drug product on May 2010.

4.5 Consult Reviews

N/A

Following this page, 130 pages withheld in full - (b)(4) SAS data

(b) (4)



4.7 Additional Attachments

N/A

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Morphine Sulfate Extended Release Capsules,
80 mg and 100 mg

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. Your pre-study bioanalytical method validation report no. 064.5 does not provide the description of solid phase extraction procedure used to extract morphine and morphine-6-glucuronide (morphine-6G) from human plasma samples, concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples for analysis of morphine and morphine-6G in human plasma. Please provide the description of solid phase extraction procedure as well as the concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples.
2. Your pre-study bioanalytical method validation report 064.5 mentions that precision and accuracy run of QC samples for morphine-6G can be seen in Tables 12 and 14. However, the table titles are for the parent compound, morphine (Title for Tables# 12 and 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine in Human Plasma). Please clarify the reason for this discrepancy and submit the intraday accuracy and precision data for the QC samples for morphine and morphine-6G.
3. Please provide supporting data to show that naltrexone does not affect the extraction and estimation of morphine and morphine-6G in human plasma samples.
4. Please confirm whether selection of samples with adjusted lower limit of quantitation (ALLQ) and retention time shift (RTS) was based on established procedures. The analytical site's Standard Operating Procedure (b) (4)_SOP_04_LBP_006 does not define adjusted lower limit of quantitation and retention time shift

and fails to provide the criteria for selecting samples with ALLQ and RTS.

5. For fed studies #R09-0073 and #R09-0905, the freeze-thaw stability of morphine-6G samples exceeded beyond the established 4 freeze-thaw cycle stability. Please provide the freeze-thaw stability data to cover the stability of morphine-6G during bioanalytical study conduct.
6. You have not provided the actual amount of (b) (4) (b) (4) and (b) (4) in your test product's formulation. Please provide this information including the total amount of elemental iron per tablet in your formulation.
7. You have not provided the comparative dissolution testing data using USP method. Please conduct the dissolution testing on 12 dosage units each of the test and reference 80 mg and 100 mg formulations using the current USP method for morphine sulfate extended release capsules, and submit the individual dissolution data, mean, range and coefficient of variation (CV%) values. Division of Bioequivalence will recommend dissolution specifications upon review of submitted data.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 200812

Enter Review Productivity and Generate Report

Completed Assignment for 200812 ID: 11705

Reviewer: Kaur, Paramjeet

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description:

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal		
11705	12/16/2009	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
11705	12/16/2009	Bioequivalence Study	Fed Study	1	1	Edit	Delete
11705	12/16/2009	Bioequivalence Study	Sprinkle Study	1	1	Edit	Delete
11705	12/16/2009	Bioequivalence Study	Fed Study	1	1	Edit	Delete
11705	12/16/2009	Other	In-vitro dose-dumping in alcohol	1	1	Edit	Delete
				Bean Total:	5		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

BE Study Fasting (80 mg)	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
<i>Fasting Study Total</i>	<i>4</i>
BE Study Fed (80 mg)	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
<i>Fed Study Total</i>	<i>4</i>

BE Fasting Sprinkle Study Fed (80 mg)	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
<i>Fasting Sprinkle Study Total</i>	<i>4</i>
BE Study Fed (100 mg)	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
<i>Fed Study Total</i>	<i>4</i>
Dissolution Study/ Dissolution Waiver(s)	
Dissolution Study (as part of dissolution review)	0
<i>Dissolution Study/Waiver Total</i>	<i>0</i>
In vitro alcohol dose dumping	1
Total number of Complexity Points	17

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PARAMJEET KAUR
09/17/2010

CHANDRA S CHAURASIA
09/17/2010

BARBARA M DAVIT
09/21/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200812			
Drug Product Name	Morphine Sulfate Extended-Release Capsules, USP			
Strength(s)	20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg			
Applicant Name	Watson Laboratories Inc.			
Address	4955 Orange Drive Ft. Lauderdale, FL 33314			
Applicant's Point of Contact	Alberto E. Rivalta, Manager Regulatory Affairs			
Contact's Telephone Number	(954) 358-6109			
Contact's Fax Number	(954) 358-6350			
Original Submission Date(s)	December 16, 2009			
Submission Date(s) of Amendment(s) Under Review	September 30, 2010 December 09, 2010			
Reviewer	Chandra S. Chaurasia, Ph.D.			
Study Number (s) ¹	R09-0072	R09-0073	R09-0074	R09-0905
Study Type (s)	Fasting	Fed	Fasting sprinkle-in-applesauce	Fed
Strength (s)	80 mg	80 mg	80 mg	100 mg
Clinical Site	Cetero Research			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	(b) (4)			
Analytical Site Address				
OUTCOME DECISION	INADEQUATE			

OVERALL REVIEW RESULT	INADEQUATE		
WAIVER REQUEST RESULT	INADEQUATE		
DSI REPORT RESULT	ADEQUATE		
BIOEQUIVALENCE STUDY	STUDY/TEST TYPE	STRENGTH	REVIEW

¹ The firm submitted fasting (80 mg), fed (80 mg and 100 mg) and fasting sprinkle-in-applesauce BE studies (80 mg) on 12/16/09 before posting of current revised individual product recommendations for this drug product in May 2010, which recommends six BE studies, namely, fasting (10 mg, 100 mg and 200 mg), fed (100 mg and 200 mg) and fasting sprinkle-in-applesauce (100 mg); and waiver of 20 mg, 30 mg, 50 mg, 60 mg and 80 mg strengths based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) acceptable in vitro dissolution testing for all the strengths, and (iii) proportional similarity of formulations across all strengths. Since BE studies were conducted prior to posting of revised BE recommendations for this drug product, therefore waiver of 20 mg, 30 mg, 50 mg, 60 mg strengths based on fasting (80 mg), fed (80 mg and 100 mg) and fasting sprinkle-in-applesauce BE studies (80 mg) should be acceptable.

TRACKING/SUPPORTING DOCUMENT#			RESULT
1 & 4	FASTING STUDY	80 mg	ADEQUATE
1 & 4	FED STUDY	80 mg	ADEQUATE
1 & 4	FASTING SPRINKLE STUDY	80 mg	ADEQUATE
1 & 4	FED STUDY	100 mg	ADEQUATE
1 & 2	DISSOLUTION	80 mg and 100 mg	INADEQUATE
2	DISSOLUTION	20 mg, 30 mg, 50 mg and 60 mg	INADEQUATE

REVIEW OF TWO STUDY AMENDMENTS

1 EXECUTIVE SUMMARY

In the original submission dated December 16, 2009, the firm conducted fasting, fed and fasting sprinkle bioequivalence (BE) studies comparing Watson Laboratories' test product, Morphine Sulfate Extended Release Capsules, 80 mg, to the corresponding Actavis Elizabeth's reference product, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg strength. In addition, the firm submitted a fed study comparing Watson Laboratories' test product, Morphine Sulfate Sustained Release Capsules, 100 mg, to the corresponding Actavis Elizabeth's reference product, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 100 mg strength. The bioequivalence (fasting, fed and fasting sprinkle) studies were found acceptable; however, the application was found to be incomplete due to (i) bioanalytical deficiencies, (ii) formulation deficiency, and (iii) dissolution deficiency [DARRTS N200812, REV-BIOEQ-01(General Review), dated 9/21/2010].

The firm submitted two amendments dated 9/30/10 and 12/09/10 for the addition of four new strengths, 20 mg, 30 mg, 50 mg and 60 mg and in response to the deficiency letter sent to the firm on 9/29/2010². The firm has provided acceptable responses to the bioanalytical and formulation deficiencies.

The firm has conducted comparative dissolution testing on all strengths using USP-recommended dissolution method, however, for the Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg strengths, the firm has not taken the dissolution samples for morphine sulfate analysis at 4, 6 and 9 hrs as per USP. The firm will be asked to repeat dissolution testing for its test products, 80 mg and 100 mg including sampling times at 4, 6 and 9 hrs similar to 20 mg, 30 mg, 50 mg and 60 mg strengths.

In addition, the firm's dissolution testing is incomplete. Some units have a total release greater than (b) (4)% for both the test and reference products. The firm will be asked to clarify this observation and repeat the dissolution testing.

The firm has conducted acceptable dissolution testing on all strengths under different pH conditions (pH 1.2, pH 4.5 buffer and pH 6.8 buffer). In addition, the firm has previously conducted acceptable in vitro alcohol-dumping study on the 80 mg and 100 mg strengths

² DARRTS: N200812, COR-ANDA-01(Bio Incomplete Deficiencies); final date: 9/29/10

(DARRTS, ANDA 200812, REV-BIOEQ-01(General Review), dated 9/21/2010).
However, the firm did not provide any in vitro alcohol-dumping dissolution testing data on the 20 mg, 30 mg, 50 mg and 60 mg strengths. The firm is requested to conduct in vitro alcohol dose-dumping testing on these four strengths as well.

The application is incomplete due to the above mentioned deficiencies.

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3 SUBMISSION SUMMARY

3.1 Review of Submission

3.1.1 Review of Amendment Dated – 12/09/2010

Deficiency Comment# 1:

Your pre-study bioanalytical method validation report no. 064.5 does not provide the description of solid phase extraction procedure used to extract morphine and morphine-6-glucuronide (morphine-6G) from human plasma samples, concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples for analysis of morphine and morphine-6G in human plasma. Please provide the description of solid phase extraction procedure as well as the concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples.

Firm's Response to the Deficiency Comment# 1:

A description of the solid phase extraction procedure can be found in [Attachment 1: Analytical Procedure Morphine and Morphine-6 \$\beta\$ -D-glucuronide in Human Plasma](#), Section G. The concentration and amount of stock solutions used for the preparation of the calibration curve standards and quality control samples are described in [Attachment 1: Analytical Procedure Morphine and Morphine-6 \$\beta\$ -D-glucuronide in Human Plasma](#), Sections E and F, respectively.

Reviewer's Comment on the Deficiency# 1:

In Attachment 1 (Analytical Procedure LC/MS.MS 064.5.B), the firm has provided the description of solid phase extraction procedure as well as the concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples.

Briefly, for solid phase extraction procedure,

(b) (4)

system for analysis.

The firm's response to concentration and amount of stock solutions used to prepare calibration curve standard and quality control samples for morphine and morphine-6 β -D-glucuronide as provided in the sections E and F, respectively in Attachment I is adequate.

The firm's response to deficiency comment# 1 is acceptable.

Deficiency Comment# 2:

Your pre-study bioanalytical method validation report 064.5 mentions that precision and accuracy run of QCs samples for morphine-6G can be seen in Tables 12 and 14. However, the table titles are for the parent compound, morphine (Title for Tables# 12 and 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine in Human Plasma). Please clarify the reason for this discrepancy and submit the intraday accuracy and precision data for the QC samples for morphine and morphine-6G.

Firm's Response to the Deficiency Comment# 2:

The data that is listed in Tables 12 and 14 of the method validation report has been verified and is accurate for the metabolite morphine-6G. The titles of these tables contained a typo when referencing the compound. The titles of the tables should read "Table 12: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine-6G in Human Plasma" and "Table 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine-6G in Human Plasma." The updated tables are included as [Attachment 2](#).

Reviewer's Comment on the Deficiency# 2:

In the Attachment 2, firm has updated the titles for Tables# 12 and 14 to read as Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine-6G in Human Plasma.

The firm's response to deficiency comment# 2 is acceptable.

Deficiency Comment# 3:

Please provide supporting data to show that naltrexone does not affect the extraction and estimation of morphine and morphine-6G in human plasma samples.

Firm's Response to the Deficiency Comment# 3:

Attached Attachment 3-First Addendum to the Method Validation of Morphine and Morphine-6 β -D-Glucuronide (Morphine-6G) in Human Plasma, reports the data of the Interference Test with Naltrexone/6 β -Naltrexol. **Section 1.2** for morphine and **Section 2.2** for morphine-6G establish that the presences of Naltrexone/6 β - Naltrexone do not interfere with the quantitation of either morphine or morphine- 6G.

Reviewer's Comment on the Deficiency# 3:

As provided in Attachment 3 (report 064.5 addendum 1), firm has evaluated the effect of naltrexone and it metabolite, 6 β -naltrexol on the estimation of morphine and morphine-6G. Briefly, firm evaluated the effect of naltrexone and 6 β -naltrexol at a concentration of 100 ng/mL using low QC (675 pg/mL) and high QC(144000 pg/mL) samples for morphine and morphine-6G. The comparison of mean concentrations of low and high QCs spiked with naltrexone/6 β -naltrexol with mean concentration of low and high QCs without naltrexone/6 β -naltrexol met the acceptance criteria of $\leq 15\%$ difference between the means demonstrating that the presence of naltrexone/6 β -naltrexol does not interfere with the quantitation of morphine and morphine 6-G.

The firm's response to deficiency comment# 3 is acceptable.

Deficiency Comment# 4:

Please confirm whether selection of samples with adjusted lower limit of quantitation (ALLQ) and retention time shift (RTS) was based on established procedures. The analytical site's Standard Operating Procedure (b) (4)_SOP_04_LBP_006 does not define adjusted lower limit of quantitation and retention time shift and fails to provide the criteria for selecting samples with ALLQ and RTS.

Firm's Response to the Deficiency Comment# 4:

The selection of samples for ALLQ and RTS was based on established procedures. The selection of samples for ALLQ followed SOP (b) (4)_SOP_04 LBP_006, Version 1 Section 3.2, which was included in the Sample Analysis report, Appendix A of the original ANDA (Sequence # 0000). The selection of samples for RTS follows the Analytical Procedure LC/MS.MS 064.5.B, **Section A**, Instrumentation provided in **Attachment 1**.

Reviewer's Comment on the Deficiency# 4:

The SOP (b) (4) SOP_04 LBP_006, Version 1 Section 3.2 defines the criteria for “Samples with Values Below the Limits of Quantitation (BLQ)”. Firm’s response as provided in response to deficiency comment# 4 above indicates that criteria for selection of samples with ALLQ and BLQ is same, which is acceptable.

In Attachment 1 (Analytical Procedure LC/MS.MS 064.5.B)-section A, firm has provides the following windows for the retention time of morphine, morphine-6G and internal standards:

- Morphine and (b) (4)
- Morphine-6G and (b) (4)

The firm’s response to deficiency comment# 4 is acceptable.

Deficiency Comment# 5:

For fed studies #R09-0073 and #R09-0905, the freeze-thaw stability of morphine-6G samples exceeded beyond the established 4 freeze-thaw cycle stability. Please provide the freeze-thaw stability data to cover the stability of morphine-6G during bioanalytical study conduct.

Firm’s Response to the Deficiency Comment# 5:

[Attachment 3-First Addendum](#) to the Method Validation of Morphine and Morphine-6-β-D-Glucuronide (Morphine-6G) in Human Plasma, [Section 2.1](#), establishes that morphine-6G is stable for 8 freeze/thaw cycles.

Reviewer’s Comment on the Deficiency# 5:

The freeze-thaw stability data of morphine-6G at low (750 pg/mL) and high QC’s (160,000 pg/mL) as provided in Attachment 3 (report 064.5-addendum 1) shows that % bias for the low and high QCs is -2.0% and -2.4%, respectively, and %CV for the low and high QCs is 9.7% and 1.3%, respectively, after 8 freeze-thaw cycles. These results demonstrate that morphine-6G is stable for 8 freeze/thaw cycles.

The firm’s response to deficiency comment# 5 is acceptable.

Deficiency Comment# 6:

You have not provided the actual amount of (b) (4) and (b) (4) in your test product’s formulation. Please provide this information including the total amount of elemental iron per tablet in your formulation.

Firm's Response to the Deficiency Comment# 6:

(b) (4) and (b) (4) are the inks used to imprint the empty gelatin capsules. Only trace amounts are found in the test product's formulation; hence, less than (b) (4)% of (b) (4) and (b) (4) is present per capsule. The elemental iron content (from Iron Oxide Black) in (b) (4) % of (b) (4) black inks is therefore also less than (b) (4)% w/w of the total formulation.

Furthermore, studies performed in cooperation with (b) (4) manufacturers to determine the amount of dry solids remaining on the surface of a printed product, using (b) (4), have demonstrated that an average of (b) (4) of dry solid is deposited on a single product. Please refer to [Attachment# 4](#) for a copy of (b) (4) (b) (4) Statement on the estimated average weight amount of dry solid deposited on a printed product. Based on this estimation, the range presented below is an approximation of the amount of ink (dry solid) that would be deposited on a single Morphine Sulfate Extended-release Capsule USP, 20 mg (worst case scenario).

Ingredient	Morphine Sulfate Extended-release Capsules USP, 20 mg	
	mg/capsule	% Weight
(b) (4) and (b) (4)	Range: (b) (4)	Range: (b) (4)

Based on the range presented above, we can estimate the amount of elemental iron per capsule as follows:

- Molecular Weight for Iron Oxide Black (Fe_2O_3)³: 159.69 g/mol.
- Molecular Weight for Iron (Fe_2): 111.7 g/mol.
- Amount of Iron Oxide Black per Capsule: between (b) (4) mg and (b) (4) mg.
- Maximum Daily Intake of Morphine Sulfate Extended-release Capsules: 400 mg/day equivalent to 20 capsules of the 20 mg strength.
- Elemental iron content per capsule is between $(111.7 \text{ g/mol}/159.69 \text{ g/mol}) \times (b) (4) \text{ mg} = (b) (4) \text{ mg}$ and $(111.7 \text{ g/mol}/159.69 \text{ g/mol}) \times (b) (4) \text{ mg} = (b) (4) \text{ mg}$
- Maximum daily intake of elemental iron is between (b) (4) mg/capsule x 20 capsules = (b) (4) mg and (b) (4) mg/capsule x 20 capsules = (b) (4) mg

Hence, the amount of elemental iron in test product's formulation complies with 21 CFR 73.1200 requirement of NMT 5 mg elemental iron/day

³ The molecular formula for iron oxide black as provided by the firm is not correct. Molecular formula Fe_2O_3 is for iron oxide red.

Reviewer's Comment on the Deficiency# 6:

A copy of statement from (b) (4) in **Attachment # 4** mentions that amount of solids deposited on the surface of a printed single product ranges from (b) (4) (b) (4), with an average of (b) (4) when determined using (b) (4) (b) (4).

Considering that (b) (4) and (b) (4) contain (b) (4)% of iron oxide black, the maximum amount of iron oxide black deposited onto the capsule shell be (b) (4) mg.

- Molecular Weight for Iron Oxide Black (Fe_3O_4): 231.54 g/mol.
- Molecular Weight for Iron (Fe_3): 167.535 g/mol.
- Maximum amount of Iron Oxide Black per capsule: (b) (4) mg.
- Based on maximum daily dose of this drug (20 capsules of 20 mg strength), the maximum daily intake of element iron = (b) (4) mg

The amount of elemental iron in test product's formulation complies with the 21 CFR 73.1200 requirement of NMT 5 mg elemental iron/day.

The firm's response to deficiency comment# 6 is acceptable.

Deficiency Comment# 7:

You have not provided the comparative dissolution testing data using USP method. Please conduct the dissolution testing on 12 dosage units each of the test and reference 80 mg and 100 mg formulations using the current USP method for morphine sulfate extended release capsules, and submit the individual dissolution data, mean, range and coefficient of variation (CV%) values. Division of Bioequivalence will recommend dissolution specifications upon review of submitted data.

Firm's Response to the Deficiency Comment# 7:

Please note that comparative dissolution testing data on 12 dosage units of the test and reference 80 mg and 100 mg formulation, using the current USP method for morphine sulfate extended-release capsules, was submitted along with the comparative dissolution testing data of additional strengths (20 mg, 30 mg, 50 mg and 60 mg). Please refer to [Section 2.7.1.2 "Summary of Results of Individual Studies" of Sequence # 0001](#).

Reviewer's Comment on the Deficiency# 7:

The firm has provided the following dissolution data for the 80 mg and 100 mg strengths using USP-recommended dissolution method:

Dissolution Conditions			Apparatus:		USP Apparatus 1										
			Speed of Rotation:		100 rpm										
			Medium:		0.1N HCl for 1 hour and replace with pH 7.5 Phosphate Buffer										
			Volume:		500 mL										
			Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331												
Firm's Proposed Specifications			1 hr: NMT 10%; 5 hr: (b) (4)%; 7 hr: (b) (4)%; 10 hr: NLT 85%												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	N		Collection Times (hours)								Study Report Location	
						0	0.5	1	2	5	7	10	14		
WSR2041, p.11 WSR0980, p.56 WSR0980, p.50	08/21/09	Test Product Morphine Sulfate ER capsules Lot # 3576R0013 (Mfg. 06/09/2009)	80 mg Capsule	12	Mean	0	0	0	4	41	74	102	105	Section 2.7.1.2; pages 52-53	
					Range	(b) (4)									
					% RSD	-	346.4	346.4	19.3	4.9	4.0	3.0	3.1		
	08/17/09	Reference Product Kadian Lot # 510M81 (Exp.10/2010)	80 mg Capsule	12	Mean	0	2	3	9	55	88	106	108		
					Range	(b) (4)									
					% RSD	-	33.4	24.6	10.9	2.4	2.0	1.2	1.4		

*It is noted that for test product, the % of morphine sulfate released from 1 and 6 tablets is more than (b) (4)%, at 10 and 14 hrs, respectively; and for reference product, the % of morphine sulfate released from 8 and 12 tablets is more than (b) (4)%, at 10 and 14 hrs, respectively.

Dissolution Conditions			Apparatus:		USP Apparatus 1												
			Speed of Rotation:		100 rpm												
			Medium:		0.1N HCl for 1 hour and replace with pH 7.5 Phosphate Buffer												
			Volume:		500 mL												
			Temperature:		37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Firm's Proposed Specifications			1 hr: NMT 10%; 5 hr: (b) (4) %; 7 hr: (b) (4) %; 10 hr: NLT 85%														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)											Study Report Location
						0	0.5	1	2	4	5	6	7	9	10	14	
WSR203 3, p.42 WSR147 5, p.70 WSR203 3, p.40	09/16/09	Test Product Morphine Sulfate ER capsules Lot # 3453R0001 (Mfg. 08/26/2009)	100 mg Capsule	12	Mean	0	0	0	4	-	40	-	74	-	99	102	Section 2.7.1.2; Sequence# 0001 pages 55-56
					Range	(b) (4)											
					% RSD	-	-	-	10.2	-	4.7	-	3.7	-	2.6	3.0	
	09/21/10	Reference Product Kadian Lot # 438E81** (Exp.05/2011)	100 mg Capsule	12	Mean	0	0	1	6	33	49	67	83	101	103	105	
					Range	(b) (4)											
					% RSD	-	233.5	36.2	7.2	2.5	2.1	1.8	1.8	1.5	1.5	1.4	

*It is noted that for test and reference products, the % of morphine sulfate released from 2 and 4 tablets is more than (b) (4) %, at 14 hrs, respectively.

** The lot# 438E81 is different than that used for fed BE study on 100 mg strength (lot #320E71).

Comments:

The dissolution method for this drug product as per USP33-NF 28 is as follow:

Source of Method (USP, FDA or Firm)	USP
Medium	0.1 N HCl for 1 hour, followed by replacing with pH 7.5 Phosphate buffer for NLT 8 hours
Volume (mL)	500 mL
USP Apparatus type	Type I (Basket)
Rotation (rpm)	100 rpm
Sampling Time Points	1, 4, 6 and 9hr
USP-recommended specifications	1 hr: NMT 10%; 4 hr: 25-50%; 6 hr: 50-90%; 9 hr: NLT 85%

- The firm has conducted comparative dissolution testing on all strengths (please refer to [section 3.1.2.1, pages 17-18](#) of this review for dissolution data on 20 mg, 30 mg, 50 mg and 60 mg strengths) using USP-recommended dissolution method, however, for the Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg strengths, the firm has not taken the dissolution samples for morphine sulfate analysis at 4, 6 and 9 hrs as per USP. Firm will be asked to repeat dissolution testing for its test products, 80 mg and 100 mg including sampling times at 4, 6 and 9 hrs similar to 20 mg, 30 mg, 50 mg and 60 mg strengths.
- In addition, the dissolution testing of test and reference products, Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg exhibits more than (b) (4) % of morphine sulfate release from 1-12 tablets of each strength. Firm will be asked to provide the reason(s) for the excessively greater than (b) (4) % release of the morphine sulfate from the test and reference morphine sulfate extended release capsules, 80 mg and 100 mg, and repeat the dissolution testing.
- For comparative dissolution testing on morphine sulfate extended release capsules, 100 mg strength, firm has used the reference product, lot# 438E81 that is different from lot# 320E71 used for fed BE study on 100 mg strength. For future submissions, firm will be requested to conduct the dissolution testing on same lot number as that used for BE study.

3.1.2 Review of Amendment Dated – 09/30/2010**Addition of 20 mg, 30 mg, 50 mg and 60 mg strengths**

In amendment dated 9/30/10, firm requested for a waiver to conduct *in vivo* bioequivalence studies for the 20 mg, 30 mg, 50 mg and 60 mg strengths of morphine sulfate extended release capsules based on (i) acceptable fasting, fed and fasting sprinkle bioequivalence studies on the 80 mg strength and fed bioequivalence study on the 100 mg strength, (ii) acceptable *in vitro* dissolution testing for the 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg strengths, and (iii) proportional similarity of the formulations across 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg strengths.

In this amendment, the firm has provided the following formulation and dissolution data for 20 mg, 30 mg, 50 mg, 60 mg strengths:

3.1.2.1 Formulation Data

Ingredients/Grade	20 mg		30 mg		50 mg		60 mg	
	mg/cap	% w/w (per capsule)	mg/cap	% w/w (per capsule)	mg/cap	% w/w (per capsule)	mg/cap	% w/w (per capsule)
(b) (4)								
² Size “0” CS, hard gelatin capsules, yellow opaque cap printed with “WATSON/3449” and white opaque body printed with “20 mg”.	³ (b) (4)	-	-	-	-	-	-	-
² Size “0” CS, hard gelatin capsules, blue violet opaque cap printed with “WATSON/3450” and white opaque body printed with “30 mg”.	-	-	³ (b) (4)	-	-	-	-	-
² Size “0” CS, hard gelatin capsules, flesh opaque cap printed with “WATSON/3451” and white opaque body printed with “50 mg”.	-	-	-	-	³ (b) (4)	-	-	-
² Size “0” CS, hard gelatin capsules, blue-green opaque cap printed with “WATSON/3452” and white opaque body printed with “60 mg”.	-	-	-	-	-	-	³ (b) (4)	-
Total fill weight (with capsule shell)	99.66	100.0	141.04	100.0	216.2	100.0	262.5	100.0

Ingredients/Grade	80 mg		100 mg		IIG limits (mg)
	mg/cap	%w/w capsule	mg/cap	%w/w capsule	
(b) (4)					
</					

¹ (b) (4) ² The gelatin capsules are manufactured with commonly used excipients. For the quantitative composition of these capsules please refer to the below table on page# 15 of this review.

³ Based on average weight of 50 empty capsule shells.

⁴ Retrieved from DPRF database, ANDA (b) (4) (approved: (b) (4)) (b) (4) contain (b) (4) of Hypromellose 2910/tablet. IIG limits for hypromelloses: 670.04mg
Retrieved from DPRF Database, ANDA (b) (4) (approved: (b) (4)) (b) (4) contain (b) (4) of Povidone K-30/tablet and (b) (4) of Diethyl Phthalate/tablet. The maximum daily dose of this drug product in children 6 yrs of age or older is 2 gm/day. Based on the maximum daily dose of this drug product, the amount of (b) (4) is (b) (4) mg/day and of (b) (4) is (b) (4) mg/day.

The quantitative composition for 20, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg capsules is provided in the table below:

	20 mg	30 mg	50 mg	60 mg	80 mg	100 mg	IIG limits
Capsule Components	mg/caps	mg/caps	mg/caps	mg/caps	mg/caps	mg/caps	(mg)
(b) (4)							

**Based on the breakdown of each individual components and compositions of (b) (4) and (b) (4) – please see the table below – the amount of these inactives in the test formulations are within the acceptable limit based on the maximum daily dose.*

3.1.2.2 Dissolution Data

USP Recommended Dissolution Method

Dissolution Conditions			Apparatus:		USP Apparatus 1												
			Speed of Rotation:		100 rpm												
			Medium:		0.1N HCl for 1 hour and replace with pH 7.5 Phosphate Buffer												
			Volume:		500 mL												
			Temperature:		37 ± 0.5 °C												
Dissolution Testing Site			Watson Laboratories, Inc.– Florida; 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Firm's Proposed Specifications			1 hr: NMT 10%; 5 hr: (b) (4)%; 7 hr: (b) (4)%; 10 hr: NLT 85%														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)											Study Report Location
						0	0.5	1	2	4	5	6	7	9	10	14	
WSR1998, p.52 WSR1554, p.79 WSR1998, p.51	02/11/10	Test Product Morphine Sulfate ER capsules Lot #3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	0	0	3	24	39	55	71	96	100	104	Section 2.7.1.2; Sequence# 0001 pages: 13 - 14
					Range	(b) (4)											
					% RSD	NA	346.4	346.4	21.7	5.3	3.7	3.7	3.3	2.3	2.4	1.8	
	09/14/10	Reference Product Kadian Lot#660E01 (Exp.03/2013)	20 mg Capsule	12	Mean	0	1	3	8	37	56	75	91	105	106	108	
					Range	(b) (4)											
					% RSD	NA	58.4	25.9	10.0	5.5	5.3	5.4	5.0	5.1	5.2	5.2	
WSR2033, p.32 WSR1554, p.64 WSR2033, p.30	02/09/10	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	0	0	3	24	40	56	73	99	103	108	Section 2.7.1.2; Sequence# 0001 pages: 25-26
					Range	(b) (4)											
					% RSD	NA	346.4	346.4	13.9	2.6	2.3	1.5	1.5	2.4	2.4	2.1	
	09/15/10	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	1	2	7	37	55	74	90	102	104	105	
					Range	(b) (4)											
					% RSD	NA	114.6	41.4	15.3	7.3	6.9	6.1	5.9	4.8	4.9	4.7	

Dissolution Conditions			Apparatus:		USP Apparatus 1												
			Speed of Rotation:		100 rpm												
			Medium:		0.1N HCl for 1 hour and replace with pH 7.5 Phosphate Buffer												
			Volume:		500 mL												
			Temperature:		37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Firm's Proposed Specifications			1 hr: NMT 10%; 5 hr: (b) (4) %; 7 hr: (b) (4) %; 10 hr: NLT 85%														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)											Study Report Location
						0	0.5	1	2	4	5	6	7	9	10	14	
WSR2001, p.72 WSR1554, p.72 WSR2001, p.71	02/09/10	Test Product Morphine Sulfate ER capsules Lot#3451R0001 (Mfg.10/23/2009)	50 mg Capsule	12	Mean	0	0	0	3	24	39	56	72	97	102	106	Section 2.7.1.2; Sequence# 0001 pages: 37-38
					Range	(b) (4)											
					% RSD	NA	233.5	180.9	13.9	5.1	4.6	4.0	3.5	2.5	2.1	1.6	
	09/15/10	Reference Product Kadian Lot # 715L91 (Exp.11/2012)	50 mg Capsule	12	Mean	0	0	2	7	37	56	75	90	103	105	107	
					Range	(b) (4)											
					% RSD	NA	160.5	44.9	12.2	3.2	2.7	2.9	2.7	2.8	2.7	3.0	
WSR2041, p.8 WSR1554, p.86 WSR2041, p.6	02/16/10	Test Product Morphine Sulfate ER capsules Lot #3452R0001 (Mfg.10/23/2009)	60 mg Capsule	12	Mean	0	0	0	3	23	38	55	71	97	101	106	Section 2.7.1.2; Sequence# 0001 pages: 49-50
					Range	(b) (4)											
					% RSD	NA	346.4	233.5	14.2	3.3	3.4	3.3	3.0	2.1	1.6	1.2	
	09/16/10	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	60 mg Capsule	12	Mean	0	1	3	9	39	57	76	90	103	105	107	
					Range	(b) (4)											
					% RSD	NA	33.4	12.3	5.7	2.8	2.4	2.2	2.0	1.7	1.8	1.9	

Comments on Dissolution Testing:

The firm has conducted the dissolution testing using USP-recommended dissolution method, however, it is noted that for test and reference products, the % of morphine sulfate released from 20 mg, 30 mg, 50 mg and 60 mg strengths is more than (b) (4) %:

- 20 mg strength: For test product: 3 tablets at 14 hr; and for reference product: 3 tablets at 9 hr, 6 tablets at 10 hr and 8 tablets at 14 hr.
- 30 mg strength: For test product: 2 tablets at 10 hr and 10 tablets at 14 hr; and for reference product: 3 tablets at 9 hr, 4 tablets at 10 hr and 6 tablets at 14 hr.
- 50 mg strength: For test product: 7 tablets at 14 hr; and for reference product: 2 tablets at 9 hr, 6 tablets at 10 hr and 9 tablets at 14 hr.
- 60 mg strength: For test product: 7 tablets at 14 hr; and for reference product: 1 tablets at 9 hr, 2 tablets at 10 hr and 8 tablets at 14 hr.

Firm will be asked to provide the reason(s) for the excessively greater than (b) (4) % release of the morphine sulfate from the test and reference morphine sulfate extended release capsules; 20 mg, 30 mg, 50 mg and 60 mg, and repeat the dissolution testing for these strengths of the test and reference products.

F2 Metrics – USP Recommended Dissolution Media

Test vs. Reference (Whole Capsule)	USP Media	Test vs. Test	USP Media
Test 20 mg vs. Reference 20 mg	47.10	Test 20 mg vs. Test 100 mg	Will be calculated upon firm's response to dissolution deficiencies
Test 30 mg vs. Reference 30 mg	50.42	Test 30 mg vs. Test 100 mg	
Test 50 mg vs. Reference 50 mg	48.88	Test 50 mg vs. Test 100 mg	
Test 60 mg vs. Reference 60 mg	46.42	Test 60 mg vs. Test 100 mg	
Test 80 mg vs. Reference 80 mg	55.94	Test 80 mg vs. Test 100 mg	
Test 100 mg vs. Reference 100 mg	65.05		

Multimedia Dissolution Testing:

pH 1.2

Dissolution Conditions		Apparatus:	USP Apparatus 1													
		Speed of Rotation:	100 rpm													
		Medium:	pH 1.2													
		Volume:	900 mL													
		Temperature:	37 ± 0.5 °C													
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0	1	2	4	6	8	10	12	14	16	
WSR20011, p.48 WSR2001, p.30 WSR2001, p.41	08/16/10	Test Product Morphine Sulfate ER capsules Lot # 3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	0	1	8	13	19	24	30	35	41	Section 2.7.1.2; Sequence# 0001, pages: 4-5
					Range	(b) (4)										
					% RSD	-	-	33.4	12.1	8.0	6.6	4.9	5.2	5.1	4.8	
	08/30/10	Reference Product Kadian Lot # 660E01 (Exp.03/2013)	20 mg Capsule	12	Mean	0	2	6	12	17	22	26	31	36	41	
					Range	(b) (4)										
					% RSD	-	27.7	16.1	6.2	5.8	5.0	4.7	4.6	4.3	4.5	
WSR2001, p.65 WSR1731, p.100 WSR2001, p.27	08/12/10	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	1	2	9	15	21	27	33	39	45	Section 2.7.1.2; Sequence# 0001, pages: 16-17
					Range	(b) (4)										
					% RSD	-	180.9	33.5	11.0	4.8	3.4	3.1	2.6	2.4	2.1	
	08/31/10	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	2	5	12	16	21	26	31	37	42	
					Range	(b) (4)										
					% RSD	-	27.6	14.6	7.6	6.0	4.5	4.8	4.4	3.6	3.5	

Dissolution Conditions			Apparatus:		USP Apparatus 1												
			Speed of Rotation:		100 rpm												
			Medium:		pH 1.2												
			Volume:		900 mL												
			Temperature:		37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location	
						0	1	2	4	6	8	10	12	14	16		
WSR2022, p.37 WSR2022, p.11 WSR2022, p.14	09/02/10	Test Product Morphine Sulfate ER capsules Lot # 3451R0001 (Mfg. 10/23/2009)	50 mg Capsule	12	Mean	0	0	2	9	15	21	27	33	39	46	Section 2.7.1.2; Sequence# 0001, pages: 28- 29	
					Range	(b) (4)											
					% RSD	-	346.4	15.1	15.2	4.2	3.0	2.5	2.7	2.5	2.2		
	09/02/10	Reference Product Kadian Lot # 715L91 (Exp.11/2012)	50 mg Capsule	12	Mean	0	2	5	11	16	20	25	30	35	40		
					Range	(b) (4)											
					% RSD	-	21.2	14.8	8.1	7.0	5.4	5.3	4.9	4.4	3.8		
WSR2033, p.25 WSR2033, p.19 WSR2033, p.22	09/14/10	Test Product Morphine Sulfate ER capsules Lot # 3452R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	0	1	8	14	20	25	31	37	43	Section 2.7.1.2; Sequence# 0001, pages: 40- 41	
					Range	(b) (4)											
					% RSD	-	233.5	36.2	3.6	3.3	2.5	2.6	2.6	2.4	2.8		
	09/14/10	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	3	7	13	18	23	28	33	38	43		
					Range	(b) (4)											
					% RSD	-	16.7	10.5	5.7	3.6	3.9	3.0	2.2	2.3	2		

pH 4.5

Dissolution Conditions		Apparatus:	USP Apparatus 1														
		Speed of Rotation:	100 rpm														
		Medium:	pH 4.5														
		Volume:	900 mL														
		Temperature:	37 ± 0.5 °C														
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331															
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location	
						0	1	2	4	6	8	10	12	14	16		
WSR 2001, P.63 WSR1998, p.20 WSR2001, p.24	08/12/10	Test Product Morphine Sulfate ER capsules Lot # 3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	0	2	8	13	17	22	26	31	35	Section 2.7.1.2; Sequence # 0001, pages: 7-8	
					Range	(b) (4)											
					% RSD	-	-	13.9	8.4	5.6	5.7	5.5	5.9	5.3	5.4		
	08/30/10	Reference Product Kadian Lot # 660E01 (Exp.03/2013)	20 mg Capsule	12	Mean	0	2	6	12	17	22	26	30	33	37		
					Range	(b) (4)											
					% RSD	-	21.3	13.1	9.3	7.8	7.3	7.3	6.3	6.4	6.6		
WSR2001, p.49 WSR1998, p.22 WSR2001, p.38	08/12/10	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	0	2	8	14	18	23	27	32	37	Section 2.7.1.2; Sequence # 0001, pages: 19- 20	
					Range	(b) (4)											
					% RSD	-	180.9	27.9	7.8	5.0	3.7	3.0	1.8	2.3	2.6		
	09/01/10	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	2	6	12	17	22	27	31	35	39		
					Range	(b) (4)											
					% RSD	-	24.7	12.3	6.6	4.6	4.4	3.4	3.1	3.3	3.1		

Dissolution Conditions		Apparatus:		USP Apparatus 1												
		Speed of Rotation:		100 rpm												
		Medium:		pH 4.5												
		Volume:		900 mL												
		Temperature:		37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0	1	2	4	6	8	10	12	14	16	
WSR2022, p.27 WSR2022, p.18 WSR2022, p.21	09/07/10	Test Product Morphine Sulfate ER capsules Lot # 3451R0001 (Mfg. 10/23/2009)	50 mg Capsule	12	Mean	0	0	2	8	12	17	21	25	29	33	Section 2.7.1.2; Sequence # 0001, pages: 31-32
					Range	(b) (4)										
					% RSD	NA	346.4	0.0	5.8	4.0	2.7	3.2	2.7	3.0	2.3	
	09/07/10	Reference Product Kadian Lot # 715L91 (Exp.11/2012)	50 mg Capsule	12	Mean	0	1	5	11	16	20	25	29	32	36	
					Range	(b) (4)										
					% RSD	NA	36.2	5.7	3.9	3.8	3.6	2.7	3.3	4.0	2.8	
WSR2025, p.34 WSR2025, p.31 WSR2025, p.28	09/10/10	Test Product Morphine Sulfate ER capsules Lot # 3452R0001 (Mfg. 10/23/2009)	60 mg Capsule	12	Mean	0	0	2	7	12	16	20	25	29	33	Section 2.7.1.2; Sequence # 0001, pages: 43-44
					Range	(b) (4)										
					% RSD	NA	346.4	0.0	6.9	3.2	4.1	3.8	3.3	3.5	2.4	
	09/10/10	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	60 mg Capsule	12	Mean	0	2	6	12	17	21	26	29	33	37	
					Range	(b) (4)										
					% RSD	NA	13.9	6.7	2.4	3.5	3.1	3.1	2.7	2.0	2.5	

pH 6.8

Dissolution Conditions		Apparatus:	USP Apparatus 1													
		Speed of Rotation:	100 rpm													
		Medium:	pH 6.8													
		Volume:	900 mL													
		Temperature:	37 ± 0.5 °C													
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0	1	2	4	6	8	10	12	14	16	
WSR 2001, p.64 WSR 2001, p.32 WSR 2001, p.44	08/16/2010	Test Product Morphine Sulfate ER capsules Lot # 3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	1	9	31	56	81	97	102	103	103	Section 2.7.1.2; Sequence # 0001, pages: 10- 11
					Range	(b) (4)										
					% RSD	-	82.9	11.5	6.4	4.8	3.5	2.6	2.3	2.2	2.1	
	08/31/2010	Reference Product Kadian Lot # 660E01 (Exp.03/2013)	20 mg Capsule	12	Mean	0	4	13	33	55	78	96	104	105	106	
					Range	(b) (4)										
					% RSD	-	20.5	10.3	5.3	5.3	4.4	4.2	4.0	4.0	4.0	
WSR2001, p.53 WSR1731, p.96 WSR2001, p.47	08/11/10	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	1	10	32	58	83	99	104	105	105	Section 2.7.1.2; Sequence # 0001, pages: 22- 23
					Range	(b) (4)										
					% RSD	-	49.5	10.0	3.9	2.7	2.2	1.9	1.9	1.8	1.9	
	09/01/10	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	4	13	32	54	76	94	102	105	105	
					Range	(b) (4)										
					% RSD	-	13.9	4.9	3.1	2.5	2.2	1.9	2.0	2.1	2.3	

It is noted that for test product, 20 mg strength, the % morphine released from 2 tablets is more than (b) (4)%, at 12, 14 and 16 hrs, and for reference product, 20 mg, the % morphine released from 3, 7 and 7 tablets is more than (b) (4)%, at 12, 14 and 16 hrs, respectively.

For test product, 30 mg strength, the % morphine released from 3, 4 and 5 tablets is more than (b) (4)%, at 12, 14 and 16 hrs, respectively; and for reference product, 30 mg, the % morphine released from 1, 4 and 5 tablets is more than (b) (4)%, at 12, 14 and 16 hrs, respectively.

Dissolution Conditions		Apparatus:		USP Apparatus 1												
		Speed of Rotation:		100 rpm												
		Medium:		pH 6.8												
		Volume:		900 mL												
		Temperature:		37 ± 0.5 °C												
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0	1	2	4	6	8	10	12	14	16	
WSR2033, p.16 WSR2033, p.13 WSR 2033, p.10	09/13/10	Test Product Morphine Sulfate ER capsules Lot # 3451R0001 (Mfg. 10/23/2009)	50 mg Capsule	12	Mean	0	1	9	31	56	82	100	105	106	106	Section 2.7.1.2; Sequence # 0001, pages: 34-35
					Range	(b) (4)										
					% RSD	NA	0.0	7.4	5.9	4.5	4.2	3.4	2.8	2.6	2.6	
	09/13/10	Reference Product Kadian Lot # 715L91 (Exp.11/2012)	50 mg Capsule	12	Mean	0	4	12	31	52	74	93	102	105	105	
					Range	(b) (4)										
					% RSD	NA	19.3	6.9	4.9	4.5	4.1	3.9	3.5	3.3	3.0	
WSR2025, p.23 WSR2025, p.20 WSR2025, p.17	09/09/10	Test Product Morphine Sulfate ER capsules Lot # 3452R0001 (Mfg. 10/23/2009)	60 mg Capsule	12	Mean	0	1	9	29	53	79	97	103	104	104	Section 2.7.1.2; Sequence # 0001, pages: 46-47
					Range	(b) (4)										
					% RSD	NA	60.3	9.4	4.0	2.8	2.8	2.1	1.6	1.4	2.2	
	09/09/10	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	60 mg Capsule	12	Mean	0	4	13	32	53	74	91	100	102	102	
					Range	(b) (4)										
					% RSD	NA	11.4	4.6	2.1	2.2	1.8	1.9	2.2	2.3	2.4	

It is noted that for test product, 50 mg strength, the % morphine released from 4, 8 and 8 tablets is more than (b) (4)%, at 12, 14 and 16 hrs, respectively; and for reference product, 50 mg strength, the % morphine released from 3, 6 and 6 tablets is more than (b) (4)%, at 12, 14 and 16 hrs, respectively.

For test product, 60 mg strength, the % morphine released from the 1, 2 and 2 tablets is more than (b) (4)%, at 12, 14 and 16 hrs, respectively; and for reference product, 60 mg strength, the % morphine released from the 1 tablet is more than (b) (4)%, at 16 hrs.

F2 Metrics Test Vs Reference – Multi Media Dissolution Testing

Whole Capsule	pH 1.2	pH 4.5 Buffer	pH 6.8 Buffer
Test 20 mg vs. Reference 20 mg	76.64	72.40	79.35
Test 30 mg vs. Reference 30 mg	82.97	73.39	72.84
Test 50 mg vs. Reference 50 mg	75.67	74.57	69.37
Test 60 mg vs. Reference 60 mg	73.11	68.09	72.84
Test 80 mg vs. Reference 80 mg	73.20	66.39	61.21
Test 100 mg vs. Reference 100 mg	59.44	80.19	56.10
Test 20 mg vs. Reference 80 mg	77.29	65.86	60.36
Test 30 mg vs. Reference 80 mg	78.87	69.43	56.63
Test 50 mg vs. Reference 80 mg	77.15	62.54	56.85
Test 60 mg vs. Reference 80 mg	78.72	61.34	62.61
Test 20 mg vs. Reference 100 mg	86.09	81.16	62.37
Test 30 mg vs. Reference 100 mg	78.42	83.43	57.97
Test 50 mg vs. Reference 100 mg	76.76	80.19	57.55
Test 60 mg vs. Reference 100 mg	83.91	81.10	63.44
Test 80 mg vs. Reference 100 mg	71.90	83.91	62.34

F2 Metrics Test Vs. Test - MultiMedia Dissolution Testing

Whole Capsule	pH 1.2	pH 4.5 Buffer	pH 6.8 Buffer
Test 20 mg vs. Test 80 mg	72.24	98.97	93.03
Test 30 mg vs. Test 80 mg	91.44	93.62	83.67
Test 50 mg vs. Test 80 mg	93.62	91.44	84.95
Test 60 mg vs. Test 80 mg	79.35	88.44	95.60
Test 20 mg vs. Test 100 mg	59.55	82.75	76.89
Test 30 mg vs. Test 100 mg	69.24	90.49	82.53
Test 50 mg vs. Test 100 mg	70.31	75.44	75.11
Test 60 mg vs. Test 100 mg	63.40	74.27	69.24
Test 80 mg vs. Test 100 mg	75.22	83.43	72.24

Comments on Multimedia Dissolution Testing:

The firm has conducted acceptable dissolution testing on 20 mg, 30 mg, 50 mg and 60 strength in three different pH media (pH 1.2, pH 4.5 and pH 6.8). The f2 values indicate that the release of drug from the test formulations is comparable to RLD products under three different pH conditions. The firm has previously conducted acceptable dissolution testing on 80 mg and 100 strengths as well in three different pH media (pH 1.2, pH 4.5 and pH 6.8) (DARRTS, ANDA 200812, REV-BIOEQ-01 (General Review), final date: 9/21/10).

Comments on In vitro alcohol dose-dumping:

The firm has previously submitted acceptable *in vitro* alcohol dose-dumping testing data using the FDA-recommended method for Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg strengths (DARRTS, ANDA 200812, REV-BIOEQ-01 (General Review), final date: 9/21/10). However, firm has not submitted the in vitro alcohol dose-dumping data for 20 mg, 30 mg, 50 mg and 60 mg strengths. Firm will be asked to conduct the in vitro alcohol dose-dumping testing for the Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg and 60 mg strengths as well as per the Individual Product Bioequivalence Recommendations for this drug product posted on FDA's website at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm088709.pdf> (last revised: May 2010)

3.2 Deficiency Comments

1. The firm has conducted dissolution testing using the USP-recommended dissolution method for this drug product, however, for the Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg strengths, firm has not taken the dissolution samples for morphine sulfate analysis at 4, 6 and 9 hrs as per USP. Firm will be asked to repeat dissolution testing for its test products, 80 mg and 100 mg including sampling times at 4, 6, and 9 hrs similar to 20 mg, 30 mg, 50 mg and 60 mg strengths.
2. The dissolution testing of test and reference products, Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg exhibits more than (b) (4) % of morphine sulfate release from 1 to 12 tablets of each strength. Firm is requested to provide the reason(s) for the excessively greater than (b) (4) % release of the morphine sulfate from the test and reference morphine sulfate extended release capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg, and repeat the dissolution testing for all these strengths of the test and reference products.
3. The firm should conduct in vitro alcohol dose dumping study on the 20 mg, 30 mg, 50 mg and 60 mg strengths using the following testing conditions:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution profiles.

3.3 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study R09-0072 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot# 3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
2. The Division of Bioequivalence accepts the fed BE study R09-0073 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot#3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
3. The Division of Bioequivalence accepts the fasting sprinkle BE study R09-0074 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot#3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
4. The Division of Bioequivalence accepts fed BE study R09-0905 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 100 mg, lot# 3453R0001B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 100 mg, lot #320E71.
5. The dissolution testing conducted by Watson Laboratories on its test product, Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg is incomplete due to deficiencies# 1 and 2 mentioned above.
6. The dissolution testing conducted by Watson Laboratories on its test product, Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg and 60 mg is incomplete due to deficiency# 2 mentioned above.
7. The application is incomplete due to the above mentioned deficiencies.

3.4 Comments for Other OGD Disciplines

Discipline	Comment
	None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg.

The Division of Bioequivalence (DBE) has completed its review as noted on the cover page, and the following deficiencies have been identified.

1. The DBE acknowledges that you have conducted dissolution testing using the USP-recommended dissolution method for Morphine Sulfate Extended Release Capsules. However, for the Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg strengths, you did not sample dissolution at 4, 6 and 9 hours as per the USP. Please repeat dissolution testing for 80 mg and 100 mg strengths including sampling times at 4, 6, and 9 hours similar to 20 mg, 30 mg, 50 mg and 60 mg strengths.
2. A number of units released more than (b) (4)% for both test and reference products. Please provide the reason(s) for the higher than expected release for both the test and reference morphine sulfate extended release capsules for the following strengths: 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg. Please repeat the dissolution testing for all these strengths of the test and reference products.
3. Please conduct in vitro alcohol dose dumping study on the 20 mg, 30 mg, 40 mg and 50 mg strengths using the following testing conditions:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution profiles.

Additional comment for future submissions:

For comparative dissolution testing on morphine sulfate extended release capsules, 100 mg strength using USP-recommended dissolution method, you used reference product lot# 438E81, which was not the lot used for the fed BE study on the 100 mg strength. For future submissions, please conduct the dissolution testing using same lot number for test and reference products that is used for the BE study.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4 Outcome Page

ANDA: 200812

Completed Assignment for 200812 ID: 12845

Productivity:

Reviewer: Kaur, Paramjeet

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Morphine Sulfate Extended Release Capsules

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
12845	12/9/10	Other	Study Amendment	1	1	Edit	Delete
12845	12/9/10	Other	Dissolution Amendment	1	1	Edit	Delete
12845	9/30/10	Other	Dissolution Waiver	1	1	Edit	Delete
12845	9/30/10	Other	Dissolution Waiver	1	1	Edit	Delete
12845	9/30/10	Other	Dissolution Waiver	1	1	Edit	Delete
12845	9/30/10	Other	Dissolution Waiver	1	1	Edit	Delete
				Bean Total:	6		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment-dated 12/9/10	
Study Amendment-deficiency comments-dated 12/9/2010	1
Dissolution Study (Not part of dissolution review)	1
Study Amendment-dated 9/30/10	
Strength 1 (DIW)	0.5
Strength 2 (DIW)	0.5
Strength 3 (DIW)	0.5
Strength 4 (DIW)	0.5
Total number of Complexity Points	4.0

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHANDRA S CHAURASIA

03/15/2011

ETHAN M STIER on behalf of BARBARA M DAVIT

03/22/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200812			
Drug Product Name	Morphine Sulfate Extended-Release Capsules, USP			
Strength(s)	20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg			
Applicant Name	Watson Laboratories Inc.			
Address	4955 Orange Drive Ft. Lauderdale, FL 33314			
Applicant's Point of Contact	Alberto E. Rivalta, Manager Regulatory Affairs			
Contact's Telephone Number	(954) 358-6109			
Contact's Fax Number	(954) 358-6350			
Original Submission Date(s)	December 16, 2009			
Submission Date(s) of Amendment(s) Under Review	September 30, 2010 December 09, 2010 May 18, 2011			
Reviewer	Chandra S. Chaurasia, Ph.D.			
Study Number (s) ¹	R09-0072	R09-0073	R09-0074	R09-0905
Study Type (s)	Fasting	Fed	Fasting sprinkle-in-applesauce	Fed
Strength (s)	80 mg	80 mg	80 mg	100 mg
Clinical Site	Cetero Research			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	(b) (4)			
Analytical Site Address				
OUTCOME DECISION	INADEQUATE			

OVERALL REVIEW RESULT	INADEQUATE
WAIVER REQUEST RESULT	INADEQUATE
DSI REPORT RESULT	ADEQUATE

¹ The firm submitted fasting (80 mg), fed (80 mg and 100 mg) and fasting sprinkle-in-applesauce BE studies (80 mg) on 12/16/09 before posting of current revised individual product recommendations for this drug product in May 2010, which recommends six BE studies, namely, fasting (10 mg, 100 mg and 200 mg), fed (100 mg and 200 mg) and fasting sprinkle-in-applesauce (100 mg); and waiver of 20 mg, 30 mg, 50 mg, 60 mg and 80 mg strengths based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) acceptable in vitro dissolution testing for all the strengths, and (iii) proportional similarity of formulations across all strengths. Since BE studies were conducted prior to posting of revised BE recommendations for this drug product, therefore waiver of 20 mg, 30 mg, 50 mg, 60 mg strengths based on fasting (80 mg), fed (80 mg and 100 mg) and fasting sprinkle-in-applesauce BE studies (80 mg) should be acceptable.

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1 & 4	FASTING STUDY	80 mg	ADEQUATE
1 & 4	FED STUDY	80 mg	ADEQUATE
1 & 4	FASTING SPRINKLE STUDY	80 mg	ADEQUATE
1 & 4	FED STUDY	100 mg	ADEQUATE
1, 2 & 8	DISSOLUTION	80 mg and 100 mg	INADEQUATE
2 & 8	DISSOLUTION	20 mg, 30 mg, 50 mg and 60 mg	INADEQUATE

REVIEW OF A STUDY AMENDMENT

1 EXECUTIVE SUMMARY

In the original submission dated December 16, 2009, the firm conducted fasting, fed and fasting sprinkle bioequivalence (BE) studies comparing Watson Laboratories' test product, Morphine Sulfate Extended Release Capsules, 80 mg, to the corresponding Actavis Elizabeth's reference product, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg strength. In addition, the firm submitted a fed study comparing Watson Laboratories' test product, Morphine Sulfate Sustained Release Capsules, 100 mg, to the corresponding Actavis Elizabeth's reference product, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 100 mg strength. The bioequivalence (fasting, fed and fasting sprinkle) studies were found acceptable; however, the application was found to be incomplete due to (i) bioanalytical deficiencies, (ii) formulation deficiency, and (iii) dissolution deficiency [DARRTS N200812, REV-BIOEQ-01(General Review), dated 9/21/2010]. In subsequent amendments dated 9/30/10 and 12/09/10, the firm provided acceptable responses to the bioanalytical and formulation deficiencies. However, the application was still incomplete due to (i) dissolution deficiencies on the 80 mg and 100 mg strength, (ii) greater than (b) (4) % drug release from all the strengths of test and reference products, and (ii) in vitro alcohol dose-dumping deficiency.

In the current amendment dated May 18, 2011, the firm has responded to these deficiencies. The firm's dissolution testing data with the USP method are acceptable. However, the firm's proposed specifications (1hr: NMT 10%; 4 hrs: (b) (4) %; 6 hrs: (b) (4) %; 9 hrs: NLT 85%), which are different from the USP are not acceptable. Based on the submitted data, the Division of Bioequivalence (DBII) recommends the following specifications:

Time (hr.)	DBII Recommended Specifications
1 hr	NMT 10%
4 hrs	(b) (4) %
6 hrs	%
9 hrs	NLT 85%

The firm should acknowledge the FDA-recommended dissolution method and specifications.

The firm has previously conducted acceptable dissolution testing on all strengths under different pH conditions (pH 1.2, pH 4.5 buffer and pH 6.8 buffer). The test products demonstrate no potential for dose-dumping.

The firm also conducted in vitro alcohol dose-dumping test on all strengths² of the test and reference product, using the following dissolution method: 900 mL, 0.1N HCl, USP Apparatus I (basket) at 100 rpm, with addition of 0%, 5%, 20% and 40% of alcohol to the dissolution media. The risk of dose-dumping from generic product is no more than that for the reference product.

The application is incomplete pending firm's acknowledgement of FDA-recommended dissolution method and specifications.

²Results of in vitro alcohol dose-dumping test conducted on 80 mg and 100 mg strengths are archived in DARRTS, ANDA 200812, REV-BIOEQ-01(General Review), dated 9/21/2010.

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3 SUBMISSION SUMMARY

3.1 Review of Submission

Deficiency Comment# 1:

The Division of Bioequivalence acknowledges that you have conducted dissolution testing using the USP-recommended dissolution method for Morphine Sulfate Extended Release Capsules. However, for the Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg strengths, you did not sample dissolution at 4, 6 and 9 hours as per the USP. Please repeat dissolution testing for 80 mg and 100 mg strengths including sampling times at 4, 6, and 9 hours similar to 20 mg, 30 mg, 50 mg and 60 mg strengths.

Firm's Response to the Deficiency Comment# 1:

The firm has performed the dissolution profile testing for the 80 mg and 100 mg strengths of the drug product with sampling times at 4, 6 and 9 hours. The data is provided in **Section 2.7.1.2** of this amendment.

Based on the dissolution data for all the strengths of the drug product, the firm is proposing the following dissolution specifications

Current Proposed Specification	
Time (Hr.)	Specification
1	NMT 10 %
4	(b) (4) %
6	(b) (4) %
9	NLT 85 %

Reviewer's Comment on the Deficiency# 1:

The firm has provided the following dissolution data for the 80 mg and 100 mg strengths using USP-recommended dissolution method:

Dissolution Conditions			Apparatus:		USP Apparatus 1													
			Speed of Rotation:		100 rpm													
			Medium:		0.1N HCl for 1 hour and replace with pH 7.5 Phosphate Buffer													
			Volume:		500 mL													
			Temperature:		37 ± 0.5 °C													
Dissolution Testing Site			Watson Laboratories, Inc.– Florida; 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331															
Firm's Proposed Specifications			1 hr: NMT 10%; 4 hr: (b) (4) %; 6 hr: (b) (4) %; 9 hr: NLT 85%															
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (hours)												Study Report Location	
					0	0.5	1	2	4	5	6	7	9	10	14			
WSR2211 page 51	04/12/11	Test Product Morphine Sulfate ER capsules Lot# 3576R0013 (Mfg. 10/23/2009)	80 mg Capsule	12	Mean	0	0	1	4	26	41	58	74	96	101	104	Modules 2.7.1.2	
					Range	(b) (4)												
					% RSD	NA	180.9	104.4	15	4.0	3.8	3.5	3.4	2.5	2.1	1.9		
WSR2284 Page 51	05/03/11	Reference Product Kadian Lot # 510M81 (Exp. 03/2013)	80 mg Capsule	12	Mean	0	1	2	8	37	54	72	87	103	105	107		
					Range	(b) (4)												
					% RSD	NA	97.7	18.0	6.4	2.2	1.7	1.8	1.9	2.0	2.3	2.5		

*For test product, 80 mg at 14 hr sampling time point, the % of drug released from 5 tablets is greater than (b) (4)%. For reference product, 80 mg at 9 hr, 10 hr, and 17 hr sampling time points, the % of drug released from 1, 6, and 8 tablets, respectively, is greater than (b) (4)%.

Dissolution Conditions			Apparatus:		USP Apparatus 1														
			Speed of Rotation:		100 rpm														
			Medium:		0.1N HCl for 1 hour and replace with pH 7.5 Phosphate Buffer														
			Volume:		500 mL														
			Temperature:		37 ± 0.5 °C														
Dissolution Testing Site			Watson Laboratories, Inc.– Florida; 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331																
Firm's Proposed Specifications			1 hr: NMT 10%; 4 hr: (b) (4) %; 6 hr: (b) (4) %; 9 hr: NLT 85%																
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)											Study Report Location		
						0	0.5	1	2	4	5	6	7	9	10	14			
WSR2033 Page 94	04/11/11	Test Product Morphine Sulfate ER capsules Lot# 3453R0001 (Mfg. 8/26/2009)	100 mg Capsule	12	Mean	0	0	0	4	26	42	59	75	96	100	104	Modules 2.7.1.2		
					Range	(b) (4)													
					% RSD	NA	NA	19.3	5.4	5.4	4.3	3.4	3.2	2.4	2.2	2.2			
WSR2266 Page 37	05/03/11	Reference Product Kadian Lot # 320E71 (Exp. 03/2013)	100 mg Capsule	12	Mean	0	0	1	6	36	54	72	87	101	103	104			
					Range	(b) (4)													
					% RSD	NA	NA	26.6	4.7	2.2	2.5	1.8	1.7	1.7	1.9	2.1			

For test product, 100 mg at 14 hr sampling time point, the % of drug released from 4 tablets is greater than (b) (4) %. For reference product, 100 mg at 10 hr and 14 hr sampling time points, the % of drug released from 1 and 3 tablets, respectively, is greater than (b) (4) %.

The dissolution method for this drug product as per USP34-NF 29 is as follow:

Source of Method (USP, FDA or Firm)	USP
Medium	0.1 N HCl for 1 hour, followed by replacing with pH 7.5 phosphate buffer for NLT 8 hours
Volume (mL)	500 mL
USP Apparatus type	Type I (Basket)
Rotation (rpm)	100 rpm
Sampling Time Points	1, 4, 6 and 9 hr
USP-recommended specifications	1 hr: NMT 10%; 4 hr: 25-50%; 6 hr: 50-90%; 9 hr: NLT 85%

The firm has previously conducted the dissolution testing on 20 mg, 30 mg, 40 mg, and 50 strengths using USP dissolution method (DARRTS N200812, REV-BIOEQ-01(General Review), dated 3/22/11), which was found incomplete due to greater than (b) (4) % drug release from some units of test and reference products as mentioned in the deficiency comment# 2 below. The f2 values for all the strengths of test vs. reference product and test vs. biostudy strengths in the USP recommended dissolution media are listed in the table below:

Test vs. Reference (Whole Capsule)	F2	Other Strengths vs. Biostudy Strength Test	F2	Other Strengths vs. Biostudy Strength Test	F2
Test 20 mg vs. Reference 20 mg	47.10	Test 20 mg vs. Test 80 mg	85.22	Test 20 mg vs. Test 100 mg	81.30
Test 30 mg vs. Reference 30 mg	50.42	Test 30 mg vs. Test 80 mg	82.31	Test 30 mg vs. Test 100 mg	79.51
Test 50 mg vs. Reference 50 mg	48.88	Test 50 mg vs. Test 80 mg	86.71	Test 50 mg vs. Test 100 mg	82.31
Test 60 mg vs. Reference 60 mg	46.42	Test 60 mg vs. Test 80 mg	81.89	Test 60 mg vs. Test 100 mg	78.27
Test 80 mg vs. Reference 80 mg	53.02	Test 100 mg vs. Test 80 mg	95.60		
Test 100 mg vs. Reference 100 mg	55.44				

Please refer to below table summarizing the % mean (range) of morphine sulfate dissolved at 1 hr, 4 hr, 6 hr and 9 hr sampling time points for different strengths of test product:

Time point (hrs)	20 mg	30 mg	50 mg	60 mg	80 mg	100 mg
1 hr	0 (b) (4)	0 (b) (4)	0 (b) (4)	0 (b) (4)	(b) (4)	0 (b) (4)
4 hrs	24	24	24	23	26	26
6 hrs	55	56	56	55	58	59
9 hrs	96	99	97	97	96	96

The firm has conducted acceptable dissolution testing on all strengths using USP dissolution method. However, the firm's proposed specifications, which are different from the USP specifications (see table below) are not acceptable.

Time (hr.)	USP Specifications	Firm's Proposed specifications
1 hr	NMT 10%	NMT 10%
4 hrs	25%-50%	(b) (4)%
6 hrs	50%-90%	%
9 hrs	NLT 85 %	NLT 85%

Based on the submitted dissolution data, the Division of Bioequivalence II (DBII) recommends the following specifications:

Time (hr.)	DBII Recommended Specifications
1 hr	NMT 10%
4 hrs	(b) (4)%
6 hrs	%
9 hrs	NLT 85%

Deficiency Comment# 2:

A number of units released more than (b) (4)% for both test and reference products. Please provide the reason(s) for the higher than expected release for both the test and reference morphine sulfate extended release capsules for the following strengths: 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg. Please repeat the dissolution testing for all these strengths of the test and reference products.

Firm's Response to the Deficiency Comment# 2:

Evaluation of the data shows that values at the last time point (9 hours) proposed for dissolution testing range from (b) (4)% (none above (b) (4)%) for the test drug, and (b) (4) % for the reference. An investigation into the possible reasons for values

greater than (b) (4) % reveals that the most likely causes are the true level of the active in the tablet and/or evaporation of the medium, particularly at the later time points. In Table 1 below it is clear that there is a correlation between the content uniformity data (amount active per tablet) and the dissolution results. High content uniformity values consistently yield high dissolution values, particularly for the reference drug. Thus, the dissolution data reflects the variation observed for content uniformity.

Table 1: Content Uniformity and % dissolved at 9 hr sampling time point for all strengths of test and reference product.

Strengths	Test Product Observed Data (%)		Reference Product Observed Data (%)	
	Content Uniformity	Dissolution (9 hr time point)	Content Uniformity	Dissolution (9 hr time point)
20 mg	100.6 (b) (4)	96 (b) (4)	101.2 (b) (4)	105 (b) (4)
30 mg	103.5* (b) (4)	99	102.4	102
50 mg	102.2 (b) (4)	97	100.6	103
60 mg	102.0	97	101.4	103
80 mg	103.5	96	103.2	103
100 mg	100.7	96	101.1	101

*Corrected by reviewer based on the content uniformity data in Module 2.7.1.2

The dissolution values further increase after the 9 hour time point, indicating that evaporation of the medium may also contribute to the high values observed particularly at the 10 and 14 hour time points. It should be noted however that there is no upper limit for dissolution at the last time point and all dissolution profiles meet the proposed acceptance criteria.

Therefore, a repeat of the dissolution testing for all strengths of the drug product will not provide any additional information. This is confirmed by the repeat dissolution testing of the 80 and 100 mg strengths (as requested in the deficiency comment #1) which resulted in data consistent with that previously submitted for 80 mg and 100 mg strengths.

Reviewer's Comment on the Deficiency# 2:

The firm attributed greater than (b) (4) % release of drug at 9 hr sampling time point and thereafter to high content uniformity values and evaporation of dissolution medium, which is acceptable.

The firm's response to deficiency comment# 2 is acceptable.

Deficiency Comment# 3:

Please conduct in vitro alcohol dose dumping study on the 20 mg, 30 mg, 40 mg and 50mg strengths using the following testing conditions:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution profiles.

Firm's Response to the Deficiency Comment# 3:

The firm has performed in vitro alcohol dose dumping studies on the 20 mg, 30 mg, 50 mg and 60 mg strengths of the drug product as requested by the agency. The dissolution profile data is provided in **Section 2.7.1.2.**

Reviewer's Comment on the Deficiency# 3:

The firm has provided the results of in vitro alcohol-dose dumping study on 20 mg, 30 mg, 40 mg, and 50 mg strengths in Module 2.7.1.2 summarized in the tables below:

Dissolution Medium: 0.1N HCl

Dissolution Conditions		Apparatus:		USP Apparatus 1										
		Speed of Rotation:		100 rpm					Medium:			0.1N HCl		
		Volume:		900 mL										
		Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location
						15	30	45	60	75	90	105	120	
WSR2287, page 9	4/13/11	Test Product Morphine Sulfate ER capsules Lot # 3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	0	0	0	0	0	0	1	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	346.4	346.4	346.4	346.4	346.4	346.4	248.6	
WSR2287, page 13	4/14/11	Reference Product Kadian Lot # 660E01 (Exp. 03/2013)	20 mg Capsule	12	Mean	0	1	2	3	4	5	5	6	
					Range	(b) (4)								
					% RSD	190.3	128.7	69.3	30.9	26.1	21.7	20.0	16.9	
WSR2298 page 12	4/19/11	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	0	1	0	0	0	0	0	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	346.4	NA	NA	NA	NA	239.1	
	4/19/11	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	1	1	2	3	4	4	5	6	
					Range	(b) (4)								
					% RSD	97.7	88.3	43.1	49.5	19.3	13.9	10.1	10.1	

Dissolution Conditions			Apparatus:		USP Apparatus 1										
			Speed of Rotation:		100 rpm										
			Medium:		0.1N HCl										
			Volume:		900 mL										
			Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location	
						15	30	45	60	75	90	105	120		
WSR1998 page 95	4/22/11	Test Product Morphine Sulfate ER capsules Lot # 3451R0001 (Mfg. 10/23/2009)	50 mg Capsule	12	Mean	0	0	0	0	0	0	1	1	Module 2, Section 2.7.1.2	
					Range	(b) (4)									
					% RSD	NA	NA	346.4	233.5	233.5	233.5	0.0	36.9		
	4/22/11	Reference Product Kadian Lot # 715L91 (Exp. 11/2012)	50 mg Capsule	12	Mean	0	0	1	2	3	3	4	5		
					Range	(b) (4)									
					% RSD	NA	147.7	60.3	25.8	19.9	14.8	10.6	11.2		
WSR2266 page 25	4/25/11	Test Product Morphine Sulfate ER capsules Lot # 3452R0001 (Mfg. 10/23/2009)	60 mg Capsule	12	Mean	0	0	0	0	0	0	1	2	Module 2, Section 2.7.1.2	
					Range	(b) (4)									
					% RSD	NA	NA	NA	346.4	346.4	346.4	114.6	29.5		
	4/25/11	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	60 mg Capsule	12	Mean	0	1	2	3	4	5	6	7		
					Range	(b) (4)									
					% RSD	346.4	NA	15.1	9.9	12.1	9.5	8.7	9.8		

Dissolution Conditions		Apparatus:		USP Apparatus 1										
		Speed of Rotation:		100 rpm										
		Medium:		5% Ethanol in 0.1N HCl										
		Volume:		900 mL										
		Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location
						15	30	45	60	75	90	105	120	
WSR2287, page 16	4/15/11	Test Product Morphine Sulfate ER capsules Lot # 3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	0	0	0	0	0	0	0	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	NA	NA	NA	NA	NA	346.4	
WSR2287, page 19	4/15/11	Reference Product Kadian Lot # 660E01 (Exp. 03/2013)	20 mg Capsule	12	Mean	1	1	3	5	6	7	8	9	
					Range	(b) (4)								
					% RSD	180.9	125.2	50.7	22.2	19.8	17.3	15.1	13.3	
WSR2033 page 99	4/29/11	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	0	0	0	0	0	1	2	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	346.4	346.4	346.4	346.4	346.4	248.6	49.7	27.6	
	4/29/11	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	0	1	2	3	5	6	7	
					Range	(b) (4)								
					% RSD	180.9	180.9	36.9	21.1	14.8	11.6	9.2	7.4	

Dissolution Conditions			Apparatus:		USP Apparatus 1										
			Speed of Rotation:		100 rpm										
			Medium:		5% Ethanol in 0.1N HCl										
			Volume:		900 mL										
			Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location	
						15	30	45	60	75	90	105	120		
WSR2298 page 18	4/22/11	Test Product Morphine Sulfate ER capsules Lot # 3451R0001 (Mfg. 10/23/2009)	50 mg Capsule	12	Mean	0	0	0	0	0	1	2	3	Module 2, Section 2.7.1.2	
					Range	(b) (4)									
					% RSD	NA	NA	NA	NA	233.5	114.6	21.3	17.7		
	4/22/11	Reference Product Kadian Lot # 715L91 (Exp. 11/2012)	50 mg Capsule	12	Mean	0	0	1	2	3	4	5	6		
					Range	(b) (4)									
					% RSD	346.4	NA	58.4	20.1	19.5	15.0	12.2	10.4		
WSR2285 page 28	4/25/11	Test Product Morphine Sulfate ER capsules Lot # 3452R0001 (Mfg. 10/23/2009)	60 mg Capsule	12	Mean	0	0	0	0	0	1	1	2	Module 2, Section 2.7.1.2	
					Range	(b) (4)									
					% RSD	NA	346.4	346.4	346.4	233.5	26.6	33.4	13.9		
	4/25/11	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	60 mg Capsule	12	Mean	1	2	3	4	5	6	6	9		
					Range	(b) (4)									
					% RSD	73.9	42.2	41.4	25.4	16.5	15.5	13.4	13.7		

Dissolution Conditions		Apparatus:		USP Apparatus 1										
		Speed of Rotation:		100 rpm										
		Medium:		20% Ethanol in 0.1N HCl										
		Volume:		900 mL										
		Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location
						15	30	45	60	75	90	105	120	
WSR2285, page 29	4/26/11	Test Product Morphine Sulfate ER capsules Lot # 3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	0	0	0	1	5	6	7	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	NA	346.4	182.3	14.6	15.7	13.4	
WSR2290, page 4	4/15/11	Reference Product Kadian Lot # 660E01 (Exp. 03/2013)	20 mg Capsule	12	Mean	1	2	5	8	10	13	16	19	
					Range	(b) (4)								
					% RSD	346.4	154.2	26.6	22.5	18.2	14.1	11.5	9.8	
WSR2290 page 10	4/21/11	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	0	0	0	2	3	5	7	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	346.4	147.7	32.5	14.2	8.1	8.4	
	4/21/11	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	0	2	4	7	10	12	15	
					Range	(b) (4)								
					% RSD	346.4	NA	52.0	11.7	11.2	8.3	7.3	5.8	

Dissolution Conditions			Apparatus:		USP Apparatus 1									
			Speed of Rotation:		100 rpm									
			Medium:		20% Ethanol in 0.1N HCl									
			Volume:		900 mL									
			Temperature:		37 ± 0.5 °C									
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location
						15	30	45	60	75	90	105	120	
WSR2290 page 20	4/27/11	Test Product Morphine Sulfate ER capsules Lot # 3451R0001 (Mfg. 10/23/2009)	50 mg Capsule	12	Mean	0	0	0	0	2	3	5	7	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	346.4	346.4	346.4	13.9	15.1	7.5	8.6	
	4/27/11	Reference Product Kadian Lot # 715L91 (Exp. 11/2012)	50 mg Capsule	12	Mean	0	0	1	3	6	8	11	14	
					Range	(b) (4)								
					% RSD	NA	233.5	73.9	17.7	9.5	8.3	5.5	6.5	
WSR2266 page 29	4/26/11	Test Product Morphine Sulfate ER capsules Lot # 3452R0001 (Mfg. 10/23/2009)	60 mg Capsule	12	Mean	0	0	0	1	2	4	6	8	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	233.5	233.5	123.6	33.4	18.0	17.8	9.2	6.8	
WSR2266 page 26	4/29/11	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	60 mg Capsule	12	Mean	1	3	5	7	10	13	17	20	
					Range	(b) (4)								
					% RSD	36.9	18.5	10.6	5.4	2.9	3.8	3.0	2.6	

Dissolution Conditions		Apparatus:		USP Apparatus 1										
		Speed of Rotation:		100 rpm										
		Medium:		40% Ethanol in 0.1N HCl										
		Volume:		900 mL										
		Temperature:		37 ± 0.5 °C										
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location
						15	30	45	60	75	90	105	120	
WSR2287, page 25	4/18/11	Test Product Morphine Sulfate ER capsules Lot # 3449R0001 (Mfg. 10/23/2009)	20 mg Capsule	12	Mean	0	0	0	0	0	9	17	26	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	NA	NA	NA	14.7	12.2	8.6	
WSR2287, page 22	4/18/11	Reference Product Kadian Lot # 660E01 (Exp. 03/2013)	20 mg Capsule	12	Mean	0	0	0	5	15	28	41	52	
					Range	(b) (4)								
					% RSD	NA	NA	NA	93.2	9.4	8.5	7.8	6.2	
WSR2298 page 22	4/21/11	Test Product Morphine Sulfate ER capsules Lot # 3450R0001 (Mfg. 10/23/2009)	30 mg Capsule	12	Mean	0	1	1	4	7	12	20	29	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	242.1	41.3	29.5	7.8	7.9	6.5	
	4/21/11	Reference Product Kadian Lot # 883E01 (Exp.03/2013)	30 mg Capsule	12	Mean	0	3	9	16	27	38	49	58	
					Range	(b) (4)								
					% RSD	NA	NA	14	5.8	5.1	5.1	5.0	4.6	

Dissolution Conditions			Apparatus:		USP Apparatus 1									
			Speed of Rotation:		100 rpm									
			Medium:		40% Ethanol in 0.1N HCl									
			Volume:		900 mL									
			Temperature:		37 ± 0.5 °C									
Dissolution Testing Site (Name, Address)			Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston FL, 33331											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)								Study Report Location
						15	30	45	60	75	90	105	120	
WSR2266 page 20	4/27/11	Test Product Morphine Sulfate ER capsules Lot # 3451R0001 (Mfg. 10/23/2009)	50 mg Capsule	12	Mean	0	0	0	0	2	10	20	29	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	NA	NA	78.4	11.9	7.9	6.4	
	4/27/11	Reference Product Kadian Lot # 715L91 (Exp. 11/2012)	50 mg Capsule	12	Mean	0	4	7	13	22	32	40	47	
					Range	(b) (4)								
					% RSD	NA	12.6	10.6	6.5	4.6	3.4	3.8	3.8	
WSR2298 page 21	4/26/11	Test Product Morphine Sulfate ER capsules Lot # 3452R0001 (Mfg. 10/23/2009)	60 mg Capsule	12	Mean	0	0	0	0	1	10	20	29	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					% RSD	NA	NA	NA	NA	150.0	12.1	7.0	5.0	
	4/26/11	Reference Product Kadian Lot # 656E01 (Exp.03/2013)	60 mg Capsule	12	Mean	0	3	7	15	28	41	52	61	
					Range	(b) (4)								
					% RSD	NA	NA	13	6.7	4.2	2.6	2.5	2.1	

The firm has previously conducted acceptable in vitro alcohol-dumping study on the 80 mg and 100 mg strengths (DARRTS, ANDA 200812, REV-BIOEQ-01(General Review), dated 9/21/2010). Please refer to below table summarizing mean% (range) drug release at 2 hours in various media for 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg strengths of test and reference products:

		Mean % Drug Released at 2 hours									
		0.1 N HCl		5% EtOH in 0.1 N HCl		20% EtOH in 0.1 N HCl		40% EtOH in 0.1 N HCl			
20 mg											
Test	1	(b) (4)		0	(b) (4)		7	(b) (4)		26	(b) (4)
Reference	6			9			19			52	
30 mg											
Test	0			2			7			29	
Reference	6			7			15			58	
50 mg											
Test	1			3			7			29	
Reference	5			6			14			47	
60 mg											
Test	2			2			8			29	
Reference	7			9			20			61	
80 mg											
Test	2			3			8			30	
Reference	7			8			25			74	
100 mg											
Test	2			3			8			31	
Reference	4			6			24			70	

Per DBE Policy, the DBE compares the % dissolved at 2 hours in 0.1 N HCl with no ethanol to the % dissolved at 2 hours in 40% ethanol/60% 0.1 N HCl (v/v) for the test product. If the % dissolved is comparable for no ethanol versus 40% ethanol, the test product is considered robust and no further comparisons are needed. If, however, the % dissolved from the test product increases as the amount of ethanol in the media increases, then the DBE compares % dissolved data at 2 hours in 40% ethanol for the test product and reference product. If for both products, the % dissolved at 2 hours in 40% ethanol is comparable, then the DBE concludes that the risk of dose-dumping from the generic product is the same as for the reference product³.

As shown in the above table, the mean percent released (%) at 2 hrs from the 20 mg, 30mg, 50 mg, 60 mg, 80 mg, and 100 mg strengths of the test products in 40% ethanol is 26%, 29%, 29%, 29%, 30%, and 31%, respectively, which is 18 to 44% lower compared to 52%, 58%, 47%, 61%, 74%, and 70% released (%) of the reference products, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg strengths, respectively in 0.1N HCl containing 40% ethanol and suggests the risk of dose-dumping from generic product is no more than that for the reference product.

The firm's response to deficiency comment# 2 is acceptable.

³OGD Bupropion Memorandum dated: 9/11/2006 (\\cdsnas\ogds11\DIVISION\BIO\farrarj\Xiaojian\New reviewer tool\alcohol dose dumping\Bupropionmemo.pdf)

3.2 Deficiency Comments

There is a USP dissolution method for this drug product. The firm's dissolution testing data with the USP method are acceptable. However, the firm's proposed specifications (1 hr: NMT 10%; 4 hrs: (b) (4)%; 6 hrs: (b) (4)%; 9 hrs: NLT 85%), which are different from the USP are not acceptable. Based on the submitted data, the DBII recommends the following specifications:

Time (hr.)	DBII Recommended Specifications
1 hr	NMT 10%
4 hrs	(b) (4)%
6 hrs	(b) (4)%
9 hrs	NLT 85%

The firm should indicate if it accepts the FDA-recommended dissolution testing method and specifications.

3.3 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study R09-0072 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot# 3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
2. The Division of Bioequivalence accepts the fed BE study R09-0073 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot#3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
3. The Division of Bioequivalence accepts the fasting sprinkle BE study R09-0074 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot#3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
4. The Division of Bioequivalence accepts fed BE study R09-0905 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 100 mg, lot# 3453R0001B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 100 mg, lot #320E71.
5. The dissolution testing conducted by Watson Laboratories on its test product, Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg is incomplete due to deficiency mentioned above.
6. The application is incomplete due to the above mentioned deficiency.

3.4 Comments for Other OGD Disciplines

Discipline	Comment
	None

BIOEQUIVALENCE DEFICIENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg.

The Division of Bioequivalence II (DBII) has completed its review as noted on the cover page, and the following deficiency has been identified:

Your dissolution testing data using the USP dissolution method are acceptable. However, your proposed dissolution specifications are not acceptable. Based on the submitted data, please acknowledge your acceptance of the following dissolution method and specifications:

Medium: 0.1N HCl for 1 hrs followed by phosphate buffer, pH 7.5
Apparatus: I (Basket)
Speed: 100 RPM
Temperature: 37°C ± 0.5°C
Volume: 500 mL (Acid stage); 500 mL (Buffer stage)
Specifications:
1 hrs: NMT 10%
4 hrs: (b) (4) %
6 hrs: %
9 hrs: NLT 85%

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4 Outcome Page

ANDA: 200812

Completed Assignment for 200812 ID: 14619

Productivity:

Reviewer: Chaurasia, Chandra

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Morphine Sulfate Extended Release Capsules

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
14619	5/18/2011	Other	Study Amendment	1	1	Edit	Delete
14619	5/18/2011	Other	In-vitro dose-dumping in alcohol	1	1	Edit	Delete
				Bean Total:	2		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment-dated 1	
Study Amendment date 5/18/2011	1
In vitro alcohol dose dumping 20 mg, 30 mg, 50 mg, and 60 mg	1
Total number of Complexity Points	2.0

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/s/

CHANDRA S CHAURASIA
07/28/2011

BARBARA M DAVIT
07/29/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200812			
Drug Product Name	Morphine Sulfate Extended-Release Capsules, USP			
Strength(s)	20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg			
Applicant Name	Watson Laboratories Inc.			
Address	4955 Orange Drive Ft. Lauderdale, FL 33314			
Applicant's Point of Contact	Alberto E. Rivalta, Manager Regulatory Affairs			
Contact's Telephone Number	(954) 358-6109			
Contact's Fax Number	(954) 358-6350			
Original Submission Date(s)	December 16, 2009			
Submission Date(s) of Amendment(s) Under Review	September 30, 2010 December 09, 2010 May 18, 2011 August 11, 2011			
Reviewer	Chandra S. Chaurasia, Ph.D.			
Study Number (s) ¹	R09-0072	R09-0073	R09-0074	R09-0905
Study Type (s)	Fasting	Fed	Fasting sprinkle-in-applesauce	Fed
Strength (s)	80 mg	80 mg	80 mg	100 mg
Clinical Site	Cetero Research			
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104			
Analytical Site	(b) (4)			
Analytical Site Address				
OUTCOME DECISION	INADEQUATE			

OVERALL REVIEW RESULT	INADEQUATE		
WAIVER REQUEST RESULT	INADEQUATE		
DSI REPORT RESULT	ADEQUATE		
BIOEQUIVALENCE STUDY	STUDY/TEST TYPE	STRENGTH	REVIEW

¹ The firm submitted fasting (80 mg), fed (80 mg and 100 mg) and fasting sprinkle-in-applesauce BE studies (80 mg) on 12/16/09 before posting of current revised individual product recommendations for this drug product in May 2010, which recommends six BE studies, namely, fasting (10 mg, 100 mg and 200 mg), fed (100 mg and 200 mg) and fasting sprinkle-in-applesauce (100 mg); and waiver of 20 mg, 30 mg, 50 mg, 60 mg and 80 mg strengths based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) acceptable in vitro dissolution testing for all the strengths, and (iii) proportional similarity of formulations across all strengths. Since BE studies were conducted prior to posting of revised BE recommendations for this drug product, therefore waiver of 20 mg, 30 mg, 50 mg, 60 mg strengths based on fasting (80 mg), fed (80 mg and 100 mg) and fasting sprinkle-in-applesauce BE studies (80 mg) should be acceptable.

TRACKING/SUPPORTING DOCUMENT#			RESULT
1 & 4	FASTING STUDY	80 mg	ADEQUATE
1 & 4	FED STUDY	80 mg	ADEQUATE
1 & 4	FASTING SPRINKLE STUDY	80 mg	ADEQUATE
1 & 4	FED STUDY	100 mg	ADEQUATE
1, 2, 8, & 10	DISSOLUTION	80 mg and 100 mg	INADEQUATE
2, 8, & 10	DISSOLUTION	20 mg, 30 mg, 50 mg and 60 mg	INADEQUATE

REVIEW OF A STUDY AMENDMENT

1 EXECUTIVE SUMMARY

In the original submission dated December 16, 2009, Watson Laboratories submitted fasting, fed, and fasting sprinkle bioequivalence (BE) studies comparing its Morphine Sulfate Extended Release Capsules, 80 mg, to the corresponding Actavis Elizabeth's reference product, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg strength. In addition, the firm submitted a fed study comparing Watson Laboratories' test product, Morphine Sulfate Sustained Release Capsules, 100 mg, to the corresponding Actavis Elizabeth's reference product, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 100 mg strength. The bioequivalence (fasting, fed, and fasting sprinkle) studies were found acceptable; however, the application was found to be incomplete due to (i) bioanalytical deficiencies, (ii) formulation deficiency, and (iii) dissolution deficiencies². In amendments dated 9/30/10 and 12/09/10, the firm provided acceptable responses to the bioanalytical and formulation deficiencies. However, the application was still incomplete due to dissolution deficiencies³.

In a subsequent amendment dated 5/18/11, the firm responded to dissolution deficiencies. The firm's dissolution testing data with the USP method was acceptable. However, the firm's proposed specifications (1 hr: NMT 10%; 4 hrs: (b) (4)%; 6 hrs: (b) (4)%; 9 hrs: NLT 85%), which are different from the USP (1 hr: NMT 10%; 4 hr: 25-50%; 6 hr: 50-90%; 9 hr: NLT 85%) were found to be unacceptable. Based on the submitted data, the Division of Bioequivalence II (DB II) recommended the following specifications⁴:

1 hr: NMT 10%; 4 hr: (b) (4)%; 6 hr: (b) (4)%; 9 hr: NLT 85%

In the current amendment dated August 11, 2011, the firm proposes to revise 6 hr dissolution time point specification from (b) (4)% to (b) (4)% based on dissolution data of validation batches. The firm's dissolution testing data on the fresh bio-lots (submitted in the amendments dated 9/30/10 and 5/8/11) and validation batches (submitted in current amendment dated 8/11/11) meet the DB II-recommended dissolution specification of (b) (4)% at 6 hrs. As per the DB II practice, the dissolution method and specifications are established based on the dissolution data on 12 units of the

²DARRTS N200812, REV-BIOEQ-01(General Review), final date: 9/21/2010

³DARRTS N200812, REV-BIOEQ-01(General Review), final date: 3/22/2011

⁴DARRTS, N200812, REV-BIOEQ-01(General Review), final date: 7/29/2011

fresh bio-lot that has been used in acceptable bioequivalence studies and are not widened based on validation batches. Therefore, the firm's *proposal to change the dissolution specification at 6 hrs from (b) (4) % to (b) (4) % is not acceptable.*

However, the DB II considers revision of dissolution method and specifications based on data from three fresh production lots. The firm should indicate if it accepts the DB II-recommended dissolution specifications of 1 hr: NMT 10%; 4 hrs: (b) (4) %; 6 hrs: (b) (4) %; 9 hrs: NLT 85%. Alternatively, in order to justify its proposed specification of (b) (4) % at 6 hrs, the firm should submit additional dissolution data on 12 units each of all strengths from **three fresh** production lots of the test product using USP-recommended dissolution method.

This amendment is incomplete pending firm's adequate response to the deficiency cited above.

2 TABLE OF CONTENTS

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3 SUBMISSION SUMMARY

3.1 Review of Submission

Deficiency Comment# 1:

Your dissolution testing data using the USP dissolution method are acceptable. However, your proposed dissolution specifications are not acceptable. Based on the submitted data, please acknowledge your acceptance of the following dissolution method and specifications:

Medium: 0.1N HCl for 1 hrs followed by phosphate buffer, pH 7.5

Apparatus: I (Basket)

Speed: 100 RPM

Temperature: 37°C ± 0.5°C

Volume: 500 mL (Acid stage); 500 mL (Buffer stage)

Specifications: 1 hr: NMT 10%; 4 hrs: (b) (4)%; 6 hrs: (b) (4)%; 9 hrs: NLT 85%

Firm's Response to the Deficiency Comment# 1:

The firm acknowledges the DB II dissolution recommendations. However, based on the dissolution data of both the ANDA batches and validation batches for all the strengths of the finished drug product, we ask the DB II to reconsider the 6 hr time point specification. A summary of the dissolution data at 6 hrs is summarized in the Tables 1 and 2 below:

Table 1: Dissolution Data at 6 hrs for Finished Product ANDA Batches

Time Point	20 mg ANDA Batch # 3449R0001	30 mg ANDA Batch # 3450R0001	50 mg ANDA Batch # 3451R0001	60 mg ANDA Batch # 3452R0001	80 mg ANDA Batch # 3576R0013	100 mg ANDA Batch # 3453R0001
	n= 12	n= 12	n= 12	n= 12	n= 12	n= 12
6 hours	Mean: 55% Min.: (b) (4) Max.: (b) (4)	Mean: 56% Min.: (b) (4) Max.: (b) (4)	Mean: 56% Min.: (b) (4) Max.: (b) (4)	Mean: 55% Min.: (b) (4) Max.: (b) (4)	Mean: 58% Min.: (b) (4) Max.: (b) (4)	Mean: 59% Min.: (b) (4) Max.: (b) (4)

Table 2: Dissolution Data at 6 hrs for Finished Product Validation Batches

Time Point	20 mg Batches	30 mg Batch # 404674	50 mg Batch # 404675	60 mg Batch # 404677	80 mg Batch # 404678	100 mg Batches
	n = 12	n = 12	n = 12	n = 12	n = 12	n = 12
6 hours	Batch # 404671 Mean: 61% Min.: (b) (4)% Max.: (b) (4)%	Mean: 63% Min.: (b) (4) Max.: (b) (4)	Mean: 60% Min.: (b) (4) Max.: (b) (4)%	Mean: 61% Min.: (b) (4) Max.: (b) (4)	Mean: 62% Min.: (b) (4) Max.: (b) (4)	Batch # 404679 Mean: 60% Min.: (b) (4)% Max.: (b) (4)%
	Batch # 404672 Mean: 58% Min.: (b) (4) Max.: (b) (4)					Batch # 404680 Mean: 60% Min.: (b) (4) Max.: (b) (4)
	Batch # 404673 Mean: 64% Min.: (b) (4) Max.: (b) (4)					Batch # 404681 Mean: 59% Min.: (b) (4) Max.: (b) (4)

In addition, please note that the 6 hr dissolution time point specification in the USP Monograph for Morphine Sulfate Extended-release Capsules, USP has a 40% window range (50-90 %), (b) (4) % specification. Furthermore, for routine commercial manufacturing, the firm believes that a (b) (4) is more appropriate and will not impact product quality. Based on these facts and the data tabulated above, the firm is proposing a (b) (4) % range for the 6 hour time point specification. Please see proposed limits tabulated below:

Time (Hours)	Watson's Previous Proposed Specifications	Watson's Currently Proposed Specifications
	NMT 10%	NMT 10%
4	(b) (4)%	(b) (4)%
6	(b) (4)%	(b) (4)%
9	NLT 85 %	NLT 85%

Reviewer's Comment on the Deficiency# 1:

The dissolution data on fresh bio-lots for different strengths of morphine sulfate extended release capsules as provided in the amendments dated 9/30/10 and 5/8/11 at 1 hr, 4 hrs, 6 hrs and 9 hrs sampling time points is summarized in the Table 3 below:

Table 3: %Mean (Range) of Morphine Sulfate Released for ANDA Batches

Dissolution Testing Conditions: 500 mL of 0.1N HCl for 1 hrs followed by 500 mL of phosphate buffer, pH 7.5, USP I (Basket), 100 rpm						
Time point (hrs)	20 mg	30 mg	50 mg	60 mg	80 mg	100 mg
1 hr	0 (b) (4)	0 (b) (4)	0 (b) (4)	0 (b) (4)	1 (b) (4)	0 (b) (4)
4 hrs	24	24	24	23	26	26
6 hrs	55	56	56	55	58	59
9 hrs	96 (	99 (	97 (	97 (	96 (	96 (

Based on the above dissolution data, the DB II recommended the following specifications:
1 hrs: NMT 10%; 4 hrs: (b) (4)%; 6 hrs: (b) (4)%; 9 hrs: NLT 85%⁵.

However, in the current amendment dated August 11, 2011, the firm proposes to revise 6 hr dissolution time point specification from (b) (4)% to (b) (4)% based on dissolution testing data of validation batches.

As shown in the Tables 2 and 3 above, the firm's dissolution testing data on the fresh bio-lots and validation batches meet the DB II-recommended dissolution specification of (b) (4)% at 6 hrs. As per the DB II practice, the dissolution method and specifications are established based on the dissolution data on 12 units of the fresh bio-lot that has been used in acceptable bioequivalence studies and are not widened based on validation batches. Therefore, the firm's proposal to change the dissolution specification at 6hrs from (b) (4)% to (b) (4)% is not acceptable.

However, the DB II considers revision of dissolution method and specifications based on data from three fresh production lots. The firm should indicate if it accepts the DB II-recommended dissolution specifications of 1hr: NMT 10%; 4 hrs: (b) (4)%; 6 hrs: (b) (4)%; 9hrs: NLT 85%. Alternatively, in order to justify its proposed specification of (b) (4)% at 6 hrs, the firm should submit additional dissolution data on 12 units each of all strengths from **three fresh** production lots of the test product using USP-recommended dissolution method.

Firm's response to deficiency comment #1 is **not acceptable**.

3.2 Deficiency Comments

As per the Division of Bioequivalence II (DB II) practice, the dissolution method and specifications are established based on the dissolution data on 12 units of the fresh bio-lot that has been used in acceptable bioequivalence studies and are not widened based on validation batches. The firm's dissolution testing data on the fresh bio-lots (submitted in the amendments dated 9/30/10 and 5/8/11) and validation batches (submitted in the current amendment dated 8/11/11) meet the DB II-recommended dissolution specification of (b) (4)% at 6 hrs. Therefore, *the firm's proposal to change the dissolution specification at 6 hrs from (b) (4)% to (b) (4)% is not acceptable*. However, the DB II considers revision of dissolution method and specifications based on data from three fresh production lots. The

⁵DARRTS, N 200812, REV-BIOEQ-01(General Review), final date: 07/29/2011

firm should indicate if it accepts the DB II-recommended dissolution specifications of 1 hr: NMT 10%; 4 hrs: (b) (4)%; 6 hrs: (b) (4)%; 9 hrs: NLT 85%. Alternatively, in order to justify its proposed specification of (b) (4)% at 6 hrs, the firm should submit additional dissolution data on 12 units each of all strengths from **three fresh** production lots of the test product using USP-recommended dissolution method.

3.3 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study R09-0072 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot# 3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
2. The Division of Bioequivalence accepts the fed BE study R09-0073 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot#3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
3. The Division of Bioequivalence accepts the fasting sprinkle BE study R09-0074 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 80 mg, lot#3576R0013B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 80 mg, lot #510M81.
4. The Division of Bioequivalence accepts fed BE study R09-0905 conducted by Watson Laboratories on its Morphine Sulfate Extended Release Capsules, 100 mg, lot# 3453R0001B comparing it to Actavis Elizabeth's, Kadian[®] (Morphine Sulfate) Extended Release Capsules, 100 mg, lot #320E71.
5. The dissolution testing conducted by Watson Laboratories on its test product, Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg is incomplete due to deficiency mentioned above.
6. The application is incomplete due to the above mentioned deficiency.

3.4 Comments for Other OGD Disciplines

Discipline	Comment
	None

BIOEQUIVALENCE DEFICIENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg.

The Division of Bioequivalence II (DB II) has completed its review as noted on the cover page, and the following deficiencies have been identified:

1. The DB II acknowledges that you propose to change dissolution specification at 6 hour sampling time point. However, please be advised that per the DB II practice, the dissolution method and specifications are established based on the dissolution data on 12 units of the fresh bio-lot that has been used in acceptable bioequivalence studies. The DB II does not change the dissolution specifications based on dissolution testing data of validation batches. The dissolution testing data on the fresh bio-lots (submitted in the amendments dated 9/30/10 and 5/8/11) met the DB II-recommended dissolution specification of (b) (4) % at 6 hrs. In addition, the dissolution testing data on the validation batches (submitted in the current amendment dated 8/11/11) meet the dissolution specification of (b) (4) % at 6 hrs. Therefore, your proposal to change the dissolution specification at 6 hrs from (b) (4) % to (b) (4) % is not acceptable. Please indicate if you accept the DB II recommended dissolution specifications of 1hr: NMT 10%; 4hrs: (b) (4) %; **6 hrs: (b) (4) %**; 9 hrs: NLT 85%.
2. Alternatively, in order for the DB II to reconsider if a revision of the dissolution specifications is warranted, you may submit dissolution data on 12 dosage units each of all strengths from **three fresh** production lots of the test product, using the USP-recommended dissolution method.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 200812/Watson Laboratories/Morphine Morphine Sulfate Extended Release
Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg

4 Outcome Page

ANDA: 200812

Completed Assignment for 200812 ID: 14820

Productivity:

Reviewer: Chaurasia, Chandra

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Morphine Sulfate Extended Release Capsules

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
14820	8/11/2011	Other	Study Amendment	1	1	Edit	Delete
				Bean Total:	1		

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment-dated 8/11/2011	
Study Amendment date 8/11/2011	1.0
Total number of Complexity Points	1.0

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/s/

CHANDRA S CHAURASIA
08/29/2011

BARBARA M DAVIT
08/31/2011

**DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT
REVIEW**

ANDA No.	200812
Drug Product Name	Morphine Sulfate Extended-Release Capsules
Strength	20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg
Applicant Name	Watson Laboratories, Inc. - Florida
Submission Date	December 16, 2009 (original submission) and September 12, 2011 (dissolution acknowledgement)
Reviewer	Chitra Mahadevan, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm, dated September 12, 2011.

The firm has accepted the FDA-recommended dissolution method and specification.

The bioequivalence section of the application is complete.

COMMENTS:

Watson Laboratories, Inc. - Florida acknowledges and accepts the following DB II recommended dissolution specifications:

Time (Hours)	% Drug Release Specification for the Drug Product
1	NMT 10 %
4	(b) (4) %
6	%
9	NLT 85 %

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is **ADEQUATE**.

I. Completed Assignment for 200812 ID: 15092

Reviewer: Mahadevan, Chitra

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Dissolution acknowledgement Morphine Sulfate

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
15092	9/12/2011	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

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/s/

CHITRA MAHADEVAN
10/12/2011

AARON W SIGLER
10/12/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 200812

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



December 15, 2009

Gary Buehler
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: PREASSIGNED ORIGINAL ANDA APPLICATION
200812
Morphine Sulfate Sustained-release Capsules USP, 80 mg and 100 mg

Dear Sir:

In accordance with Section 505(j) of the FD&C Act and CFR 314.94, Watson Laboratories, Inc.-Florida (WLF) is submitting an electronic original Abbreviated New Drug Application (ANDA) for approval to market its formulation of Morphine Sulfate Sustained-release Capsules USP, 80 mg and 100 mg. The reference-listed drug (RLD) is Kadian® (Morphine Sulfate Extended-release) Capsules, manufactured by Actavis Kadian LLC, under NDA # 020616. This application contains the necessary information to demonstrate that WLF's drug product is both pharmaceutically equivalent and bioequivalent to the RLD.

This is an electronic submission organized in accordance with ICH-CTD format (eCTD). To facilitate the review, WLF is submitting a copy of the FDA's "*ANDA Checklist for CTD or eCTD Format for Completeness and Acceptability of an Application for Filing*", which provides links to all the respective sections and documents in each applicable Module (copy attached).

A letter of Non-Repudiation agreement was previously submitted to the Food and Drug Administration by Watson Pharmaceuticals, Inc.¹ on October 8, 2001 (copy attached). The submission has been verified virus-free and is being submitted through the FDA Electronic Submission Gateway (ESG) Web interface in accordance with the Applicability Statement 2 (AS2) standard.

This application does not include labeling in SPL format. WLF commits to provide the Final Printed Labeling (FPL) in SPL format prior to approval of the ANDA.

A certification of Compliance form 3674 is provided along with the cover letter and the FDA 356h form.

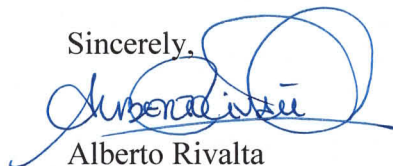
¹ WLF and Watson Laboratories, Inc. are wholly owned subsidiaries of Watson Pharmaceuticals, Inc.

Concurrently with the filing of this eCTD, we notified the Florida District Office that this ANDA is being submitted as an electronic submission.

WLF commits to resolve any issues identified in the methods validation package after approval.

For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*). For Information Technology assistance, please contact Majid Rostai at majid.rostai@watson.com (*email*), at (954) 358-6148 (*direct dial*) or (954) 552-7808 (*fax*).

Sincerely,

A handwritten signature in blue ink, appearing to read 'Alberto Rivalta', with a large, stylized circular flourish above it.

Alberto Rivalta
Manager, Regulatory Affairs

ANDA CHECKLIST FOR CTD or eCTD FORMAT FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD)

Format please go to: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

*For a Comprehensive Table of Contents Headings and Hierarchy please go to:

<http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>

** For more CTD and eCTD informational links see the final page of the ANDA Checklist

*** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage <http://www.fda.gov/cder/ogd/> ***

ANDA #: 200812

FIRM NAME: WATSON LABORATORIES INC.

PIV: NO

Electronic or Paper Submission: GATEWAY (ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: MORPHINE SULFATE

DOSAGE FORM: EXTENDED-RELEASE CAPSULES, 80 MG AND 100 MG

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC2 Team 9 ☒ Activity	Bio Team 5: Chandra Chaurasia ☒ Activity
ANDA/Quality RPM: Laura Longstaff ☒ FYI	Bio PM: Diane Nhu ☐ FYI
Quality Team Leader: Smith, Glen J No assignment needed in DARRTS	Clinical Endpoint Team Assignment: (No) ☐ Activity
Labeling Reviewer: Chan Park ☒ Activity	Micro Review (No) ☐ Activity

***Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). ***

Letter Date: DECEMBER 16, 2009	Received Date: DECEMBER 16, 2009
Comments: EC- 2 YES On Cards: YES Therapeutic Code: 5030350 ACUTE PAIN, OPIOID	
Archival copy: GATEWAY (ELECTRONIC DATA) Sections I Review copy: NA E-Media Disposition: NA Not applicable to electronic sections	
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST FELECIA (LISA) TAN Date 2/26/2010	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE
Supervisory Concurrence/Date: _____ Date: _____	

1. Edit Application Property Type in DARRTS where applicable for
 - a. First Generic Received
☐ Yes ☒ No
 - b. Market Availability
☒ Rx ☐ OTC
 - c. Pepfar
☐ Yes ☒ No
 - d. Product Type
☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
 - e. USP Drug Product (at time of filing review)
☒ Yes ☐ No
2. Edit Submission Patent Records
☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
☐ Yes
4. Requested EER
☐ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

CONTACT INFO: JANET VAUGHN OR ALBERTO RIVALTA

REQUEST: NONE

COMMUNICATION: NONE

DBE GUIDANCE FOR BIO STUDY:

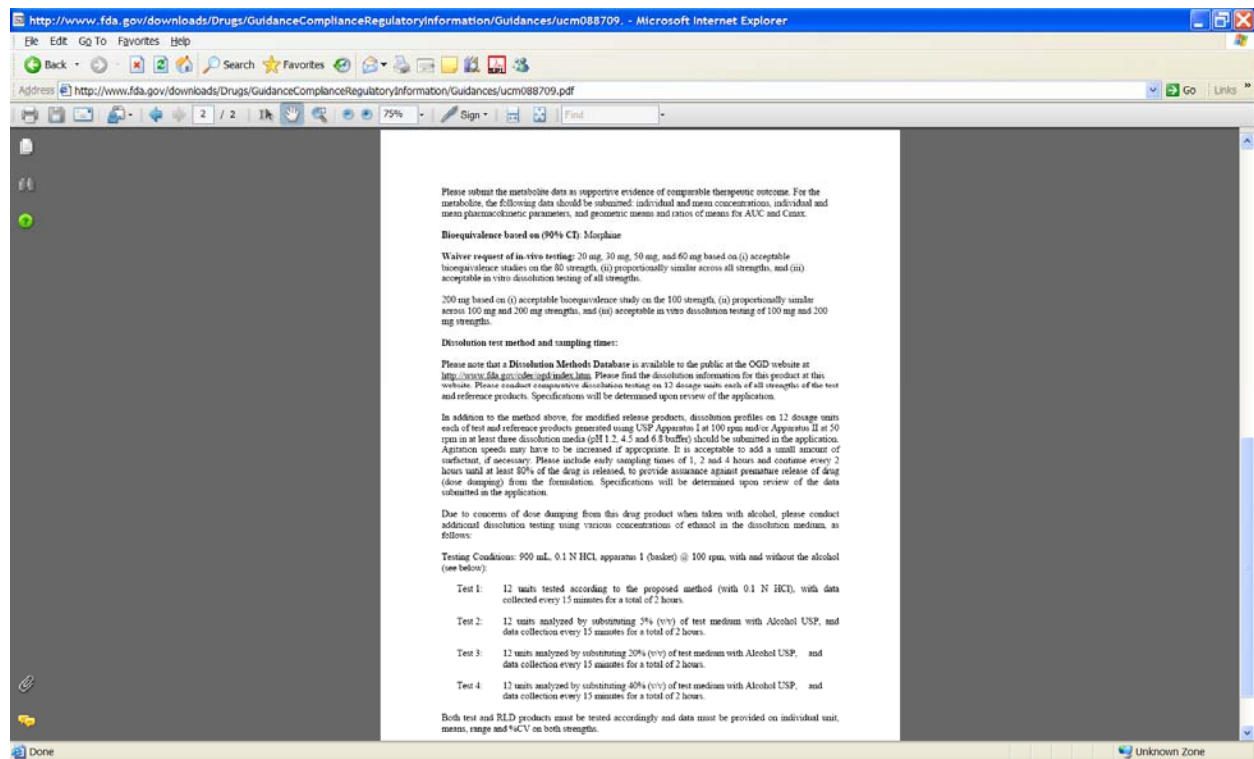
Contents: Nonbinding Recommendations
Draft Guidance on Morphine Sulfate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Morphine Sulfate
Form/Route: Extended Release Capsules Oral
Recommended studies: 5 studies

1. Type of study: Fasting
Design: Single-dose, two-way, crossover in-vivo
Strength: 30 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: For the healthy subjects recommended for this study, please use a narcotic antagonist such as naloxone. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.
2. Type of study: Fed
Design: Single-dose, two-way, crossover in-vivo
Strength: 30 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Please see comments above.
3. Type of study: Fasting
Design: Single-dose, two-way, crossover in-vivo
Strength: 30 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Please see comments above.
4. Type of study: Fed
Design: Single-dose, two-way, crossover in-vivo
Strength: 100 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Please see comments above.
5. Type of study: Fasting
Design: Single-dose, two-way, crossover in-vivo
Strength: 10 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Please see comments above.

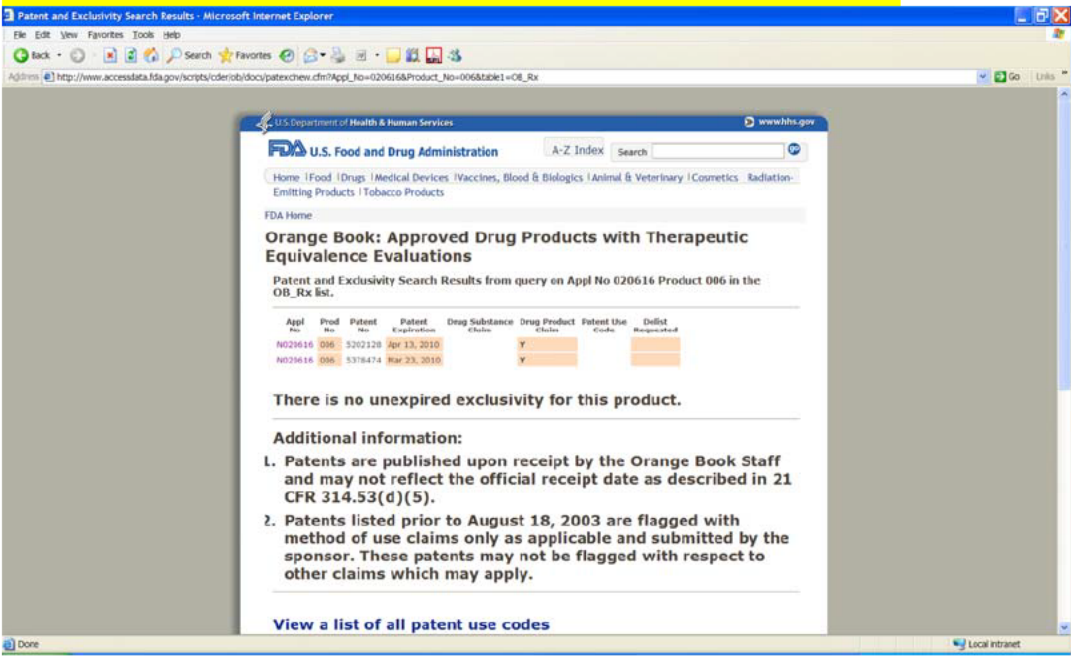
Analytes to measure: Morphine and Morphine-6-glucuronide in plasma



MODULE 1 ADMINISTRATIVE

ACCEPTABLE

1.1	1.1.2 Signed and Completed Application Form (356h) (original signature) (Check Rx/OTC Status) RX YES	☒
1.2	Cover Letter Dated: DECEMBER 16, 2009 YES	☒
1.2.1	Form FDA 3674 (PDF) YES OPTION B	☒
*	Table of Contents (paper submission only) YES	☒
1.3.2	Field Copy Certification (original signature) YES SEE SECTION 1.3.2 (N/A for E-Submissions)	☒
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: 1. Debarment Certification (original signature) YES SEE SECTION 1.3.3 2. List of Convictions statement (original signature) SAME	☒
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES SEE SECTION 1.3.4 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒

1.3.5	1.3.5.1 Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations 1.3.5.2 Patent Certification 1. Patent number(s) BOTH STRENGTHS SHARE THE SAME PATENT AND EXCLUSIVITY INFO.  2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): 4-13-2010 a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: YES NO UNEXPIRED EXCLUSIVITIES	☒
1.4.1	References Letters of Authorization - DMF letters of authorization - Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient yes Type II DMF No. (b) (4) - Type III DMF authorization letter(s) for container closure (b) (4) - US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	Basis for Submission NDA# : 20-616 YES Ref Listed Drug: KADIAN YES Firm: ACTAVIS KADIAN LLC. YES ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME <table border="1"> <thead> <tr> <th></th> <th>ANDA Product</th> <th>Reference Listed Drug</th> </tr> </thead> <tbody> <tr> <td>Product Name:</td> <td>Morphine Sulfate Sustained-release Capsules, USP</td> <td>Kadian® (Morphine Sulfate Extended-release Capsules)</td> </tr> <tr> <td>Active Ingredient(s):</td> <td>Morphine Sulfate USP</td> <td>Morphine Sulfate USP</td> </tr> <tr> <td>Inactive Ingredients:</td> <td>Corn starch, diethyl phthalate, ethylcellulose, hypromellose 2910, methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30 and talc. The capsule shells contain black iron oxide, gelatin, propylene glycol, and titanium dioxide, D&C yellow # 10, FD&C blue # 1, FD&C blue # 2, FD&C red # 40, FD&C yellow # 6 (80 mg), D&C yellow # 10, FD&C blue # 1, FD&C blue # 2, FD&C green # 3, FD&C red # 40 (100 mg).</td> <td>Hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch and sucrose. The capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide and black ink, FD&C Blue #1, FD&C Red # 40, FD&C yellow #6, D&C yellow #10, FD&C blue #1.</td> </tr> </tbody> </table>		ANDA Product	Reference Listed Drug	Product Name:	Morphine Sulfate Sustained-release Capsules, USP	Kadian® (Morphine Sulfate Extended-release Capsules)	Active Ingredient(s):	Morphine Sulfate USP	Morphine Sulfate USP	Inactive Ingredients:	Corn starch, diethyl phthalate, ethylcellulose, hypromellose 2910, methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30 and talc. The capsule shells contain black iron oxide, gelatin, propylene glycol, and titanium dioxide, D&C yellow # 10, FD&C blue # 1, FD&C blue # 2, FD&C red # 40, FD&C yellow # 6 (80 mg), D&C yellow # 10, FD&C blue # 1, FD&C blue # 2, FD&C green # 3, FD&C red # 40 (100 mg).	Hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch and sucrose. The capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide and black ink, FD&C Blue #1, FD&C Red # 40, FD&C yellow #6, D&C yellow #10, FD&C blue #1.	☒
	ANDA Product	Reference Listed Drug												
Product Name:	Morphine Sulfate Sustained-release Capsules, USP	Kadian® (Morphine Sulfate Extended-release Capsules)												
Active Ingredient(s):	Morphine Sulfate USP	Morphine Sulfate USP												
Inactive Ingredients:	Corn starch, diethyl phthalate, ethylcellulose, hypromellose 2910, methacrylic acid copolymer, polyethylene glycol 6000, sucrose, povidone K-30 and talc. The capsule shells contain black iron oxide, gelatin, propylene glycol, and titanium dioxide, D&C yellow # 10, FD&C blue # 1, FD&C blue # 2, FD&C red # 40, FD&C yellow # 6 (80 mg), D&C yellow # 10, FD&C blue # 1, FD&C blue # 2, FD&C green # 3, FD&C red # 40 (100 mg).	Hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch and sucrose. The capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide and black ink, FD&C Blue #1, FD&C Red # 40, FD&C yellow #6, D&C yellow #10, FD&C blue #1.												
1.12.14	Environmental Impact Analysis Statement YES 21CFR25.31	☒												
1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies): NO	☒												
1.14.1	Draft Labeling (Mult Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft (each strength and container) YES 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES 1.14.1.3 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) ++COMMITMENT FOR SPL	☒												
1.14.3	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES 1.14.3.3 1 RLD label and 1 RLD container label YES	☒												

2.3	Quality Overall Summary (QOS) E-Submission: PDF YES Word Processed e.g., MS Word YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ Question based Review (QbR) YES 2.3.S Drug Substance (Active Pharmaceutical Ingredient) YES 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product YES 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	☒
2.7	Clinical Summary (Bioequivalence) Model Bioequivalence Data Summary Tables E-Submission: PDF YES Word Processed e.g., MS Word YES 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution YES 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES 2.7.1.4 Appendix 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3**3.2.S DRUG SUBSTANCE**

ACCEPTABLE

3.2.S.1	General Information SUBMITTED 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties	☒
3.2.S.2	Manufacturer 3.2.S.2.1 Manufacturer(s) (This section includes contract manufacturers and testing labs) Drug Substance (Active Pharmaceutical Ingredient) 1. Name and Full Address(es) of the Facility(ies) (b) (4) 2. Function or Responsibility YES 3. Type II DMF number for API (b) (4) 4. CFN or FEI numbers NOT PROVIDED	☒
3.2.S.3	Characterization SUBMITTED	☒
3.2.S.4	Control of Drug Substance (Active Pharmaceutical Ingredient) 3.2.S.4.1 Specification Testing specifications and data from drug substance manufacturer(s) YES 3.2.S.4.2 Analytical Procedures YES 3.2.S.4.3 Validation of Analytical Procedures 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) 30324 3.2.S.4.4 Batch Analysis 1. COA(s) specifications and test results from drug substance mfr(s) YES 2. Applicant certificate of analysis YES 3.2.S.4.5 Justification of Specification SUBMITTED	☒
3.2.S.5	Reference Standards or Materials SUBMITTED	☒
3.2.S.6	Container Closure Systems REFER TO DMF	☒
3.2.S.7	Stability REFER TO DMF	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.1	Description and Composition of the Drug Product 1. Unit composition YES 2. Inactive ingredients and amounts are appropriate per IIG JUSTFIED PER IIG	☒									
3.2.P.2	Pharmaceutical Development Pharmaceutical Development Report YES	☒									
3.2.P.3	Manufacture 3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es) of the Facility(ies) WATSON LABS INC FLORIDA 2. CGMP Certification: YES SECTION 3.2.P.3.1 3. Function or Responsibility YES 4. CFN or FEI numbers 3003937607 3.2.P.3.2 Batch Formula YES 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified <table border="1" data-bbox="380 907 1409 1029"> <thead> <tr> <th></th><th>ANDA Batch</th><th>Proposed Commercial Batches</th></tr> </thead> <tbody> <tr> <td>Batch Size</td><td>80 mg: (b) (4) capsules</td><td>80 mg: (b) (4) capsules</td></tr> <tr> <td></td><td>100 mg: capsules</td><td>100 mg: capsules</td></tr> </tbody> </table> 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement 21CFR211.115 3.2.P.3.4 Controls of Critical Steps and Intermediates SUBMITTED 3.2.P.3.5 Process Validation and/or Evaluation 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A		ANDA Batch	Proposed Commercial Batches	Batch Size	80 mg: (b) (4) capsules	80 mg: (b) (4) capsules		100 mg: capsules	100 mg: capsules	☒
	ANDA Batch	Proposed Commercial Batches									
Batch Size	80 mg: (b) (4) capsules	80 mg: (b) (4) capsules									
	100 mg: capsules	100 mg: capsules									
3.2.P.4	Controls of Excipients (Inactive Ingredients) Source of inactive ingredients identified YES 3.2.P.4.1 Specifications 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES 3.2.P.4.2 Analytical Procedures SUBMITTED 3.2.P.4.3 Validation of Analytical Procedures SUBMITTED 3.2.P.4.4 Justification of Specifications Applicant COA YES	☒									

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	Controls of Drug Product 3.2.P.5.1 Specification(s) YES 3.2.P.5.2 Analytical Procedures YES 3.2.P.5.3 Validation of Analytical Procedures Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers 80MG=3576R0013 AND 100MG=3453R0001 3.2.P.5.4 Batch Analysis Certificate of Analysis for Finished Dosage Form YES 3.2.P.5.5 Characterization of Impurities SUBMITTED 3.2.P.5.6 Justification of Specifications SUBMITTED	☒
3.2.P.7	Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes (1) Bottles of 30 capsules: <u>Container/closure system:</u> 75 cc white, straight-sided, round bottom, high-density polyethylene (HDPE) bottle (Code # (b) (4)) 33 mm, white, ribbed sides, child resistant plastic closure with aluminum foil coated (b) (4) liner (Code # (b) (4)) (b) (4) coil, (b) (4) white filament like hairs (Code # (b) (4)) <u>Labeling:</u> Container label Outsert (2) Bottles of 100 capsules: <u>Container/closure system:</u> 250 cc white, straight-sided, round bottom, high-density polyethylene (HDPE) bottle (Code # (b) (4)) 45 mm, white, ribbed sides, child resistant plastic closure with aluminum foil coated (b) (4) liner (Code # (b) (4)) (b) (4) coil, (b) (4) white filament like hairs (Code # (b) (4)) 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	3.2.P.8.1 Stability (Finished Dosage Form) 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 MONTH EXP 3.2.P.8.2 Post-approval Stability and Conclusion Post Approval Stability Protocol and Commitments YES 3.2.P.8.3 Stability Data 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES: 80MG=3576R0013 AND 100MG=3453R0001	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	3.2.R.1.S Executed Batch Records for drug substance (if available) 3.2.R.2.S Comparability Protocols 3.2.R.3.S Methods Validation Package Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐
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3.2.R (Drug Product)	3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES Theoretical Yield SEE BELOW Actual Yield SEE BELOW Packaged Yield SEE BELOW 3.2.R.1.P.2 Information on Components N/A 3.2.R.2.P Comparability Protocols N/A 3.2.R.3.P Methods Validation Package YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒
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MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	Tabular Listing of Clinical Studies SUBMITTED	☒
5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) 2. Lot Numbers of Products used in BE Study(ies): 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	☐

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)SEE BELOW 2. Summary Bioequivalence tables: Table 10. Study Information YES Table 12. Dropout Information YES Table 13. Protocol Deviations YES 5.3.1.3 In Vitro-In-Vivo Correlation Study Reports 1. Summary Bioequivalence tables: Table 11. Product Information YES Table 16. Composition of Meal Used in Fed Bioequivalence Study YES 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples YES Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES 5.3.7 Case Report Forms and Individual Patient Listing YES	☒
5.4	Literature References	☐
	Possible Study Types:	
Study Type	IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) FASTING, FED AND SPRINKLE ON 80 MG AND FED ONLY ON 100 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)YES, SEE BELOW 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: YES SEE SECTION 2.7 (TABLE 5)	☒
Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	NASALLY ADMINISTERED DRUG PRODUCTS <u>Solutions</u> (Q1/Q2 sameness): - In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) <u>Suspensions</u> (Q1/Q2 sameness): <u>In-Vivo PK Study</u> - Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) - EDR Email: Data Files Submitted <u>In-Vivo BE Study with Clinical End Points</u> - Properly defined BE endpoints (eval. by Clinical Team) - Summary results meet BE criteria (90% CI within +/- 20% of 80-125) - Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) - EDR Email: Data Files Submitted <u>In-Vitro Studies</u> (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) - Pilot Study (determination of ED50) - Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	TRANSDERMAL DELIVERY SYSTEMS <u>In-Vivo PK Study</u> - Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) - In-Vitro Dissolution - EDR Email: Data Files Submitted <u>Adhesion Study</u> <u>Skin Irritation/Sensitization Study</u>	☐

Updated 10/19/2009

Active Ingredient Search - Microsoft Internet Explorer

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Address <http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm> Go Links

N020616	Yes	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	100MG	KADIAN	ACTAVIS ELIZABETH
N020616	Yes	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	10MG	KADIAN	ACTAVIS ELIZABETH
N020616	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	200MG	KADIAN	ACTAVIS ELIZABETH
N020616	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	20MG	KADIAN	ACTAVIS ELIZABETH
N020616 BX	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	30MG	KADIAN	ACTAVIS ELIZABETH
N020616	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	50MG	KADIAN	ACTAVIS ELIZABETH
N020616 BX	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	60MG	KADIAN	ACTAVIS ELIZABETH
N020616	Yes	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	80MG	KADIAN	ACTAVIS ELIZABETH
N021260	Yes	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	120MG	AVINZA	KING PHARMS
N021260 BX	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	30MG	AVINZA	KING PHARMS
N021260	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	45MG	AVINZA	KING PHARMS
N021260 BX	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	60MG	AVINZA	KING PHARMS
N021260	No	MORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	75MG	AVINZA	KING PHARMS

Local intranet

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020616&TABLE1=OB_Rx Go Links

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	100MG
Application Number:	N020616
Product Number:	003
Approval Date:	Jul 3, 1996
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product: View	

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	30MG
Application Number:	N020616
Product Number:	004
Approval Date:	Mar 9, 2001
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	BX
Patent and Exclusivity Info for this product: View	

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	60MG
Application Number:	N020616
Product Number:	005
Approval Date:	Mar 9, 2001
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	BX
Patent and Exclusivity Info for this product: View	

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020616&TABLE1=OB_Rx Go Links

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	80MG
Application Number:	N020616
Product Number:	006
Approval Date:	Oct 27, 2006
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product: View	

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	200MG
Application Number:	N020616
Product Number:	007
Approval Date:	Feb 27, 2007
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product: View	

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	10MG
Application Number:	N020616
Product Number:	008
Approval Date:	Apr 20, 2007
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product: View	

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020616 Product 003 in the OB_Rx list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020616	003	5202128	Apr 13, 2010				
N020616	003	5378474	Mar 23, 2010				

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexcdnew.cfm?Appl_No=020616&Product_No=006&table1=OB_Rx Go Links

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FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020616 Product 006 in the OB_Rx list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020616	006	5202128	Apr 13, 2010		Y		
N020616	006	5378474	Mar 23, 2010		Y		

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

Done Local intranet

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-200812	ORIG-1	WATSON LABORATORIES INC	MORPHINE SULFATE

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/s/

FELECIA TAN
03/08/2010

MARTIN H Shimer
03/10/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 200812

Watson Laboratories Inc, Florida
Attention: Janet Vaughn
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

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

NAME OF DRUG: Morphine Sulfate Extended-release Capsules USP,
80 mg and 100 mg

DATE OF APPLICATION: December 16, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 16, 2009

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

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

Should you have questions concerning this application, contact:

Laura Longstaff
Project Manager
240-276-8566

Sincerely yours,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-200812	ORIG-1	WATSON LABORATORIES INC	MORPHINE SULFATE

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/s/

FELECIA TAN
03/08/2010

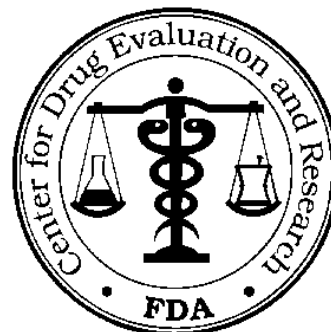
MARTIN H Shimer
03/10/2010
Signing for Wm Peter Rickman

**** Please email me at soon.oh@fda.hhs.gov to confirm that you have received this labeling comment.**

Telephone Fax

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8951



TO: Watson Laboratories, Inc

TEL: 954-358-6109

ATTN: Janet Vaughn

FAX: 954-358-6350

FROM: Soon Oh

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate extended-release capsule.

Pages (including cover): 5

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

**Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857**

After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT** submit your ANDA Regulatory documents to this address prior to **01-Aug-2010**. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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

ANDA Number: 200812

Date of Submission: December 16, 2009

Applicant's Name: Watson Laboratories, Inc

Established Name: Morphine Sulfate Extended-Release Capsules USP, 80 mg and 100 mg

Labeling Deficiencies;

1. GENERAL COMMENT

Please note that the term "(b) (4)" is not an official USP dosage form. Please revise the name of the drug product to read "Morphine Sulfate Extended-Released Capsules, USP" in all labeling pieces. Please also be advised that the reference listed drug, Kadian® Capsules, uses "Morphine Sulfate Extended-Released Capsules, USP" as the established name.

1. CONTAINER- 30s and 100s

- a. See GENERAL COMMENT above.
- b. We ask that you include the phrase "(Once or twice Daily Formulation)" in a prominent manner immediately above the drug product name. We believe that inclusion of this phrase help to distinguish your drug product from the morphine sulfate extended-release capsules modeled after other reference listed drug products.
- c. Please be advised that your drug product is a controlled substance. Please include the controlled substance symbol on the label, preferably in association with the drug product name. The symbol on labels shall be clear and large enough to afford easy identification of the schedule of the controlled substance upon inspection without removal from the dispenser's shelf.
- d. Decrease prominence of company logo and move further down the label.
- e. Increase prominence of net quantity statement and "Rx only"
- f. Please revise the net quantity statement to read "30 Capsules" rather than "(b) (4)"
- g. Please include a statement "Protect from light and moisture" in association with the storage temperature statement.
- i. We encourage you to include pictorial of the capsule like the RLD. The picture of your drug product is to reflect the actual product including unique markings rather than a simulated drawing of the product.
- j. 1st line of the side panel- Revise to read:

"Each extended-release capsule contains..." [note "extended- release" inserted]

- k. Please ensure that you complete the bar code when submitting the final printed labels.
- l. Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please ensure that these criteria are met prior to submission of final print.
- m. Please complete the address of the distributor.

2. INSERT

a. GENERAL

- i. See GENERAL COMMENT above.
- ii. We recommend that you allow one line space between paragraphs to increase the readability of your labeling.

b. WARNING

Please put the warning statement in a box. We refer you to the Kadian labeling.

c. DESCRIPTION

- i. We note that your drug product is the subject of a USP monograph. Please verify that your dissolution test meets the USP specification.
- ii. Please note that you have included the strengths that you are not proposing. Please delete the strengths from the DESCRIPTION section other than 80 mg and 100 mg.
- iii. We encourage you to revise the chemical name using letter "α" rather than using "a".
- iv. We note that you included "corn starch" in the listing of inactive ingredients, which is not included in your Composition section. Please delete this and/or comment.
- v. We recommend that you revise the last sentence to read as follows:

"The capsule shells contain black iron oxide,...FD&C red #40. The 80 mg capsule shell also contain FD&C yellow #6 and the 100 mg capsule shell contains FD&C green #3. "
- vi. We note that your coating material contains iron complex. In accordance with the 21 CFR 73.1200(c), the amount of elemental iron contained in the formulation cannot exceed 5 mg per day at the maximum recommended dosage, which is two capsules per day for this drug product. Is the elemental iron of this product consumed at the maximum daily recommended dosage under 5 mg per day? Please comment.

d. CLINICAL PHARMACOLOGY

- i. Pharmacokinetics:

Please insert solid lines on Table 1 to improve readability. We refer you to RLD labeling.

ii. Absorption

Graph 1 (Study # MOB-1/90) - Revise to read:

...for morphine sulfate extended-release capsule (twice-a-day), extended-release morphine tablet... [note "capsule" inserted]

e. DOSAGE AND ADMINISTRATION

i. Individualization of Dosage - 2nd paragraph, 1st sentence:

Please note that twice-a-day is not spaced out in the sentence. Please revise to read "(twice-a-day)".

ii. Conversion from morphine sulfate extended-release capsules, USP to other Extended-Release Oral Morphine Formulations

A. The statement "morphine sulfate extended-release capsules, USP" should be presented in bold face type. Please revise accordingly.

B. Last sentence - Revise to read:

...the same total daily dose if other extended-release morphine... [note the word "other" inserted]

f. HOW SUPPLIED

We note that you stated "(b) (4) dose strengths" are available in this section while you are proposing only two strengths. Please revise accordingly.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Soon Oh at 240-276-8996 or send e-mail to Soon.oh@fda.hhs.gov.

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-200812	ORIG-1	WATSON LABORATORIES INC	MORPHINE SULFATE

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/s/

LILLIE D GOLSON
07/14/2010
for Wm. Peter Rickman

QUALITY DEFICIENCY - MINOR

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Watson Laboratories, Inc.-Florida

TEL: 954-358-6125

ATTN: Janet Vaughn

FAX: 954-358-6350

FROM: Tina Nhu

FDA CONTACT PHONE: (240) 276-8548

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 16, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended-Release Capsules, 80 mg and 100 mg.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

***Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855***

After the effective date, 01-Aug-2010, ANDAs will only be accepted at the new mailing address listed above. DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

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CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc. - Florida

DRUG PRODUCT: Morphine Sulfate Extended-Release Capsules USP, 80 mg and 100mg

The deficiencies presented below represent **MINOR** deficiencies.

A. Chemistry Deficiencies:

1. You have submitted your ANDA 200812 for Morphine Sulfate Extended-Release Capsules, USP 80 mg and 100 mg strengths. However, in the introduction to the Quality Overall Summary you reported strengths 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100mg. Please clarify and/or correct.

2. Regarding your manufacturing process:

a.

(b) (4)

b.

c.

d.

3. Regarding your in-process controls:

a.

(b) (4)

b.

c.

- 4.

(b) (4)

5.

6.

7.

8.

- c. We will defer the acceptance of the dissolution specifications until the DBE completes its review. We may request additional information based on DBE review.

9.

(b) (4)

Please justify the employment of alternative methods. In the event of dispute, only the results obtained by the official methods in the USP will be considered conclusive.

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

1. Your Product Development Report includes information on lots that have similar dissolution profiles, yet did not pass the in-vivo criteria. Please discuss whether the in-vitro dissolution method is discriminating in identifying lots that are not in-vivo equivalent.
2. You have submitted long term stability data up to three months for the 80 mg strength only. Please provide available long-term stability data for both 80 mg and 100 mg strengths lots # 3576R0013 and 3453R0001.
3. In the description section of the package insert you have stated that "Each morphine sulfate extended -release capsule contains either 80 mg or 100 mg of Morphine Sulfate USP and the following inactive ingredients common to all strengths: corn starch, diethyl phthalate, -----". The corn starch is not used as ingredient in this formula. Please address.

4. We refer you to the labeling comment on July 14, 2010 stated “Please note that the term “extended-released capsules” is not an official USP dosage form. Please revise the name of the drug product to read “Morphine Sulfate Extended-Released Capsules, USP” in all labeling pieces. Please also be advised that the reference listed drug, Kadian® Capsules, uses “Morphine Sulfate Extended-Released Capsules, USP” as the established name. Please revise and correct the CMC part as needed.

Sincerely yours,

(See appended electronic signature page)

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-200812	ORIG-1	WATSON LABORATORIES INC	MORPHINE SULFATE

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/s/

UBRANI V VENKATARAM
08/05/2010

BIOEQUIVALENCE AMENDMENT

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Watson Laboratories Inc.

TEL: (954) 358-6109

ATTN: Janet Vaughn

FAX: (954) 358-6350

FROM: Diane Nhu

FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on December 16, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended Release Capsules, USP, 80 mg and 100 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement
Bioequivalence Missing Information not Included in Original
Bioequivalence Other
Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

**Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810**

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

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BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Morphine Sulfate Extended Release Capsules,
80 mg and 100 mg

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. Your pre-study bioanalytical method validation report no. 064.5 does not provide the description of solid phase extraction procedure used to extract morphine and morphine-6-glucuronide (morphine-6G) from human plasma samples, concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples for analysis of morphine and morphine-6G in human plasma. Please provide the description of solid phase extraction procedure as well as the concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples.
2. Your pre-study bioanalytical method validation report 064.5 mentions that precision and accuracy run of QCs samples for morphine-6G can be seen in Tables 12 and 14. However, the table titles are for the parent compound, morphine (Title for Tables# 12 and 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine in Human Plasma). Please clarify the reason for this discrepancy and submit the intraday accuracy and precision data for the QC samples for morphine and morphine-6G.
3. Please provide supporting data to show that naltrexone does not affect the extraction and estimation of morphine and morphine-6G in human plasma samples.
4. Please confirm whether selection of samples with adjusted lower limit of quantitation (ALLQ) and retention time shift (RTS) was based on established procedures. The analytical site's Standard Operating Procedure (b) (4) SOP_04_LBP_006 does not define adjusted lower limit of quantitation and retention time shift and fails to provide the criteria for selecting samples with ALLQ and RTS.

5. For fed studies #R09-0073 and #R09-0905, the freeze-thaw stability of morphine-6G samples exceeded beyond the established 4 freeze-thaw cycle stability. Please provide the freeze-thaw stability data to cover the stability of morphine-6G during bioanalytical study conduct.
6. You have not provided the actual amount of (b) (4) (b) (4) and (b) (4) in your test product's formulation. Please provide this information including the total amount of elemental iron per tablet in your formulation.
7. You have not provided the comparative dissolution testing data using USP method. Please conduct the dissolution testing on 12 dosage units each of the test and reference 80 mg and 100 mg formulations using the current USP method for morphine sulfate extended release capsules, and submit the individual dissolution data, mean, range and coefficient of variation (CV%) values. Division of Bioequivalence will recommend dissolution specifications upon review of submitted data.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BARBARA M DAVIT
09/29/2010



Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

ANDA # 200812

Sequence # 0001

September 30, 2010

Dr. Keith Webber
Acting Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

RE: Additional Strengths Amendment – 20 mg, 30 mg , 50 mg and 60 mg strengths

Dear Sir:

In accordance with CFR 314.96, Watson Laboratories, Inc.-Florida (WLF) is submitting an amendment to the above referenced Abbreviated New Drug Application (ANDA) for approval to market four (4) additional strengths of Morphine Sulfate Extended-release Capsules USP. The reference-listed drug (RLD) is Kadian® (Morphine Sulfate Extended-release) Capsules, manufactured by Actavis Kadian LLC, under NDA # 020616.

This amendment contains a request for a waiver to conduct *in vivo* bioequivalence study for the 20 mg, 30 mg, 50 mg and 60 mg strengths of the drug product. *In vivo* bioequivalence studies under fasting, fed and sprinkle conditions for 80 mg and fed conditions for 100 mg, which demonstrate that the 80 mg and 100 mg strengths of Morphine Sulfate Extended-release Capsules USP are bioequivalent to the reference listed drug (RLD), were provided in the original application (Module 5, Sequence # 0000). The 20 mg, 30 mg, 50 mg and 60 mg strengths of the drug product are proportionally similar¹ with respect to active and inactive ingredients to the 80 mg and 100 mg strengths that underwent *in vivo* bioequivalence testing, are the same dosage form and meet an appropriate *in-vitro* test requirement. *In-vitro* comparative dissolution data for the 20 mg, 30 mg, 50 mg and 60 mg strengths are provided in **Section 2.7.1.2** of this amendment (**Sequence # 0001**).

In addition to submitting information on the additional strengths of the drug product, WLF is also providing a response to the labeling deficiency letter dated and received on 07/14/2010 from Soon Oh (Office of Generic Drugs) providing comments for the above referenced application (see copy attached). Please refer to the responses provided in the corresponding labeling sections (1.14.1.2 for the container labels and 1.14.3.1 for the outsert).

¹ Definition from "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations," Section V. *Documentation of BA and BE*.

Please note that this application contains references to Andrx Pharmaceuticals, Inc. Through an acquisition completed on November 3, 2006, Andrx Pharmaceuticals, Inc. became a wholly owned subsidiary of Watson Pharmaceuticals, Inc. As a result, Andrx Pharmaceuticals, Inc. is now "Doing Business As" (DBA) Watson Laboratories, Inc.-Florida (WLF).

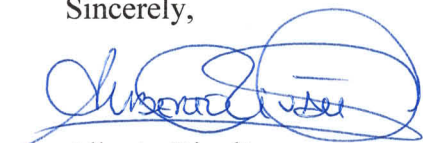
This is an electronic submission organized in accordance with ICH-CTD format (eCTD). Module 1, Module 2 (Quality Overall Summary (QOS)) and Module 3 have been updated accordingly. To facilitate the review, WLF is submitting a copy of the FDA's "*ANDA Checklist for CTD or eCTD Format for Completeness and Acceptability of an Application for Filing*", which provides links to all the respective sections and documents in each applicable Module (copy attached).

The submission has been verified virus-free. WLF is submitting this application through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

A certification of Compliance form 3674 is provided along with the cover letter and the FDA 356h form.

For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*). For Information Technology assistance, please contact Majid Rostai at majid.rostai@watson.com (*email*), at (954) 358-6148 (*direct dial*) or (954) 552-7808 (*cell*) or (954) 552-7808 (*fax*).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs



Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

ANDA # 200812

Sequence # 0002

November 10, 2010

Keith Webber, Ph.D
Acting Director, Office of Generic Drugs,
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: INFORMATION REQUESTED

Dear Sir:

Reference is made to Watson Laboratories, Inc. – Florida's (WLF's) abbreviated new drug application, Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg (ANDA # 200812), and to an email from Felecia Tan, at the FDA, on November 2, 2010, requesting the following information:

1. A cGMP Certification for the API manufacturer.

Response:

The cGMP certification for the API manufacturer is provided in **Section 3.2.S.2.1** of this amendment.

WLF is submitting this application through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*).

Sincerely,

A handwritten signature in blue ink, appearing to read "Alberto Rivalta", is written over a circular blue ink stamp.

Alberto Rivalta
Manager, Regulatory Affairs

**ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR
FILING**

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD)

Format please go to: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

*For a Comprehensive Table of Contents Headings and Hierarchy please go to:

<http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>

** For more CTD and eCTD informational links see the final page of the ANDA Checklist

*** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage <http://www.fda.gov/cder/ogd/> ***

ANDA #: 200812

FIRM NAME: WATSON LABORATORIES INC.-FLORIDA

PIV: NO

Electronic or Paper Submission: ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: MORPHINE SULFATE

DOSAGE FORM: EXTENDED-RELEASE CAPSULES USP, 20 MG, 30 MG, 50 MG, 60 MG,
80 MG AND 100 MG (NEW STRENGTHS 20 MG, 30 MG, 50 MG, 60 MG)

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC2 TM 23 ☒ Activity	Bio Team 5: Chandra Chaurasia ☒ Activity
ANDA/Quality RPM: Laura Longstaff ☒ FYI	Bio PM: Diane Nhu ☐ FYI
Quality Team Leader: Capella, Peter No assignment needed in DARRTS	Clinical Endpoint Team Assignment: (No) ☐ Activity
Labeling Reviewer: Chan Park ☒ Activity	Micro Review (No) ☐ Activity

***Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). ***

Letter Date: SEPTGEMBER 30, 2010	Received Date: OCTOBER 1, 2010
Comments: 2 + 4 = 6 YES On Cards: YES Therapeutic Code: 5030350 ACUTE PAIN, OPIOID	
Archival copy: ELECTRONIC (GATEWAY) Sections I Review copy: NA E-Media Disposition: NA Not applicable to electronic sections	
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST FELECIA (LISA) TAN Date 11/10/2010 Reference ID: 2863847	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE
--	---

Supervisory Concurrence/Date: _____

Date: _____

1. Edit Application Property Type in DARRTS where applicable for
 - a. First Generic Received
☐ Yes ☒ No
 - b. Market Availability
☒ Rx ☐ OTC
 - c. Pepfar
☐ Yes ☒ No
 - d. Product Type
☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
 - e. USP Drug Product (at time of filing review)
☒ Yes ☐ No
2. Edit Submission Patent Records
☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
☐ Yes N/A
4. Requested EER
☐ Yes N/A

ADDITIONAL COMMENTS REGARDING THE ANDA:

CONTACT INFO: JANET VAUGHN PR ALBERTO RIVALTA

REQUEST:

1.) SUBMIT CGMP FOR API MANUF.

COMMUNICATION:

11/2/2010: EMAILED FOR ABOVE TO VAUGHN.

11/10/2010: REQUESTED ITEM RECED.

Draft Guidance on Morphine Sulfate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Morphine Sulfate

Form/Route: Extended Release Capsule/Oral

Recommended studies: 6 Studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 100 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: A naltrexone blockade should be used to remove the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid receptors. A common approach is to administer 50 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug. Please consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 100 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see comments above.

3. Type of study: Fasting Sprinkle in applesauce
Design: Single-dose, two-way crossover in-vivo
Strength: 100 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see comments above.

4. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 200 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see comments above.

5. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 200 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see comments above.
6. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 10 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see comments above.

Analytes to measure: Morphine and Morphine-6-glucuronide in plasma

Bioequivalence based on (90% CI): Morphine

Waiver request of in-vivo testing: 20 mg, 30 mg, 50 mg, 60 mg and 80 mg strengths based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) acceptable in vitro dissolution testing for the 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg strengths, and (iii) proportional similarity of formulations across 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2 and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

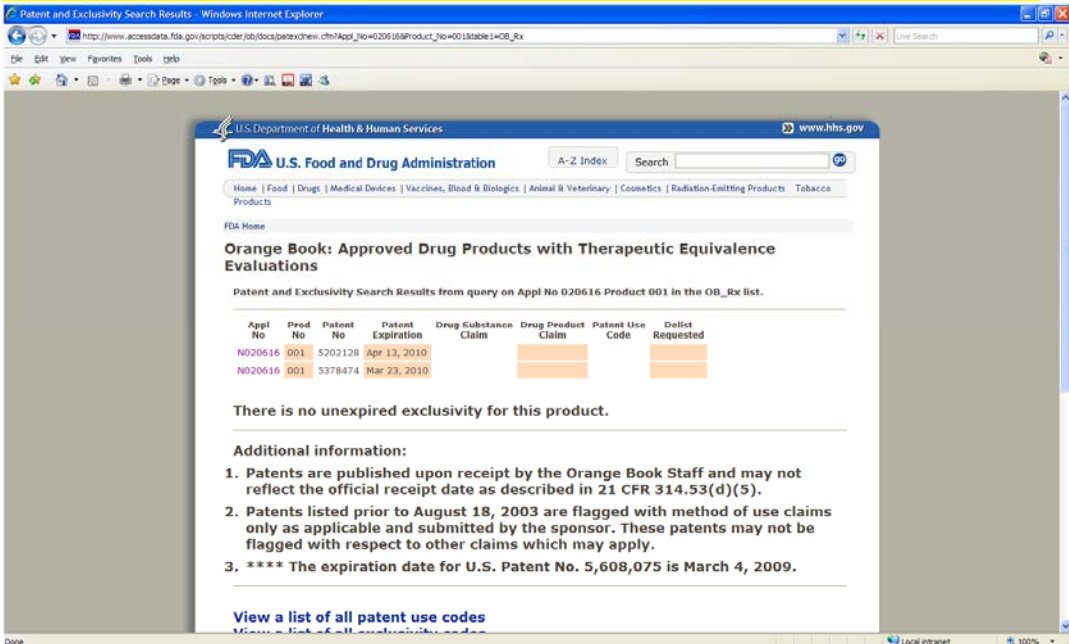
Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	1.1.2 Signed and Completed Application Form (356h) (original signature) (Check Rx/OTC Status) RX YES	☒
1.2	Cover Letter Dated: SEPTGEMBER 30, 2010	☒
1.2.1	Form FDA 3674 (PDF) YES OPTION A	☒
*	Table of Contents (paper submission only) YES	☒
1.3.2	Field Copy Certification (original signature) NA (N/A for E-Submissions)	☒
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	Financial Certifications SEE WAIVER SECTION Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) N/A Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	1.3.5.1 Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations 1.3.5.2 Patent Certification 1. Patent number(s) PATENT AND EXCLUSIVITY INFO SAME FOR ALL SUBMITTED STRENGTHS.  2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): 4/13/2010 a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: YES NO UNEXPIRED EXCLUSIVITY	☒

1.4.1	References Letters of Authorization - DMF letters of authorization - Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES Type II DMF No. (b) (4) - Type III DMF authorization letter(s) for container closure (b) (4) - US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	Basis for Submission NDA# : 20-616 YES Ref Listed Drug: KADIAN YES Firm: ACTAVIS KADIAN LLC YES ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) - Conditions of use SAME - Active ingredients SAME - Inactive ingredients JUSTIFIED - Route of administration YES - Dosage Form YES - Strength YES	☒
1.12.14	Environmental Impact Analysis Statement YES 21CFR25.31	☒
1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 20 MG, 30 MG, 50 MG AND 60 MG In Vivo Bioequivalence: WLF has performed <i>in-vivo</i> bioequivalence studies under fasting, fed and sprinkle conditions comparing its formulation of Morphine Sulfate Extended-release Capsules, 80 mg and 100 mg (fed studies only) strengths to the reference listed drug (RLD) Kadian® (Morphine Sulfate Extended-release) Capsules, 80 mg and 100 mg manufactured by Actavis Kadian LLC, under NDA # 020616. WLF's formulation for 80 mg strength was shown to be bioequivalent to Kadian®, 80 mg strength under fasting, fed and sprinkle conditions. Additionally, a bioequivalence study (fed) was performed comparing WLF's 100 mg strength and the Kadian®, 100 mg strength. The bioequivalency data were previously submitted in Section 5.3 of the original ANDA (Sequence # 0000). Formulation Proportionality: WLF's Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg and 60 mg are proportionally similar¹ with respect to active and inactive ingredients to the 80 mg and 100 mg strength that underwent <i>in vivo</i> bioequivalence testing under fasting, fed and sprinkle conditions for 80 mg and fed conditions for 100 mg. The quantitative composition of all the four (20 mg, 30 mg, 50 mg and 60 mg) strengths of the drug product is provided in Section 2.7.1.1 of this amendment (Sequence # 0001). The potency and content uniformity data for WLF's drug product and the RLD are also provided in Section 2.7.1.2 of this amendment (Sequence # 0001) for the 20 mg, 30 mg, 50 mg and 60 mg strengths of the drug product.	☒

1.14.1	Draft Labeling (Mult Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft (each strength and container) YES 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES 1.14.1.3 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) ++COMMITMENT FOR SPL	☒
1.14.3	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES 1.14.3.3 1 RLD label and 1 RLD container label YES	☒

Table 6. Ingredients in Gelatin Capsule – 100 mg

Capsule components:	Amount per capsule in mg	IID Max Level
Titanium Dioxide	(b) (4)	Up to 1387 mg
Gelatin		Up to 756 mg
FD&C Green #3		Up to 40.00 mg
(b) (4)		(b) (4)
		(b) (4)

(b) (4) and (b) (4) are commercially available prepared mixtures of commonly used excipients. Their quantitative compositions are contained in the manufacturer's (b) (4) DMF# (b) (4). A copy of the DMF Letter of Access from (b) (4) is provided in Module 1.14.1, and the qualitative formula is provided in this section.

² Complies with the 21 CFR 73.1200 requirement of NMT 5 mg elemental iron/day.

2.3	Quality Overall Summary (QOS) E-Submission: PDF YES Word Processed e.g., MS Word YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ Question based Review (QbR) YES 2.3.S Drug Substance (Active Pharmaceutical Ingredient) YES 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product YES 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	☒
2.7	Clinical Summary (Bioequivalence) ONLY HI-LITED TABLES ARE APPLICABLE. Model Bioequivalence Data Summary Tables E-Submission: PDF YES Word Processed e.g., MS Word YES 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation N/A Table 6. Formulation Data YES 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution YES 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies N/A Table 3. Statistical Summary of the Comparative BA Data N/A 2.7.1.4 Appendix 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study N/A 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies N/A	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	General Information SUBMITTED 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties	☒
3.2.S.2	Manufacturer 3.2.S.2.1 Manufacturer(s) (This section includes contract manufacturers and testing labs) Drug Substance (Active Pharmaceutical Ingredient) 1. Name and Full Address(es) of the Facility(ies) 2. Function or Responsibility 3. Type II DMF number for API 4. CFN or FEI numbers (b) (4) Company Name: (b) (4) Address: (b) (4) Responsibility: (b) (4) Name/Address of Contact Person: (b) (4) Telephone and Fax Number for Contact Person: (b) (4)	☒
3.2.S.3	Characterization REFERENCE TO DMF WITH IMPURITY DETAILS.	☒
3.2.S.4	Control of Drug Substance (Active Pharmaceutical Ingredient) REFERENCE TO ORIGINAL 3.2.S.4.1 Specification Testing specifications and data from drug substance manufacturer(s) YES 3.2.S.4.2 Analytical Procedures YES 3.2.S.4.3 Validation of Analytical Procedures 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) 30324 3.2.S.4.4 Batch Analysis 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES 3.2.S.4.5 Justification of Specification SUBMITTED	☒
3.2.S.5	Reference Standards or Materials SUBMITTED	☒
3.2.S.6	Container Closure Systems DMF	☒
3.2.S.7	Stability DMF	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.1	Description and Composition of the Drug Product 1. Unit composition YES 2. Inactive ingredients and amounts are appropriate per IIG JUSTIFIED PER IIG JUSTIFICATION MADE FOR THE ORIGINAL CAN STAND FOR THE NEW STRENGTH AMENDMENT. ALL LEVELS OF EXCIPIENTS USED IN THE NSA FALL FAR BELOW THE LEVELS USED IN THE ORIGINAL SUBMISSION FOR THE 80MG AND 100MG STRENGTHS. NO FURTHER JUSTIFICATION IS REQUIRED.	☒																									
3.2.P.2	Pharmaceutical Development Pharmaceutical Development Report 3.2.P.2.1 PHARMACEUTICAL DEVELOPMENT Refer to the Pharmaceutical Development report provided in Section 3.2.P.2.1 of the Original ANDA submission, Sequence # 0000.	☒																									
3.2.P.3	Manufacture 3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es) of the Facility(ies) 2. CGMP Certification: 3. Function or Responsibility 4. CFN or FEI numbers <table border="1"> <tr> <td>Production Site:</td><td>Watson Laboratories, Inc.-Florida</td></tr> <tr> <td>Address:</td><td>4955 Orange Drive Ft. Lauderdale, FL 33314 FDA Registration #3003194604</td></tr> <tr> <td>Responsibility:</td><td> • Drug substance, inactive ingredients, and packaging components analytical testing and release (except for certain specialized test done by contract testing laboratories). • Finished product pharmaceutical manufacturing, packaging and labeling of finished product. • Intermediate, finished product and stability testing. • Finished product storage and distribution. </td></tr> <tr> <td>Name of Contact Person:</td><td>Maritza Adrover, Director of Regulatory Compliance</td></tr> <tr> <td>Telephone Number for Contact Person:</td><td>Tel. (954) 585-1445 Fax. (954) 585-1828</td></tr> </table> 3.2.P.3.2 Batch Formula YES 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Comparative Manufacturing Summary (ANDA Batches vs. Proposed Commercial Batches). <table border="1"> <thead> <tr> <th></th><th>ANDA Batch</th><th>Proposed Commercial Batches</th></tr> </thead> <tbody> <tr> <td>Batch Size</td><td>20 mg (b) (4) capsules</td><td>20 mg (b) (4) capsules</td></tr> <tr> <td></td><td>30 mg capsules</td><td>30 mg capsules</td></tr> <tr> <td></td><td>50 mg capsules</td><td>50 mg capsules</td></tr> <tr> <td></td><td>60 mg capsules</td><td>60 mg capsules</td></tr> </tbody> </table> 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement 21CFR211.115 3.2.P.3.4 Controls of Critical Steps and Intermediates SUBMITTED 3.2.P.3.5 Process Validation and/or Evaluation N/A 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	Production Site:	Watson Laboratories, Inc.-Florida	Address:	4955 Orange Drive Ft. Lauderdale, FL 33314 FDA Registration #3003194604	Responsibility:	• Drug substance, inactive ingredients, and packaging components analytical testing and release (except for certain specialized test done by contract testing laboratories). • Finished product pharmaceutical manufacturing, packaging and labeling of finished product. • Intermediate, finished product and stability testing. • Finished product storage and distribution.	Name of Contact Person:	Maritza Adrover, Director of Regulatory Compliance	Telephone Number for Contact Person:	Tel. (954) 585-1445 Fax. (954) 585-1828		ANDA Batch	Proposed Commercial Batches	Batch Size	20 mg (b) (4) capsules	20 mg (b) (4) capsules		30 mg capsules	30 mg capsules		50 mg capsules	50 mg capsules		60 mg capsules	60 mg capsules	☒
Production Site:	Watson Laboratories, Inc.-Florida																										
Address:	4955 Orange Drive Ft. Lauderdale, FL 33314 FDA Registration #3003194604																										
Responsibility:	• Drug substance, inactive ingredients, and packaging components analytical testing and release (except for certain specialized test done by contract testing laboratories). • Finished product pharmaceutical manufacturing, packaging and labeling of finished product. • Intermediate, finished product and stability testing. • Finished product storage and distribution.																										
Name of Contact Person:	Maritza Adrover, Director of Regulatory Compliance																										
Telephone Number for Contact Person:	Tel. (954) 585-1445 Fax. (954) 585-1828																										
	ANDA Batch	Proposed Commercial Batches																									
Batch Size	20 mg (b) (4) capsules	20 mg (b) (4) capsules																									
	30 mg capsules	30 mg capsules																									
	50 mg capsules	50 mg capsules																									
	60 mg capsules	60 mg capsules																									

3.2.P.4	Controls of Excipients (Inactive Ingredients) REFERENCE TO ORIGINAL Source of inactive ingredients identified 3.2.P.4.1 Specifications 1. Testing specifications (including identification and characterization) 2. Suppliers' COA (specifications and test results) 3.2.P.4.2 Analytical Procedures 3.2.P.4.3 Validation of Analytical Procedures 3.2.P.4.4 Justification of Specifications Applicant COA	☐
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MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	Controls of Drug Product REFERENCE TO ORIGINAL 3.2.P.5.1 Specification(s) 3.2.P.5.2 Analytical Procedures 3.2.P.5.3 Validation of Analytical Procedures Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers 1. <u>Drug Product (Biobatch, Method Validation and Stability Lot)</u> Morphine Sulfate Extended-release Capsules USP, 20 mg – Batch # 3449R0001 (not packaged), Batch # 3449R0001A (finished product packaged in bottles of 30 count) and Batch # 3449R0001B (finished product packaged in bottles of 100 count). Morphine Sulfate Extended-release Capsules USP, 30 mg – Batch # 3450R0001 (not packaged), Batch # 3450R0001C (finished product packaged in bottles of 30 count) and Batch # 3450R0001B (finished product packaged in bottles of 100 count). Morphine Sulfate Extended-release Capsules USP, 50 mg – Batch # 3451R0001 (not packaged), Batch # 3451R0001A (finished product packaged in bottles of 30 count) and Batch # 3451R0001B (finished product packaged in bottles of 100 count). Morphine Sulfate Extended-release Capsules USP, 60 mg – Batch # 3452R0001 (not packaged), Batch # 3452R0001A (finished product packaged in bottles of 30 count) and Batch # 3452R0001B (finished product packaged in bottles of 100 count). 3.2.P.5.4 Batch Analysis Certificate of Analysis for Finished Dosage Form yes 3.2.P.5.5 Characterization of Impurities SAME AS ORIGINAL 3.2.P.5.6 Justification of Specifications SUBMITTED	☒
3.2.P.7	Container Closure System REFERENCE TO ORIGINAL 1. Summary of Container/Closure System (if new resin, provide data) 2. Components Specification and Test Data 3. Packaging Configuration and Sizes (1) Bottles of 30 capsules: <u>Container/closure system:</u> 75 cc white, straight-sided, round bottom, high-density polyethylene (HDPE) bottle (Code # (b) (4)) 33 mm, white, ribbed sides, child resistant plastic closure with aluminum foil coated (b) (4) liner (Code # (b) (4)) (b) (4) coil, (b) (4) white filament like hairs (Code # (b) (4)) <u>Labeling:</u> Container label Outsert (2) Bottles of 100 capsules: <u>Container/closure system:</u> 250 cc white, straight-sided, round bottom, high-density polyethylene (HDPE) bottle (Code # (b) (4)) 45 mm, white, ribbed sides, child resistant plastic closure with aluminum foil coated (b) (4) liner (Code # (b) (4)) (b) (4) coil, (b) (4) white filament like hairs (Code # (b) (4)) <u>Labeling:</u> Container label Outsert 4. Container/Closure Testing 5. Source of supply and suppliers address	☒

3.2.P.8	3.2.P.8.1 Stability (Finished Dosage Form) 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 MONTH EXP 3.2.P.8.2 Post-approval Stability and Conclusion Post Approval Stability Protocol and Commitments YES 3.2.P.8.3 Stability Data 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES W/LOT #'S	☒
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MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	3.2.R.1.S Executed Batch Records for drug substance (if available) 3.2.R.2.S Comparability Protocols 3.2.R.3.S Methods Validation Package Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐
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3.2.R (Drug Product)	3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES Theoretical Yield SEE BELOW Actual Yield SEE BELOW Packaged Yield SEE BELOW 3.2.R.1.P.2 Information on Components N/A 3.2.R.2.P Comparability Protocols N/A 3.2.R.3.P Methods Validation Package YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒
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MODULE 5

CLINICAL STUDY REPORTS

N/A

ACCEPTABLE

5.2	Tabular Listing of Clinical Studies	☐
5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) 2. Lot Numbers of Products used in BE Study(ies): 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	☐

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: - Table 10. Study Information - Table 12. Dropout Information - Table 13. Protocol Deviations 5.3.1.3 In Vitro-In-Vivo Correlation Study Reports 1. Summary Bioequivalence tables: - Table 11. Product Information - Table 16. Composition of Meal Used in Fed Bioequivalence Study 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies 1. Summary Bioequivalence table: - Table 9. Reanalysis of Study Samples - Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses - Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples 5.3.7 Case Report Forms and Individual Patient Listing	☐
5.4	Literature References	☐
	Possible Study Types:	
Study Type	IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) FASTING, FED AND SPRINKLE STUDY DONE ON 80 MG DATED 12/15/2009 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution:	☐
Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	NASALLY ADMINISTERED DRUG PRODUCTS <u>Solutions</u> (Q1/Q2 sameness): - In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) <u>Suspensions</u> (Q1/Q2 sameness): - In-Vivo PK Study - Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) - EDR Email: Data Files Submitted - In-Vivo BE Study with Clinical End Points - Properly defined BE endpoints (eval. by Clinical Team) - Summary results meet BE criteria (90% CI within +/- 20% of 80-125) - Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) - EDR Email: Data Files Submitted - In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) - Pilot Study (determination of ED50) - Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	TRANSDERMAL DELIVERY SYSTEMS <u>In-Vivo PK Study</u> - Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) - In-Vitro Dissolution - EDR Email: Data Files Submitted <u>Adhesion Study</u> <u>Skin Irritation/Sensitization Study</u>	☐

Updated 10/19/2009

Following this page, 5 pages withheld in full - (b)(4)

(b) (4)

Active Ingredient Search - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/label/labelsearch.jsp

N020616	Yes	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	100MG	KADIAN	ACTAVIS ELIZABETH
N020616	Yes	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	10MG	KADIAN	ACTAVIS ELIZABETH
N020616	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	200MG	KADIAN	ACTAVIS ELIZABETH
N020616	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	20MG	KADIAN	ACTAVIS ELIZABETH
N020616 EX	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	30MG	KADIAN	ACTAVIS ELIZABETH
N020616	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	50MG	KADIAN	ACTAVIS ELIZABETH
N020616 EX	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	60MG	KADIAN	ACTAVIS ELIZABETH
N020616	Yes	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	80MG	KADIAN	ACTAVIS ELIZABETH
N021260	Yes	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	120MG	AVINZA	KING PHARMS
N021260 EX	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	30MG	AVINZA	KING PHARMS
N021260	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	45MG	AVINZA	KING PHARMS
N021260 EX	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	60MG	AVINZA	KING PHARMS
N021260	No	NORPHINE SULFATE	CAPSULE, EXTENDED RELEASE; ORAL	75MG	AVINZA	KING PHARMS

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Orange Book Detail Record Search - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?App1_No=020616&LE1=OB_Rx

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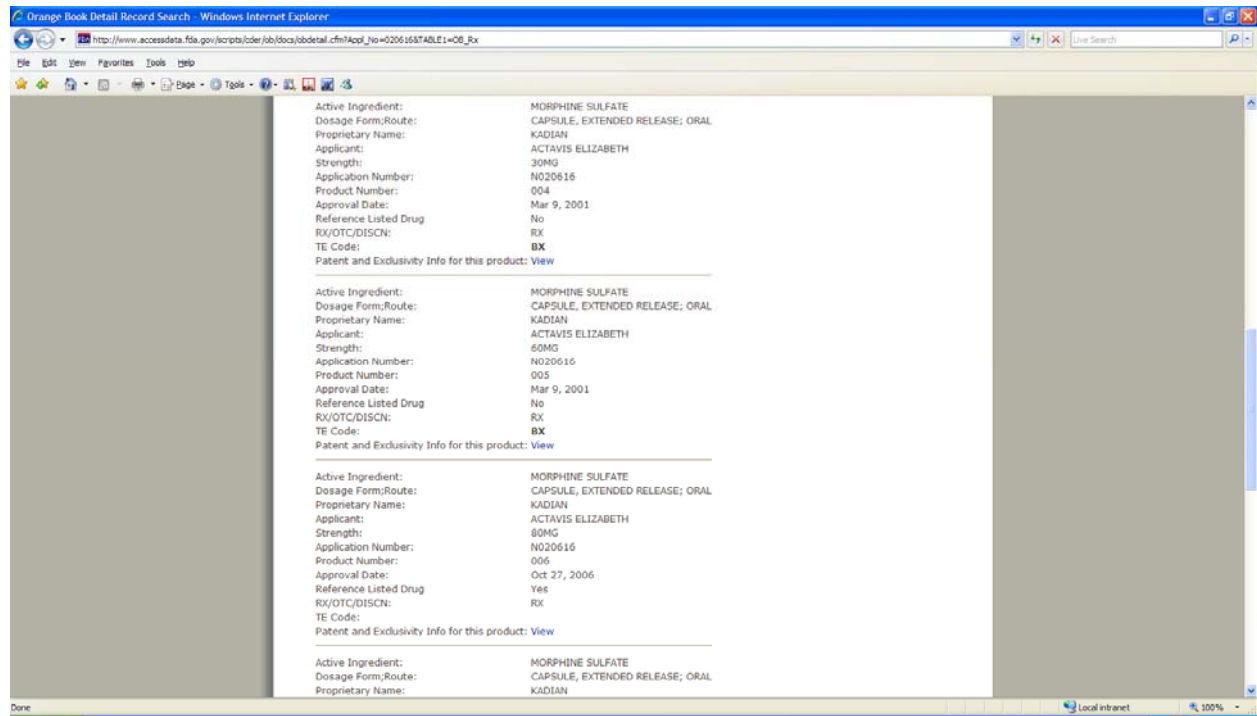
Evaluations

Search results from the "OB_Rx" table for query on "020616."

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	20MG
Application Number:	N020616
Product Number:	001
Approval Date:	Jul 3, 1996
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product: View	

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	50MG
Application Number:	N020616
Product Number:	002
Approval Date:	Jul 3, 1996
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product: View	

Active Ingredient:	MORPHINE SULFATE
Dosage Form/Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	KADIAN
Applicant:	ACTAVIS ELIZABETH
Strength:	100MG
Application Number:	N020616
Product Number:	003
Approval Date:	Jul 3, 1996
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	



Patent and Exclusivity Search Results - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclusiv.cfm?Appl_No=020616&Product_No=001&table1=OB_Rx

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020616 Product 001 in the OB_Rx list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020616	001	5202128	Apr 13, 2010				
N020616	001	5378474	Mar 23, 2010				

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.

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http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclusiv.cfm?Appl_No=020616&Product_No=002&table1=OB_Rx

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www.hhs.gov

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Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020616	002	5202128	Apr 13, 2010				
N020616	002	5378474	Mar 23, 2010				

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http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclusiv.cfm?Appl_No=020616&Product_No=003&table1=OB_Rx

U.S. Department of Health & Human Services
www.hhs.gov

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Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020616	003	5202128	Apr 13, 2010				
N020616	003	5378474	Mar 23, 2010				

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2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.

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Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020616	004	5202128	Apr 13, 2010				
N020616	004	5378474	Mar 23, 2010				

There is no unexpired exclusivity for this product.

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2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
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Patent and Exclusivity Search Results from query on Appl No 020616 Product 006 in the OB_Rx list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020616	006	5202128	Apr 13, 2010		Y		
N020616	006	5378474	Mar 23, 2010		Y		

There is no unexpired exclusivity for this product.

Additional information:

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2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.

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/s/

FELECIA TAN

11/15/2010

MARTIN H Shimer

11/18/2010

**** Please email me at chan.park@fda.hhs.gov to confirm that you have received this labeling comment.**

Telephone Fax

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8951



TO: Watson Lab

TEL: 954-358-6109

ATTN: Janet Vaughn

FAX: 954-358-6350

FROM: Chan Park

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate E-R Capsules.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:

**Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855**

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

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

ANDA Number: 200812

Date of Submission: September 30, 2010

Applicant's Name: Watson Laboratories, Inc.

Established Name: Morphine Sulfate Extended-Release Capsules USP, 20 mg, 30 mg, 50 mg,
60 mg, 80 mg, and 100 mg

Labeling Deficiencies;

1. GENERAL COMMENT

We note that you did not include the point-to-point responses to the Agency's comments. Please include this in your future submissions.

2. CONTAINER- 30s and 100s

- a. Please put the text "Once or Twice Daily Formulation" in a parenthesis and relocate so that it is more closely associated with the drug product name.
- b. We note that you used blue color background for all strengths for the bar appearing at the bottom of the label. If feasible, we recommend that you use the same color as the specific one used for the background for the expression of strength to make further distinction between labels of various strengths.
- c. Your labels do not appear to reflect actual size. As addressed in the last deficiency letter, please be advised that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please ensure that these criteria are met prior to submission of final print.
- d. We believe that your drug product is light sensitive. Please verify that your container/closure system is light-resistant.

3. INSERT

a. GENERAL

- i. We note that you did not include the Structured Product Labeling (SPL) in your submission. You are required to submit SPL prior to approval as well as post-approval. Please refer to the guidance at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072331.pdf>.
- ii. We note that the breakdown of the paragraphs in your proposed labeling is not consistent with that of the Kadian® labeling. Please revise accordingly.
- iii. The sub-section titles are dissociated with the corresponding text in numerous places throughout the insert labeling. Please revise so that the sub-section titles appear immediately before the text.

- iv. It is not necessary to include the term "USP" in association with the drug product name throughout the text. Please delete this except in the TITLE, DESCRIPTION, INDICATIONS AND USAGE, and HOW SUPPLIED sections.
 - v. Please ensure that all text associated with graphs appear sufficiently legible throughout the insert labeling.
 - vi. It is preferable to use the term "to" rather than a hyphen when expressing a numerical range.
 - vii. We recommend that the font size of the final printed labeling not be less than 6 pts.
- b. DESCRIPTION - Last paragraph, 4th sentence:
- i. You made references to 80 mg and 100 mg strengths only. Please include additional strengths you are proposing.
 - ii. We note that you included "corn starch" in the listing of inactive ingredients and "propylene glycol" as a component of capsule shell, which are not included in your "Description and Composition" section. Please delete these and/or comment.
- c. CLINICAL PHARMACOLOGY - Table 1:
- i. 1st column, 2nd item:
"Extended-Release" rather than "(b) (4)"
 - ii. 1st column, 4th item:
"Morphine Sulfate Extended-Release Capsules" rather than "KADIAN® Capsules"

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Chan Park at 240-276-8951 or send e-mail to Chan.park@fda.hhs.gov.

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LILLIE D GOLSON
12/08/2010
for Wm. Peter Rickman



Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

ANDA # 200812

Sequence # 0003

December 09, 2010

Keith Webber, Ph.D
Acting Director, Office of Generic Drugs,
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: BIOEQUIVALENCE AMENDMENT

Dear Dr. Webber:

Watson Laboratories, Inc.-Florida (WLF) is submitting this electronic bioequivalence amendment to its original Abbreviated New Drug Application # 200812 for Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg to provide a complete response to the Bioequivalence comments included in the FDA facsimile dated September 29, 2010 (**copy attached**) pertaining to the above product. For convenience of review, the FDA comments are provided in bold face type followed by WLF's responses.

Deficiency:

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. Your pre-study bioanalytical method validation report no. 064.5 does not provide the description of solid phase extraction procedure used to extract morphine and morphine-6-glucouronide (morphine-6G) from human plasma samples, concentration and amount of stock solutions used to prepare the calibration curve and standards and quality control samples for analysis of morphine and morphine-6G in human plasma. Please provide the description of solid phase extraction procedure as well as the concentration and amount of stock solutions used to prepare the calibration curve standards and quality control samples.

Response:

A description of the solid phase extraction procedure can be found in **Attachment 1: Analytical Procedure Morphine and Morphine-6 β -D-glucuronide in Human Plasma, Section G.**

The concentration and amount of stock solutions used for the preparation of the calibration curve standards and quality control samples are described in **Attachment 1: Analytical Procedure Morphine and Morphine-6 β -D-glucuronide in Human Plasma, Sections E and F, respectively.**

2. Your pre-study bioanalytical method validation report no. 064.5 mentions that precision and accuracy run of QCs samples for morphine-6G can be seen in Tables 12 and 14. However, the table titles are for the parent compound, morphine (Title for Tables # 12 and 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine in Human Plasma). Please clarify the reason for this discrepancy and submit the intraday accuracy and precision data for the QC samples for morphine and morphine- 6G.

Response:

The data that is listed in Table 12 and 14 of the method validation report has been verified and is accurate for the metabolite morphine-6G. The titles of these tables contained a typo when referencing the compound. The titles of the tables should read "Table 12: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine-6G in Human Plasma" and "Table 14: Intra-Batch Precision and Accuracy of QC Samples, LLOQ and ULOQ for Morphine-6G in Human Plasma." The updated tables are included as **Attachment 2**.

3. Please provide supporting data to show that Naltrexone does not affect the extraction and estimation of morphine and morphine-6G in human plasma samples.

Response:

Attachment 3, First Addendum to the Method Validation of Morphine and Morphine-6 β -D-Glucuronide (Morphine-6G) in Human Plasma, reports the data of the Interference Test with Naltrexone/6 β -Naltrexol. **Section 1.2** for morphine and **Section 2.2** for morphine-6G establish that the presences of Naltrexone/6 β - Naltrexone do not interfere with the quantitation of either morphine or morphine- 6G.

4. Please confirm whether selection of samples with adjusted lower limit of quantitation (ALLQ) and retention time shift (RTS) was based on established procedures. The analytical site's Standard Operation Procedure (b) (4) SOP_04_LBP_006 does not define adjusted lower limit of quantitation and retention time shift and fails to provide the criteria for selecting samples with ALLQ and RTS.

Response:

The selection of samples for ALLQ and RTS was based on established procedures. The selection of samples for ALLQ followed SOP (b) (4) SOP_04_LBP_006, Version 1 Section 3.2, which was included in the Sample Analysis report, Appendix A, of the original ANDA (**Sequence # 0000**). The selection of samples for RTS follows the Analytical Procedure LC/MS.MS 064.5.B, **Section A**, Instrumentation provided in **Attachment 1**.

For fed studies #R09-0073 and #R09-0905, the freeze-thaw stability of morphine-6G samples exceeded beyond the established 4 freeze-thaw cycle stability. Please provide the freeze-thaw stability data to cover the stability of morphine-6G during bioanalytical study conduct.

Response:

Attachment 3, the First Addendum to the Method Validation of Morphine and Morphine-6 β -D-Glucuronide (Morphine-6G) in Human Plasma, **Section 2.1**, establishes that morphine-6G is stable for 8 freeze/thaw cycles.

6. You have not provided the actual amount of (b) (4) and (b) (4) in your test product's formulation. Please provide this information including the total amount of elemental iron per tablet in your formulation.

Response:

(b) (4) and (b) (4) are the inks used to imprint the empty gelatin capsules. Only trace amounts are found in the test product's formulation; hence, less than (b) (4)% of (b) (4) and (b) (4) is present per capsule. The elemental iron content (from Iron Oxide Black) in (b) (4)% of (b) (4) Black Inks is therefore also less than (b) (4)% w/w of the total formulation.

Furthermore, studies performed in cooperation with (b) (4) manufacturers to determine the amount of dry solids remaining on the surface of a printed product, using (b) (4), have demonstrated that an average of (b) (4) of dry solid is deposited on a single product. Please refer to **Attachment # 4** for a copy of (b) (4) Statement on the estimated average weight amount of dry solid deposited on a printed product. Based on this estimation, the range presented below is an approximation of the amount of ink (dry solid) that would be deposited on a single Morphine Sulfate Extended-release Capsule USP, 20 mg (worst case scenario).

Ingredient	Morphine Sulfate Extended-release Capsules USP, 20 mg	
	mg/tablet	% Weight
(b) (4) and (b) (4)	Range: (b) (4)	Range: (b) (4)

Based on the range presented above, we can estimate the amount of elemental iron per capsule as follows:

Molecular Weight for Iron Oxide Black (Fe_2O_3): 159.69 g/mol.

Molecular Weight for Iron (Fe_2): 111.7 g/mol.

Amount of Iron Oxide Black per Capsule: between (b) (4) mg and (b) (4) mg

Maximum Daily Intake of Morphine Sulfate Extended-release Capsules: 400 mg/day equivalent to 20 capsules of the 20 mg strength.

Elemental iron content per Capsule: $(111.7 \text{ g/mol} \div 159.69 \text{ g/mol}) \times (b) (4) \text{ mg} = (b) (4) \text{ mg}$
 Elemental iron content per Capsule: $(111.7 \text{ g/mol} \div 159.69 \text{ g/mol}) \times (b) (4) \text{ mg} = (b) (4) \text{ mg}$

Maximum daily intake of elemental iron: (b) (4) mg/capsule x 20 capsules = (b) (4) mg
 Maximum daily intake of elemental iron: (b) (4) mg/capsule x 20 capsules = (b) (4) mg

Hence, the amount of elemental iron in WLF's formulation complies with the 21 CFR 73.1200 requirement of NMT 5 mg element iron/day.

7. You have not provided the comparative dissolution testing data using the USP method. Please conduct the dissolution testing on 12 dosage units each of the test and reference 80 mg and 100 mg formulation using the current USP method for morphine sulfate extended-release capsules, and submit the individual dissolution data, mean, range and coefficient of variation (CV%) values. Division of Bioequivalence will recommend dissolution specifications upon review of submitted data.

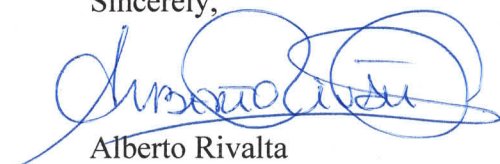
Response:

Please note that comparative dissolution testing data on 12 dosage units of the test and reference 80 mg and 100 mg formulation, using the current USP method for morphine sulfate extended-release capsules, was submitted along with the comparative dissolution testing data of additional strengths (20 mg, 30 mg, 50 mg and 60 mg). Please refer to **Section 2.7.1.2 "Summary of Results of Individual Studies"** of Sequence # 0001.

WLF is submitting this application through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

WLF trusts the information submitted is sufficient for this Bioequivalence Amendment to be evaluated. For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs



Sequence # 0004

ANDA # 200812

Morphine Sulfate Extended-release Capsules USP

20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

February 16, 2011

Dr. Keith Webber

Acting Director, Office of Generic Drugs, HFD-600

CDER, Food and Drug Administration

Document Control Room, Metro Park North VII,

7620 Standish Place,

Rockville, Maryland 20855

RE: Quality Minor Amendment

Dear Sir:

Please refer to the FDA's facsimile dated August 5, 2010 (Quality Deficiency-Minor) for Morphine Sulfate Extended-release Capsules USP, ANDA # 200812 (copy attached). Pursuant to 21 CFR §314.96, Watson Laboratories, Inc.-Florida (WLF) is submitting a quality minor amendment to the ANDA that provides a complete response to all the deficiencies listed in the facsimile.

A. Chemistry Deficiencies

1. You have submitted your ANDA 200812 for Morphine Sulfate Extended-Release Capsules, USP 80 mg and 100 mg strengths. However, in the introduction of the Quality Overall Summary you reported strengths 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg. Please clarify and/or correct.

Response:

We apologize for the oversight. Please note however that we amended the ANDA on September 30, 2010 (Sequence # 0001) to include the 20 mg, 30 mg, 50 mg and 60 mg strengths of the drug product and therefore the Quality Overall Summary needs no further revision.

2. Regarding your manufacturing process:

- a. You have proposed to (b) (4)

[Redacted]

batches.

Response:

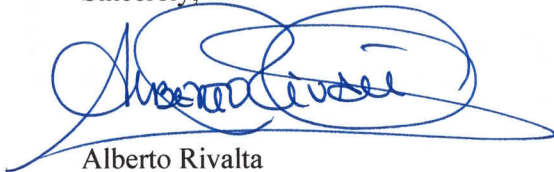
[Redacted] (b) (4)

reflecting the proposed acceptance criteria is provided in Section 3.2.P.3.4.

This is an electronic submission organized in accordance with ICH-CTD format (eCTD) and submitted through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*).

Sincerely,

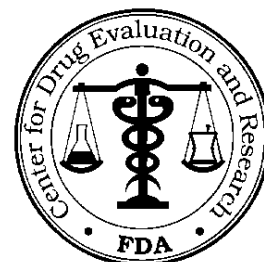
A handwritten signature in blue ink, appearing to read 'Alberto Rivalta', with a large, stylized flourish extending from the end of the signature.

Alberto Rivalta
Manager, Regulatory Affairs

QUALITY DEFICIENCY - MINOR

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Watson Laboratories, Inc.-Florida

TEL: 954-358-6125

ATTN: Janet Vaughn

FAX: 954-358-6350

FROM: Tina Nhu

FDA CONTACT PHONE: (240) 276-8548

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 16, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended-release Capsules, 80 mg and 100 mg.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

***Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855***

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT** submit your ANDA Regulatory documents to this address prior to **01-Aug-2010**. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD):*

<http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 200812

APPLICANT: Watson Laboratories, Inc. - Florida

DRUG PRODUCT: Morphine Sulfate Extended-Release Capsules USP, 80 mg and 100mg

The deficiencies presented below represent **MINOR** deficiencies.

A. Chemistry Deficiencies:

1. It is noted that the DMF holder established (b) (4)
Please consult with the drug substance manufacturer and update your specifications.
2. We acknowledge that you have provided dissolution data for (b) (4)
3. We acknowledge that you have (b) (4)
Please discuss.
4. The dissolution test results of batches # 3576P0008 and batch # 3576P0011 that (b) (4)
. In this regard:
 - a. You have determined an optimum (b) (4)
(b) (4). What is the process (b) (4)?
 - b. Please establish (b) (4) limit and justify the limit with data.
5. You have used (b) (4)
on drug product quality? Please submit results of your studies.

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

1. In table #1 "Composition of Morphine Sulfate Extended-release Capsules" you have reported the size of all hard gelatin capsules for all strengths as "Size "0" CS, hard gelatin capsules". However, you have used hard gelatin capsules sizes of 4, 3, 2 and 1 for the strengths 20mg, 30mg, 50mg and 60mg respectively. Please fix the table and submit.

2. Please provide available long-term stability data for all strengths.
3. We refer you to the labeling question regarding listing of corn starch in the inactive ingredients and "propylene glycol" as a component of capsule shell, which are not included in your "Description and Composition" section. Please harmonize your CMC response with labeling response. You may need to update the component/composition section based on your response

Sincerely yours,

(See appended electronic signature page)

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

UBRANI V VENKATARAM
03/18/2011
For Florence Fang

BIOEQUIVALENCE AMENDMENT

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Watson Laboratories Inc.-Florida

TEL: (954) 358 - 6109

ATTN: Janet Vaughn

FAX: (954) 358 - 6350

FROM: Duong (Diane) Nhu

FDA CONTACT PHONE: (240) 276 - 8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on December 16, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended Release Capsules, USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg.

Reference is also made to your amendment dated September 30, 2010, and December 09, 2010.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgment

Bioequivalence Other

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**.

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

**Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810**

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.-Florida

DRUG PRODUCT: Morphine Sulfate Extended Release Capsules,
20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg.

The Division of Bioequivalence (DBE) has completed its review as noted on the cover page, and the following deficiencies have been identified.

1. The DBE acknowledges that you have conducted dissolution testing using the USP-recommended dissolution method for Morphine Sulfate Extended Release Capsules. However, for the Morphine Sulfate Extended Release Capsules, 80 mg and 100 mg strengths, you did not sample dissolution at 4, 6 and 9 hours as per the USP. Please repeat dissolution testing for 80 mg and 100 mg strengths including sampling times at 4, 6, and 9 hours similar to 20 mg, 30 mg, 50 mg and 60 mg strengths.
2. A number of units released more than (b) (4) % for both test and reference products. Please provide the reason(s) for the higher than expected release for both the test and reference morphine sulfate extended release capsules for the following strengths: 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg. Please repeat the dissolution testing for all these strengths of the test and reference products.
3. Please conduct in vitro alcohol dose dumping study on the 20 mg, 30 mg, 40 mg and 50 mg strengths using the following testing conditions:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution profiles.

Additional comment for future submissions:

For comparative dissolution testing on morphine sulfate extended release capsules, 100 mg strength using USP-recommended dissolution method, you used reference product lot# 438E81, which was not the lot used for the fed BE study on the 100 mg strength. For future submissions, please conduct the dissolution testing using same lot number for test and reference products that is used for the BE study.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DUONG NHU
03/29/2011

BARBARA M DAVIT
03/29/2011



ANDA 200812

PRE-APPROVAL REMS NOTIFICATION

Watson Pharmaceuticals, Inc.
Attention: Beth Brannan
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Brannan:

Please refer to your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Morphine Sulfate Extended-Release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg.

We also refer to the stakeholder, industry, and public meetings, and Advisory Committee meeting held on February 10, March 3, May 4 and 5, May 27 and 28, 2009, and July 22 and 23, 2010, respectively, at which discussions took place concerning a risk evaluation and mitigation strategy (REMS) for the class of long-acting and extended-release opioid products. FDA has analyzed the advice and comments provided during these meetings and has determined the necessary elements of the class-wide REMS.

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FDCA, an abbreviated new drug application is required to have a REMS if the applicable listed drug has an approved REMS.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for certain long-acting and extended-release opioid products, including Morphine Sulfate Extended-Release Capsules, USP to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The elements of the REMS are described below.

In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class.

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Morphine Sulfate Extended-Release Capsules, USP pose a serious and significant public health concern requiring the distribution of a Medication Guide. The

Medication Guide is necessary for patients' safe and effective use of Morphine Sulfate Extended-Release Capsules, USP. FDA has determined that Morphine Sulfate Extended-Release Capsules, USP are a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Morphine Sulfate Extended-Release Capsules, USP. FDA has also determined that Morphine Sulfate Extended-Release Capsules, USP are a product for which patient labeling could help prevent serious adverse events. The Medication Guide should have both common content applicable to all extended-release and long-acting opioids, as well as product specific information that is necessary for safe and effective use of the drug.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Morphine Sulfate Extended-Release Capsules, USP.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including, at a minimum, the following:

1. The sponsor must ensure that training is provided to prescribers who prescribe Morphine Sulfate Extended-Release Capsules, USP. An outline of the content for this information is described in Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to Morphine Sulfate Extended-Release Capsules, USP and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers, to the extent practicable.
2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.
3. The sponsor must inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

Before we can continue our evaluation of this ANDA, you will need to submit the proposed REMS. Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a model for the proposed REMS (see Appendix C).

Additionally, all relevant proposed REMS materials, including educational materials, should be appended to the proposed REMS. FDA expects that the content of the educational materials will follow the attached outline, and contain more specific content on the proposed topics than is contained in the outline. FDA will review and approve the content of the training. However, FDA understands that CME providers will take the approved content and develop specific materials for training (e.g., slides, internet-based training). Accordingly, FDA does not expect

the sponsor to provide and attach to the REMS the specific materials that will be used to train prescribers.

Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include the approved documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining how the REMS will be implemented. The same supporting document may be submitted by each member of the single, shared system.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

For administrative purposes, designate the proposed REMS submission “**PROPOSED REMS for ANDA #####** and all subsequent submissions related to the proposed REMS “**PROPOSED REMS-AMENDMENT for ANDA #####.**”

Please submit revised labeling electronically in final print format.

If you have any questions, call Adolph Vezza, Labeling Reviewer, at (240) 276-8987.

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURES:

REMS Appendices A, B, and C

APPENDIX A: CONTENT OF EDUCATION PROGRAM

The training for prescribers required by the elements to assure safe use must contain the following content:

1. General information for safe opioid prescribing
 - a. Patient selection and assessment
 - i. Determine goal of therapy
 - ii. Assessment of the risk of abuse, including history of substance abuse and serious mental illness
 - iii. When relevant, determining if patient is opioid tolerant
 - b. Considerations when prescribing opioids
 - i. Pharmacokinetics and potential for overdose
 - ii. Addiction, abuse, and misuse
 - iii. Intentional abuse by patient or household contacts
 - iv. Interactions with other medications/substances
 - c. Managing patients on Extended-Release and Long-Acting Opioids
 - i. Establishing goals for treatment and evaluating pain control
 - ii. Use of Patient Provider Agreements (PPAs)
 - iii. Adherence to a treatment plan
 - iv. Recognizing aberrant behavior
 - v. Managing adverse events
 - d. Initiating and modifying dosing of opioids for chronic pain
 - i. As first opioid
 - ii. Converting from one opioid to another
 1. Converting from immediate-release to extended-release and long-acting products
 2. Converting from one extended-release and long-acting product to another
 - iii. Titrating to effect/tolerability
 - iv. How to deal with missed doses
 - e. Maintenance
 - i. Reassessment over time

- ii. Tolerance
 - f. Monitoring patients for misuse and abuse
 - i. Utilization of prescription monitoring programs to identify potential abuse
 - ii. Understanding the role of drug testing
 - iii. Screening and referral for substance abuse treatment
 - g. How to discontinue opioid therapy when it is not needed any longer
2. Product Specific Information
- a. Pharmacokinetic characteristics
 - b. Product specific toxicity
 - c. Requirements for opioid tolerance for certain long-acting and extended-release products
 - d. Individual product information modules
 - i. Fentanyl transdermal system
 - ii. Hydromorphone ER
 - iii. Methadone (For the treatment of moderate to severe pain not responsive to non-narcotic analgesics)
 - iv. Morphine ER
 - v. Oxycodone ER
 - vi. Oxymorphone ER
 - vii. Buprenorphine (for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time)
 - viii. New products
3. Patient counseling
- a. Information about prescribed opioid
 - b. How to take opioid properly
 - i. Adherence to dosing regimen
 - ii. Risk from breaking, chewing, crushing certain products
 - c. Reporting adverse effects
 - d. Concomitant use of other CNS depressants, alcohol, or illegal drugs
 - e. Discontinuation of opioid
 - f. Risks associated with sharing, i.e., overdose prevention

- g. Proper storage in the household
 - i. Avoiding accidental exposure
- h. Avoiding unsafe exposure by preventing theft and proper disposal
- i. Purpose and content of Patient Provider Agreement

APPENDIX B: PATIENT EDUCATION

Materials to provide to patients as part of patient counseling must include:

1. How to take opioid properly
 - a. Adherence to dosing regimen
 - b. Risk from breaking, chewing, crushing certain products
 - c. Symptoms of overdose
2. Reporting adverse effects
3. Concomitant use of other CNS depressants, alcohol, or illegal drugs
4. Discontinuation of opioid
5. Risks associated with sharing
6. Proper storage in the household
 - a. Avoiding accidental exposure
7. Avoiding unsafe exposure by preventing theft and proper disposal
8. Purpose and content of Patient Treatment Agreement
9. Links to websites with more information about topics 1 through 8

APPENDIX C: REMS TEMPLATE

Initial REMS Approval: XX/XXXX

Most Recent Modification: XX/XXXX

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release (ER) and long-acting (LA) opioids while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

A communication plan is not required.

C. Elements To Assure Safe Use

1. The sponsor must ensure that training is provided to prescribers who prescribe DRUG. An outline of the content for this information is described in Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to DRUG and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers, to the extent practicable.
2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.

3. The sponsor must inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

D. Implementation Plan

An implementation plan is not required.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

04/19/2011

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.



Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

ANDA # 200812

Sequence # 0005

May 04, 2011

Dr. Keith Webber
Acting Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

RE: TELEPHONE FAX -Labeling Amendment

Dear Sir,

Reference is made to the Telephone Fax labeling deficiency letter dated December 08, 2010 from Chan Park (Office of Generic Drugs) providing comments for the above referenced application (see copy attached). In accordance with 21 CFR 314.96, Watson Laboratories, Inc.-Florida (WLF) is submitting an Amendment to this ANDA that provides a complete response to the comments provided in the deficiency letter.

Response to Labeling deficiencies

1 GENERAL COMMENT

We note that you did not include the point-to-point responses to the Agency's comments. Please include this in your future submissions.

Response:

WLF acknowledges the agency's comment and ensures to include a point-to-point response in future submissions.

2 CONTAINER – 30s and 100s

- a. Please put the text "Once or Twice Daily Formulation" in a parenthesis and relocate so that it is more closely associated with the drug product name.**

Response:

As per the agency's comment the text "Once or Twice Daily Formulation" has been enclosed in parenthesis and relocated close to the drug product name. Please refer to the side by side comparison of the container labels (in pdf and word format) provided in **Section 1.14.1.2** and to the final printed container labels provided in **Section 1.14.2.1** of this amendment.

- b. We note that you used blue color background for all strengths for the bar appearing at the bottom of the label. If feasible, we recommend that you use the same color as the specific one used for the background for the expression of strength to make further distinction between labels of various strengths.

Response:

Reference is made to the telephone conversation between Mr. Chan Park (Office of Generic Drugs) and Alberto Rivalta (Manager of Regulatory Affairs) on April 06, 2011. In this conversation we explained that the use of the blue color background for all strengths for the bar appearing at the bottom of the label is the current company standard and that we would prefer to maintain the same standard for this product. Mr. Park understood our rationale and confirmed that the container labels are acceptable as proposed.

- c. Your labels do not appear to reflect actual size. As addressed in the last deficiency letter, please be advised that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please ensure that these criteria are met prior to submission of final print.

Response:

The final prints of the container labels have been updated to reflect the actual size, color and clarity. Please find copies of the final printed container labels provided in **Section 1.14.2.1** of this amendment.

- d. We believe that your product is light sensitive, please verify that your container/closure system is light resistant.

Response:

WLF confirms that the container/closure system used in the packaging of the drug product is light resistant. All the bottles, 75 cc and 250 cc are in compliance with the current USP (General Chapter) <671> and meet the acceptance criterion of not more than 10% of light transmission at any wavelength from 290 nm to 450 nm. The USP <671> data for the containers are provided in **Section 3.2.P.7** of the ANDA (Sequences # 0000 and # 0001).

3 INSERT

a. GENERAL

- i. We note that you did not include the Structured Product Labeling (SPL) in your submission. You are required to submit SPL prior to approval as well as post approval. Please refer to the guidance at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072331.pdf>

Response:

A copy of the SPL is included in **Section 1.14.2.3** of this amendment.

- ii. We note that the breakdown of the paragraphs in your proposed labeling is not consistent with that of the Kadian® labeling. Please revise accordingly.

Response:

The breakdowns of the paragraphs for the proposed labeling have been formatted to be consistent with the Kadian® labeling. Please refer to the annotated side by side comparison of the outserts (in pdf and word format) provided in **Section 1.14.3.1** of this amendment.

- iii. The sub-section titles are dissociated with the corresponding text in numerous places throughout the insert labeling. Please revise so that the sub-section titles appear immediately before the text.**

Response:

The proposed labeling has been revised so that the sub-section titles are associated with the corresponding text wherever applicable. Please refer to the annotated side by side comparison of the outserts (in pdf and word format) provided in **Section 1.14.3.1** of this amendment.

- iv. It is not necessary to include the term “USP” in association with the drug product name throughout the text. Please delete this except in the TITLE, DESCRIPTION, INDICATIONS and USAGE, and HOW SUPPLIED sections.**

Response:

The term “USP” has been deleted throughout the outsert except for the TITLE, DESCRIPTION, INDICATIONS and USAGE, and HOW SUPPLIED sections. Please refer to the annotated side by side comparison of the outserts (in pdf and word format) provided in **Section 1.14.3.1** of this amendment.

- v. Please ensure that all text associated with graphs appear sufficiently legible throughout the insert labeling.**

Response:

We have ensured that all text associated with graphs appear sufficiently legible in the final printed labeling. Please refer to the final printed outsert (in pdf and word format) provided in **Section 1.14.2.2** of this amendment.

- vi. It is preferable to use the term “to” rather than a hyphen when expressing a numerical range.**

Response:

The hyphen (-) has been replaced with the term “to” throughout the outsert when expressing a numerical range. Please refer to the annotated side by side comparison of the outserts (in pdf and word format) provided in **Section 1.14.3.1** of this amendment.

- vii. We recommend that the font size of the final printed labeling not be less than 6 pts.**

Response:

WLF confirms that the final printed labeling font size is not less than 6 pts. Please refer to the final print outsert (in pdf and word format) provided in **Section 1.14.2.2** of this amendment.

- b. DESCRIPTION – Last paragraph, 4th sentence:**

- i. You made references to 80 mg and 100 mg strengths only. Please include additional strengths you are proposing.**

Response:

The description section has been updated to list the additional strengths i.e., 20 mg, 30 mg, 50 mg and 60 mg. Please refer to the annotated side by side comparison of the outserts (in pdf and word format) provided in **Section 1.14.3.1** of this amendment.

- ii. We note that you included “corn starch” in the listing of inactive ingredients and “propylene glycol” as a component of capsule shell, which are not included in your “Description and Composition” section. Please delete these and/or comment.

Response:

(b) (4)

manufacturer in **Section 3.2.P.4.4** of the original ANDA (**Sequence # 0000**). The Description and Composition table has been updated to include corn starch, please refer to **Section 3.2.P.1** of this amendment.

Propylene glycol is used in (b) (4) the capsule shell. This information was provided in **Section 3.2.P.1** of the original ANDA (**Sequence # 0000**).

c. CLINICAL PHARMACOLOGY – Table 1:

i. 1st column, 2nd item:

“Extended-release” rather than “(b) (4),”

Response:

The table has been corrected to read “Extended-release”. Please refer to the annotated side by side comparison of the outserts (in pdf and word format) provided in **Section 1.14.3.1** of this amendment.

ii. 1st column, 4th item:

“Morphine Sulfate Extended-Release Capsules” rather than “Kadian® Capsules”

Response:

The table has been corrected to read as “Morphine Sulfate Extended-release Capsules”. Please refer to the annotated side by side comparison of the outserts (in pdf and word format) provided in **Section 1.14.3.1** of this amendment.

This application is an electronic submission organized in accordance with ICH-CTD format (eCTD) and is been submitted to the agency through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

For regulatory information regarding this ANDA, please contact the undersigned via e-mail at alberto.rivalta@watson.com, (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs



Sequence # 0007
ANDA # 200812
Morphine Sulfate Extended-release Capsules USP
20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

May 17, 2011

Dr. Keith Webber
Acting Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

RE: Quality Minor Amendment

Dear Sir:

Please refer to the FDA's facsimile dated March 18, 2011 (Quality Deficiency-Minor) for Morphine Sulfate Extended-release Capsules USP, ANDA # 200812 (copy attached). Reference is also made to the March 30, 2011 email correspondence from Tina Nhu (OGD Project Manager) in which further clarification from the reviewer was provided at Watson's request. Pursuant to 21 CFR §314.96, Watson Laboratories, Inc.-Florida (WLF) is submitting a quality minor amendment to the ANDA that provides a complete response to all the deficiencies listed in the facsimile.

A. Chemistry Deficiencies

1. It is noted that the DMF holder established [REDACTED] (b) (4)

[REDACTED] Please consult with the drug substance manufacturer and update your specifications.

Response:

We have updated our drug substance specification for the [REDACTED] (b) (4) to conform to the manufacturer's specification as follows:

[REDACTED] (b) (4)

The revised drug substance specification and test procedure are provided in **Sections 3.2.S.4.1** and **3.2.S.4.2**, respectively. The analytical method validation reports for [REDACTED] (b) (4) impurities are provided in **Section 3.2.S.4.3**.

Please note that in response to the March 30, 2011 letter from the Division of Bioequivalence, we have updated the in-process and finished product dissolution specification for all strengths of the drug product as follows:

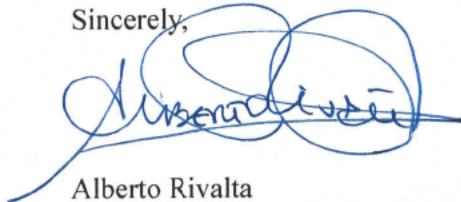
Table 4	
Time (Hr.)	Specification
1	NMT 10 %
4	(b) (4) %
6	(b) (4) %
9	NLT 85 %

Furthermore, we have clarified the criteria for the identification test by IR. The revised in-process controls, finished product release and stability specifications, as well as the revised test method are included in **Sections 3.2.P.3.4, 3.2.P.5.1 and 3.2.P.5.2** of this amendment.

This is an electronic submission organized in accordance with ICH-CTD format (eCTD) and submitted through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (email), at (954) 358-6109 (direct dial) or (954) 358-6350 (fax).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs



Sequence # 0006

ANDA # 200812

**Morphine Sulfate Extended-release Capsules USP,
20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg**

May 18, 2011

Keith Webber, Ph.D
Acting Director, Office of Generic Drugs,
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: BIOEQUIVALENCE AMENDMENT

Dear Dr. Webber:

Watson Laboratories, Inc.-Florida (WLF) is submitting this electronic bioequivalence amendment to its original Abbreviated New Drug Application # 200812 for Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg to provide a complete response to the Bioequivalence comments included in the FDA facsimile dated March 29, 2011 (**copy attached**) pertaining to the above product. For convenience of review, the FDA comments are provided in bold face type followed by WLF's responses.

Deficiency:

The Division of Bioequivalence (DBE) has completed its review as noted on the cover page, and the following deficiencies have been identified:

1. The DBE acknowledges that you have conducted dissolution testing using the USP-recommended dissolution method for Morphine Sulfate Extended-release Capsules. However, for the Morphine Sulfate Extended-release Capsules, 80 mg and 100 mg strengths, you did not sample dissolution at 4, 6 and 9 hours as per the USP. Please repeat dissolution profile testing for 80 mg and 100 mg strengths including sampling times at 4, 6, and 9 hours similar to 20 mg, 30 mg, 50 mg and 60 mg strengths.

Response:

As requested, WLF has performed the dissolution profile testing for the 80 mg and 100 mg strengths of the drug product with sampling times at 4, 6 and 9 hours. The data is provided in **Section 2.7.1.2** of this amendment.

We are also revising the proposed dissolution acceptance criteria to include the 4, 6 and 9 hour time points, in accordance with the USP monograph for the drug product. Based on the data for all the strengths of the drug product (Table 1), we are proposing the acceptance criteria in Table 2 below.

Table 1			
Summary of Dissolution Data for All Strengths			
Time (hr.)	Mean Range	Minimum	Maximum
1	0 % - 1 %	(b) (4) %	(b) (4) %
4	24 % - 26 %	(b) (4) %	(b) (4) %
6	52 % - 59 %	(b) (4) %	(b) (4) %
9	96 % - 99 %	(b) (4) %	(b) (4) %

Table 2			
Previous Specification		Current Proposed Specification	
Time (Hr.)	Specification	Time (Hr.)	Specification
1	NMT 10 %	1	NMT 10 %
5	(b) (4) %	4	(b) (4) %
7	(b) (4) %	6	(b) (4) %
10	NLT 85 %	9	NLT 85 %

2. A number of units released more than (b) (4) % for both test and reference products. Please provide reason(s) for the higher than expected release for both the test and reference morphine sulfate extended-release capsules for the following strengths: 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg. Please repeat the dissolution testing for all these strengths of the test and reference products.

Response:

Evaluation of the data shows that values at the last time point (9 hours) proposed for dissolution testing range from (b) (4) % (none above (b) (4) %) for the test drug, and (b) (4) % for the reference. An investigation into the possible reasons for values greater than (b) (4) % reveals that the most likely causes are the true level of the active in the tablet and/or evaporation of the medium, particularly at the later time points. In Table 3 below it is clear that there is a correlation between the content uniformity data (amount active per tablet) and the dissolution results. High content uniformity values consistently yield high dissolution values, particularly for the reference drug. Thus, the dissolution data reflects the variation observed for content uniformity.

Table 3								
Strengths	Test Product Observed Data (%)			Reference Product Observed Data (%)				
	Content Uniformity		Dissolution (9 hr time point)	Content Uniformity		Dissolution (9 hr time point)		
20 mg	100.6	(b) (4)	96	(b) (4)	101.2	(b) (4)	105	(b) (4)
30 mg	102.7		99		102.4		102	
50 mg	102.2		97		100.6		103	
60 mg	102.0		97		101.4		103	
80 mg	103.5		96		103.2		103	
100 mg	100.7		96		101.1		101	

The dissolution values further increase after the 9 hour time point, indicating that evaporation of the medium may also contribute to the high values observed particularly at the 10 and 14 hour time points. It should be noted however that there is no upper limit for dissolution at the last time point and all dissolution profiles meet the proposed acceptance criteria.

Therefore, a repeat of the dissolution testing for all strengths of the drug product will not provide any additional information. This is confirmed by the repeat dissolution testing of the 80 and 100 mg strengths (as requested in comment #1) which resulted in data consistent with that previously submitted in **Section 2.7.1.2 of Sequence # 0001**.

3. Please conduct in vitro alcohol dose dumping study on the 20 mg, 30 mg, 40 mg and 50 mg strengths using the following testing conditions:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5 % (v/v) of test medium with Alcohol USP, and data collected every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20 % (v/v) of test medium with Alcohol USP, and data collected every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40 % (v/v) of test medium with Alcohol USP, and data collected every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution profiles.

Response:

WLF has performed in vitro alcohol dose dumping studies on the 20 mg, 30 mg, 50 mg and 60 mg strengths of the drug product as requested by the agency. The dissolution profile data is provided in **Section 2.7.1.2** of this amendment.

Additional comment for future submissions:

For comparative dissolution testing on morphine sulfate extended-release capsules, 100 mg strength using USP-recommended dissolution method, you used reference product lot # 438E81, which was not the lot used for the BE study on the 100 mg strength. For future submissions, please conduct the dissolution testing using same lot number for test and reference products that is used for the BE study.

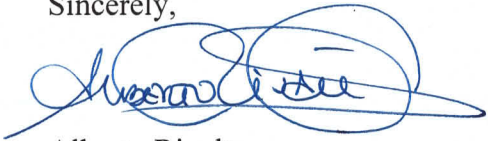
Response:

WLF acknowledges the agency's comment and confirms that the comparative dissolution testing performed on morphine sulfate extended-release capsules 100 mg, submitted in this amendment, was done on the same RLD lot number (320E71) used for the BE study.

WLF is submitting this application through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

We trust the information submitted is sufficient for this Bioequivalence Amendment to be evaluated. For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs



Sequence # 0008

ANDA # 200812

Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

June 27, 2011

Dr. Keith Webber
Acting Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

Re: Gratuitous Chemistry Amendment

Dear Dr. Webber:

Please refer to Watson Laboratories, Inc.-Florida's (WLF's) 02/14/2011 minor amendment, which was submitted in response to the FDA's facsimile dated August 5, 2010. Per our commitment, we are providing in **Exhibit # 1** a table containing a summary comparison of the data for the ANDA batches and validation batches following the validation matrix tabulated below:

Product Description	Number of Process Validation Batches
(b) (4)	(b) (4)
Morphine Sulfate Extended-release Pellets	
Morphine Sulfate Extended-release Capsules USP, 20 mg	
Morphine Sulfate Extended-release Capsules USP, 30 mg	
Morphine Sulfate Extended-release Capsules USP, 50 mg	
Morphine Sulfate Extended-release Capsules USP, 60 mg	
Morphine Sulfate Extended-release Capsules USP, 80 mg	
Morphine Sulfate Extended-release Capsules USP, 100 mg	

In addition, WLF is providing in **Section 3.2.P.3.3** copies of the current commercial manufacturing batch records for all the strengths. The batch records have been updated based on knowledge gained during scale-up and process validation activities. An updated summary table comparing the process parameters used for the ANDA batches and the proposed commercial batches is provided in **Section 3.2.P.2**.

Finally, WLF is providing in **Section 3.2.P.5.1** and **3.2.P.5.2** copies of the current finished product specifications and test method, respectively. These documents were revised to remove the (b) (4) (b) (4) as this test is not necessary because the finished product (b) (4) is already being tested by (b) (4) techniques.

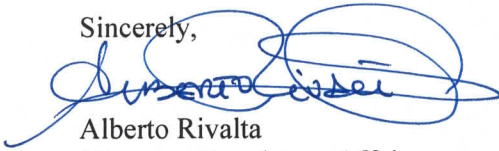
This is an electronic submission organized in accordance with ICH-CTD format (eCTD) and submitted through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

Quality Minor Amendment
Morphine Sulfate Extended-release Capsules USP
20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

Watson Laboratories, Inc.-Florida
ANDA # 200812
Sequence # 0008

For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs

BIOEQUIVALENCE AMENDMENT

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Watson Laboratories, Inc.

TEL: (954) 358 – 6109

ATTN: Janet Vaughn

FAX: (954) 358 – 6350

FROM: Duong (Diane) Nhu

FDA CONTACT PHONE: (240) 276 - 8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on December 16, 2009, September 30, 2010, December 09, 2010, and May 18, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended Release Capsules, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg.

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**.

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

*Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810*

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCY

ANDA: 200812
APPLICANT: Watson Laboratories, Inc.
DRUG PRODUCT: Morphine Sulfate Extended Release Capsules,
20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg.

The Division of Bioequivalence II (DBII) has completed its review as noted on the cover page, and the following deficiency has been identified:

Your dissolution testing data using the USP dissolution method are acceptable. However, your proposed dissolution specifications are not acceptable. Based on the submitted data, please acknowledge your acceptance of the following dissolution method and specifications:

Medium: 0.1N HCl for 1 hrs followed by
phosphate buffer, pH 7.5
Apparatus: I (Basket)
Speed: 100 RPM
Temperature: 37°C ± 0.5°C
Volume: 500 mL (Acid stage); 500 mL (Buffer
stage)
Specifications:
1 hrs: NMT 10%
4 hrs: (b) (4)%
6 hrs: %
9 hrs: NLT 85%

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA M DAVIT
08/03/2011



Sequence # 0009

ANDA # 200812

Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

August 11, 2011

Keith Webber, Ph.D
Acting Director, Office of Generic Drugs,
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: BIOEQUIVALENCE AMENDMENT

Dear Dr. Webber:

Watson Laboratories, Inc.-Florida (WLF) is submitting this electronic bioequivalence amendment to its original Abbreviated New Drug Application # 200812 for Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg to provide a complete response to the Bioequivalence comments included in the FDA facsimile dated August 3, 2011 (**copy attached**) pertaining to the above product. For convenience of review, the FDA comments are provided in bold face type followed by WLF's responses.

Deficiency:

The Division of Bioequivalence II (DBII) has completed its review as noted on the cover page, and the following deficiency has been identified:

1. Your dissolution testing data using the USP dissolution method are acceptable. However, your proposed dissolution specifications are not acceptable. Based on the submitted data, please acknowledge your acceptance of the following dissolution method and specifications:

Medium: 0.1 N HCl for 1 hrs followed by phosphate buffer, pH 7.5

Apparatus: I (Basket)

Speed: 100 RPM

Temperature: 37°C ± 0.5°C

Volume: 500 mL (Acid stage); 500 mL (Buffer stage)

Specifications:

1 hrs: NMT 10 %

4 hrs: (b) (4) %

6 hrs: %

9 hrs: NLT 85 %

Response:

WLF acknowledges the DBE's dissolution recommendations. However, based on the dissolution data of both the ANDA batches and validation batches for all the strengths of the finished drug product, we ask the Division of Bioequivalence to reconsider the 6 hour time point specification. A summary of the dissolution data at 6 hours is summarized in the tables below:

Finished Product ANDA Batches

Time Point	20 mg ANDA Batch # 3449R0001	30 mg ANDA Batch # 3450R0001	50 mg ANDA Batch # 3451R0001	60 mg ANDA Batch # 3452R0001	80 mg ANDA Batch # 3576R0013	100 mg ANDA Batch # 3453R0001
6 hours	n = 12	n = 12	n = 12	n = 12	n = 12	n = 12
	Mean: 55 % Min.: (b) (4) % Max.: %	Mean: 56 % Min.: (b) (4) % Max.: %	Mean: 56 % Min.: (b) (4) % Max.: %	Mean: 55 % Min.: (b) (4) % Max.: %	Mean: 58 % Min.: (b) (4) % Max.: %	Mean: 59 % Min.: (b) (4) % Max.: %

Finished Product Validation Batches

Time Point	20 mg Batches	30 mg Batch # 404674	50 mg Batch # 404675	60 mg Batch # 404677	80 mg Batch # 404678	100 mg Batches
6 hours	n = 12	n = 12	n = 12	n = 12	n = 12	n = 12
	Batch # 404671 Mean: 61 % Min.: (b) (4) % Max.: %					Batch # 404679 Mean: 60 % Min.: (b) (4) % Max.: %
	Batch # 404672 Mean: 58 % Min.: (b) (4) % Max.: %	Mean: 63 % Min.: (b) (4) % Max.: %	Mean: 60 % Min.: (b) (4) % Max.: %	Mean: 61 % Min.: (b) (4) % Max.: %	Mean: 62 % Min.: (b) (4) % Max.: %	Batch # 404680 Mean: 60 % Min.: (b) (4) % Max.: %
	Batch # 404673 Mean: 64 % Min.: (b) (4) % Max.: %					Batch # 404681 Mean: 59 % Min.: (b) (4) % Max.: %

In addition, please note that the 6 hour dissolution time point specification in the USP Monograph for Morphine Sulfate Extended-release Capsules, USP has a 40 % window range (50 % - 90 %), (b) (4) % specification. Furthermore, for routine commercial manufacturing, we believe that a (b) (4) % is more appropriate and will not impact product quality. Based on these facts and the data

tabulated above, we are proposing a (b) (4) % range for the 6 hour time point specification. Please see proposed limits tabulated below:

Time (Hours)	Previous % Drug Release Specification for the Drug Product	Proposed % Drug Release Specification for the Drug Product
1	NMT 10 %	NMT 10 %
4	(b) (4) %	(b) (4) %
6	(b) (4) %	(b) (4) %
9	NLT 85 %	NLT 85 %

WLF is submitting this application through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

We trust the information submitted is sufficient for this Bioequivalence Amendment to be evaluated. For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (email), at (954) 358-6109 (direct dial) or (954) 358-6350 (fax).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs



Sequence # 0010

ANDA # 200812

Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

August 17, 2011

Keith Webber, Ph.D.
Deputy Director, Office of Pharmaceutical Science, FDA
and Acting Director
OGD, CDER, FDA
Document Control Room, Metro Park VII
7620 Standish Place
Rockville, MD 20855-2773

RE: PROPOSED REMS for ANDA # 200812

Dear Dr. Webber:

Watson Laboratories, Inc.-Florida (WLF) is submitting this electronic Proposed Risk Evaluation and Mitigation Strategy (REMS) to its original Abbreviated New Drug Application # 200812 for Morphine Sulfate Extended-Release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg to provide a complete response to the Pre-Approval REMS Notification letter dated April 19, 2011 (**copy attached**).

WLF joined the industry working group (IWG) which was formed at FDA's request, and has been involved in the monthly meetings to develop and implement the single, shared system for the class of long-acting and extended-release opioid products. WLF's enclosed Proposed REMS (**Section 1.16.1**) and REMS Supporting Document (**Section 1.16.2**), provided in both Adobe pdf and MS Word format, are in accordance with the class-wide REMS as agreed upon by industry and FDA. WLF confirms that the texts in the MS Word documents are exactly the same as the text in the 'non-Word' documents.

Please note that WLF's draft Medication Guide for Morphine Sulfate Extended-Release Capsules, USP is provided in MS Word format in **Sections 1.14.1.3 and 1.16.1.3**, and Adobe pdf format in **Sections 1.14.1.3 and 1.16.1.1**, along with the REMS Elements to Assure Safe Use (Prescriber Training Program, Patient Education Materials, and Prescriber Notification of REMS). Additionally, Watson has revised its container labels with the instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed. Please refer to **Section 1.14.2.1** for the revised final printed container labels in Adobe pdf format.

Watson has included the side-by-side comparisons of its revised final printed container labels (version 08/11) with the version previously submitted in **Sequence # 0005** (version 04/11), with all differences annotated and explained. Please see **Section 1.14.1.2** for the side-by-side container label comparison.

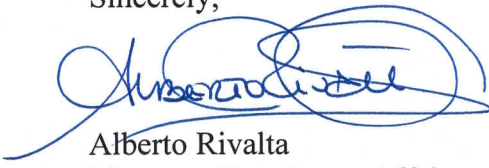
WLF has revised the outsert to include the information on the proposed medication guide. Please

refer to **Section 1.14.1.3** for a copy of the revised draft outsert and **Section 1.14.3.1** for a copy of the side-by-side comparison of its revised draft outsert in both MS Word and Adobe pdf formats.

This is an electronic submission organized in accordance with ICH-CTD format (eCTD). To facilitate the review, WLF is submitting a copy of the FDA's Table of Content (TOC) for IWG REMS, which provides links to all the respective sections and documents in each applicable Section (**copy attached**).

Finally, it is WLF's view that its Proposed REMS is suitable for evaluation as part of the single, shared system for the class of long-acting and extended-release opioid products. Please contact Alberto Rivalta at alberto.rivalta@watson.com (*email*), at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*) if you have any questions or if I can assist you with the review of this amendment.

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs

BIOEQUIVALENCE AMENDMENT

ANDA 200812

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Watson Laboratories, Inc.

TEL: (954) 358 - 6125

ATTN: Janet Vaughn

FAX: (954) 358 - 6350

FROM: Duong (Diane) Nhu

FDA CONTACT PHONE: (240) 276 - 8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on December 16, 2009, September 30, 2010, December 09, 2010, May 18, 2011, and August 11, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended Release Capsules, USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Other

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**.

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

**Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810**

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 200812

APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Morphine Sulfate Extended Release Capsules,
20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg

The Division of Bioequivalence II (DB II) has completed its review as noted on the cover page, and the following deficiencies have been identified:

1. The DB II acknowledges that you propose to change dissolution specification at 6 hour sampling time point. However, please be advised that per the DB II practice, the dissolution method and specifications are established based on the dissolution data on 12 units of the fresh bio-lot that has been used in acceptable bioequivalence studies. The DB II does not change the dissolution specifications based on dissolution testing data of validation batches. The dissolution testing data on the fresh bio-lots (submitted in the amendments dated 9/30/10 and 5/8/11) met the DB II-recommended dissolution specification of (b) (4) % at 6 hrs. In addition, the dissolution testing data on the validation batches (submitted in the current amendment dated 8/11/11) meet the dissolution specification of (b) (4) - (b) (4) % at 6 hrs. Therefore, your proposal to change the dissolution specification at 6 hrs from (b) (4) % to (b) (4) % is not acceptable. Please indicate if you accept the DB II recommended dissolution specifications of 1hr: NMT 10%; 4hrs: (b) (4) %; **6 hrs: (b) (4) %**; 9 hrs: NLT 85%.
2. Alternatively, in order for the DB II to reconsider if a revision of the dissolution specifications is warranted, you may submit dissolution data on 12 dosage units each of all strengths from **three fresh** production lots of the test product, using the USP-recommended dissolution method.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA M DAVIT
09/10/2011



Sequence # 0011

ANDA # 200812

Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

September 12, 2011

Keith Webber, Ph.D
Acting Director, Office of Generic Drugs,
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: BIOEQUIVALENCE RESPONSE TO INFORMATION REQUEST

Dear Dr. Webber:

Watson Laboratories, Inc.-Florida (WLF) is submitting this electronic bioequivalence amendment to its original Abbreviated New Drug Application # 200812 for Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg to provide a complete response to the Bioequivalence comments included in the FDA deficiency letter dated September 10, 2011 (**copy attached**) pertaining to the above product. For convenience of review, the FDA comments are provided in bold face type followed by WLF's responses.

The Division of Bioequivalence II (DB II) has completed its review as noted on the cover page, and the following deficiencies have been identified:

- 1. The DB II acknowledges that you propose to change dissolution specification at 6 hour sampling time point. However, please be advised that per the DB II practice, the dissolution method and specifications are established based on the dissolution data on 12 units of the fresh bio-lot that has been used in acceptable bioequivalence studies. The DB II does not change the dissolution specifications based on dissolution testing data of validation batches. The dissolution testing data on the fresh bio-lots (submitted in the amendments dated 9/30/10 and 5/8/11) met the DB II-recommended dissolution specification of (b) (4)% at 6 hrs. In addition, the dissolution testing data on the validation batches (submitted in the current amendment dated 8/11/11) met the dissolution specification of (b) (4)% at 6 hrs. Therefore, your proposal to change the dissolution specification at 6 hrs from (b) (4)%, (b) (4)% to (b) (4)% is not acceptable. Please indicate if you accept the DB II recommended dissolution specifications on 1 hr: NMT 10%; 4 hrs: (b) (4)%; 6 hrs: (b) (4)%; 9 hrs: NLT 85%.**

Response

WLF acknowledges and accepts the DB II recommended dissolution specifications as tabulated below:

Time (Hours)	% Drug Release Specification for the Drug Product
1	NMT 10 %
4	(b) (4) %
6	%
9	NLT 85 %

2. Alternatively, in order for the DB II to reconsider if a revision of the dissolution specifications is warranted, you may submit dissolution data on 12 dosage units each of all strengths from three fresh production lots of the test product, using the USP-recommended dissolution method.

Response

WLF acknowledges the agency's comment. However, please refer to the above response to comment # 1.

WLF is submitting this application through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards. For regulatory information regarding this ANDA, please contact Alberto Rivalta at alberto.rivalta@watson.com (email), at (954) 358-6109 (direct dial) or (954) 358-6350 (fax).

Sincerely,



Alberto Rivalta
Manager, Regulatory Affairs



Sequence # 0012

ANDA # 200812

Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

September 13, 2011

Keith Webber, Ph.D
Acting Director, Office of Generic Drugs,
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: GRATUITOUS CMC AMENDMENT – Revised dissolution specifications

Dear Dr. Webber:

In accordance with 21CFR 314.96, Watson Laboratories, Inc.-Florida (WLF) is submitting a Gratuitous CMC Amendment to the Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg ANDA providing for revised finished drug product dissolution specifications based on the agency's recommendations described in the Bioequivalence Deficiency letter dated September 10, 2011.

The following documents are provided in this amendment:

- Copy of the revised finished product specifications in **Section 3.2.P.5.1.**
- Updated room temperature stability reports for all the strengths of the finished drug product reflecting the revised dissolution specifications in **Section 3.2.P.8.3.**

This is an electronic submission organized in accordance with ICH-CTD format (eCTD) and submitted through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

Should you have any questions regarding this amendment, please contact me at (954) 358-6109 (*direct dial*) or (954) 358-6350 (*fax*).

Sincerely,

A handwritten signature in blue ink, appearing to read "Alberto Rivalta", is written over a horizontal line.

Alberto Rivalta
Manager, Regulatory Affairs

Record of Telephone Conversation

In ANDA 200812, the firm proposed that the commercial batches will be the same batch size as the ANDA batches size (Amendment dated February 16, 2011)

Table 1 Comparative Manufacturing Summary (Exhibit Batch vs. Scale-up Production Batches) – 20 mg, 30 mg, 50 mg, 60 mg, 80 mg & 100 mg

	ANDA Batch	Previous Proposed Production Batch	New Proposed Production Batch
Batch Size	20 mg: (b) (4) capsules	20 mg (b) (4) capsules	(b) (4)
	30 mg: capsules	30 mg capsules	
	50 mg: capsules	50 mg capsules	
	60 mg: capsules	60 mg capsules	
	80 mg: capsules	80 mg capsules	
	100 mg capsules	100 mg capsules	
Equipment	(b) (4)		

¹ Not to exceed (b) (4) capsules

² Not to exceed capsules

Based on DCII Acting Division Director, Glen Smith request, the reviewer, Nashed Samaan, called the firm and talked to Mr. Alberto Rivalta, Manager, Regulatory Affairs and requested that the firm submit a commitment to submit a PAS in case of planning to scale up the commercial batches more than the current proposed batches size.

Mr. Alberto promised to submit this commitment in a telephone amendment within ten working days.

Date:
October 24, 2011

ANDA Number:
200-812

Product Name:
Morphine Sulfate
Extended-Release
Capsules USP, 20 mg, 30
mg, 50 mg, 60 mg, 80
mg and 100 mg

Firm Name:
Watson Laboratories,
Inc. Florida

Firm Representative:
Alberto Rivalta,
Manager, Regulatory
Affairs

Phone Number:
(954) 358-6109

FDA Representative:
Nashed I. Samaan, Ph.D.

Signatures:
Nashed Samaan

CC: ANDA :200-812

V:\Division of Chemistry II/Team 22/Final Version for
DARRTS\200812/Telecon

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NASHED I SAMAN
10/24/2011



Sequence # 0013
ANDA # 200812
Morphine Sulfate Extended-release Capsules USP
20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

November 07, 2011

Dr. Keith Webber
Acting Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

RE: Telephone Amendment

Dear Sir:

Please refer to Watson's abbreviated new drug application for Morphine Sulfate Extended-release Capsules USP (ANDA 200812). Reference is also made to the October 24, 2011 telephone request from the agency and to our subsequent teleconferences on October 27, 2011, November 03 and 07, 2011. The agency has requested that Watson provide a commitment to submit a prior approval supplement in the event commercial batches of the extended-release (ER) pellets used in the drug product are scaled up beyond the batch size currently proposed in the ANDA.

As clarified and agreed on in the teleconferences, Watson commits to submit a prior-approval supplement to the ANDA if the batch size of the extended-release (ER) pellets is increased beyond the validated commercial batch size of (b) (4)

(b) (4) batch size of capsules.
Furthermore, as recommended by the Division Director, Glen Smith, since the prior approval supplement is an agency request, **it will be considered appropriate for expedited review.**

This submission has been verified virus-free and is being submitted through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards.

For regulatory information regarding this ANDA, please contact the undersigned at (954) 358-6125 (*direct dial*) or (954) 358-6350 (*facsimile*).

Sincerely

Janet Vaughn
Director Regulatory Affairs

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: **II** Team: **22** PM: **Tina Nhu**

Electronic ANDA:
Yes ☒ No ☐

ANDA #: **200812**

Firm Name: **WATSON LABORATORIES INC.**

ANDA Name: **Morphine Sulfate Extended-release Capsules USP, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg**

RLD Name: **Kadian**

Electronic AP Routing Summary Located:

V:\Chemistry Division II\Team 22\Electronic AP Summary

AP/TA Letter Located:

V:\Chemistry Division II\Team 22\AP Letters

Project Manager Evaluation:

Date: **7/25** Initials: **tn**

- ☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date <u>December 16, 2009</u>	Date of Application <u>December 16, 2009</u>	Date Acceptable for Filing <u>December 16, 2009</u>
Patent Certification (type) <u>PIII</u>	Date Patent/Excl. expires April 13, 2010 and March 23, 2010	Citizens' Petition/Legal Case? Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ DMF#: _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 10/29/2010* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filing? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 20-Jul-2011 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 10/12/2011 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location: _____)
Date of Acceptable Labeling 05/12/2011 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) na

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☒

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 8/19/2011 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☐ 1st Generic Review

☒ Bob West / Peter Rickman

☐ Keith Webber

☐ Filed AP Routing Summary in DARRTS

☐ Notified Firm and Faxed Copy of Approval Letter

☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

Reference ID: 3042771

OGD APPROVAL ROUTING SUMMARY

1. **Regulatory Support Branch Evaluation**

Martin Shimer

Date: 8/23/2011

Chief, Reg. Support Branch

Initials: MHS

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)	Determ. of Involvement? Yes ☐ No ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days: Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: _____ Is applicant eligible for 180 day	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP ☐ OTHER:	
Comments: ANDA submitted on 12/16/2009, BOS=Kadian NDA 20616, PIII to '128 and '474. ANDA ack for filing on 12/16/2009 for the 80 mg and 100 mg strengths (LO dated 3/10/2010). New Strength Amendment for addition of the 20 mg, 30 mg, 50 mg and 60 mg strengths rec'd on 10/1/2010, BOS=Kadian NDA 20616, PIII to '128 and '474. There are no remainin unexpired patents or exclusivites which protect the RLD. This ANDA is eligible for immediate Full Approval. Both the '128 and '474 patents expired back in 2010. There are no other patent listed for the RLD Kadian. Therefore, there are no blocking patents nor is there the potential for a blocking 180 day exclusivity. This ANDA is eligible for immediate Full Approval.	

2. **Labeling Endorsement**

Reviewer, _____ :

Date _____

Initials _____

Labeling Team Leader, _____ :

Date _____

Initials _____

REMS required?

☐ Yes ☒ No

REMS acceptable?

☐ Yes ☐ No ☐ n/a

Comments:

From: Lee, Koung U

Sent: Friday, August 19, 2011 2:57 PM

To: Vezza, Adolph E; Nhu, Tina

Subject: RE: ANDA 200812

I concur. Thanks.

Koung

3. **Paragraph IV Evaluation**

PIV's Only

David Read

OGD Regulatory Counsel

Pre-MMA Language included ☐

Post-MMA Language Included ☐

Comments:

Date _____

Initials _____

4. **Quality Division Director /Deputy Director Evaluation**

Reference ID: 3042971

Date **10/27/2001**

5. **First Generic Evaluation**

First Generics Only

Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date _____
Initials _____

OGD Office Management Evaluation

6. **Peter Rickman**

Director, DLPS

Para.IV Patent Cert: Yes ☐ No ☒
Pending Legal Action: Yes ☐ No ☒
Petition: Yes ☐ No ☒

Comments: BOS=Kadian NDA 20616, Applicant provided a PIII cert to '128 and '474 patents (these patents have expired). There are no remaining patents or exclusivities that protect the RLD. Chemistry acceptable 10/24/2011. Bio acceptable 10/12/2011. Labeling acceptable 5/12/2011, TL sign-off 8/19/2011. Watson has submitted a REMS which is currently under review. EER acceptable 5/10/2010. This ANDA is eligible for immediate Full Approval.

Date 11/9/2011
Initials wpr

AND/OR

7. **Robert L. West**

Deputy Director, OGD

Para.IV Patent Cert: Yes ☐ No ☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes ☐ No ☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments:

Date _____
Initials _____

8. **OGD Director Evaluation**

Keith Webber

Deputy Director, OPS

Comments:
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager

Date 11-10-2011
Initials TN

Check Communication and Routing Summary into DARRTS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TINA T NHU
11/10/2011