CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-195 & 22-207

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY TOXICOLOGY REVIEW AND EVALUATION
Addendum to Primary Review (February 12, 2008)

NDA NUMBER:	22-207
PRODUCT:	Morphine Sulfate Tablets
FORMULATION:	Tablets
INDICATION:	Relief of Moderate to severe acute and chronic pain
SPONSOR:	Roxane Laboratories, Inc.
TYPE OF SUBMISSION:	Amendment
DATE RECEIVED:	20-Dec-2007
PHARM/TOX REVIEWER:	BeLinda A. Hayes, Ph.D.
PHARM/TOX SUPERVISOR:	R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR:	Bob A. Rappaport, M.D.
PROJECT MANAGER:	Lisa Basham

BACKGROUND

In 2007, the Sponsor submitted NDA 22-207 for morphine sulfate tablets (15 and 30 mg) under 505(b)(2) regulations.

During the review of NDA 22-207, the Agency became aware of several impurity issues. Review of stability data of both NDAs revealed that the morphine sulfate drug substance contained several impurities that exceeded ICH Q3A specifications. In addition to this issue, the chemist reviewing NDA 22-207 noted that the stability data for the morphine sulfate tablets revealed that — levels in the drug product increased over time. The Sponsor is proposing to set the specification at — which exceeds ICH Q3B safety qualification. The chemistry review team has requested that the specification be reduced as per ICH Q3B. b(4)

These concerns were conveyed to the Sponsor via an email on December 5, 2007 and/or during the December 14, 2007 teleconference. The requests conveyed to the Sponsor were:

According to — the morphine drug substance contains the following impurities: — b(4)
— reported that they are at a level of NMT — which exceeds ICH Q3A safety qualification threshold. You should either reduce the specifications to — or provide adequate safety qualification as per ICH Q3A. Adequate qualification should include:

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Repeat dose toxicology of appropriate duration to support the proposed indication.

Reduce specifications as per ICH Q3B. If you are unable to reduce the specifications, you may justify the safety based on: b(4)

- A repeat dose toxicology study of up to 90 days to support the proposed indication or
- Via reference to such data in the published literature.

b(4)

SUMMARY:

Drug Substance Specifications:

In their amendment to the NDA, the Sponsor did not reduce the specifications b(4) or provide adequate safety qualification to support their proposed drug substance specifications. The articles submitted for review did not provide any toxicology data that support the safety of these impurities. These articles verified the reviewer initial assessment. That is:

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b(4)

However, the Sponsor did provide a clinical justification for applying a higher qualification threshold of NMT 0.15% (the ICH specification threshold for a drug whose maximum daily dose would be less than 2 g/day). Although opioid products do not have a maximum daily dose due to the development of tolerance to the opioid, the Sponsor believes setting a maximum daily dose of 2 gram for the morphine sulfate tablets is appropriate based on published literature which details clinical use of immediate release formulations of morphine in treating chronic pain conditions. Evaluation of the Sponsor's rationale and proposal to set a maximum feasible daily dose of 2 gm has been discussed with the medical review team. Given the large number of tablets required to reach a daily dose of 2 grams, the Division accepts the proposal to set the impurity qualification thresholds based on a NMT 2 gram/day dose. However, given a 2 g maximum daily dose limit for immediate release morphine products, the proposed specifications for both drug substance and drug product still will not meet ICH qualification threshold level of NMT 0.15% for drug substance impurities and as indicated in the table below, a maximum daily dose of up to 2 g should meet the specification qualification of NMT for the drug product.

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Drug Substance (Q3A)	
Maximum Daily Dose	**Identification**
≤ 2 g	0.15%
> 2 g	
Drug Product (Q3B)	
10 mg – 100 mg	
>100 mg - 2 g	
> 2g	0.15%

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Drug Product Specifications:

The Sponsor did not submit any data or information to address the agency concerns about the safety at their proposed specifications. As with the drug substance specifications, the Sponsor did provide a clinical justification for applying a higher qualification threshold of NMT (the ICH Q3B specification threshold for a drug whose maximum daily dose would be less than 2 g/day). As noted above, this justification is acceptable to the Division. However, the Sponsor was still seeking a specification of NMT which exceeds the safety qualification threshold for drug product impurities.

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A review of the existing data c indicates that the compound is not a completely benign substance. is a minor metabolite of morphine in several species (Nagamatsu *et al.*, 1986; Kumagai, et al., 1990). Results from *in vitro* studies have shown that is a toxic metabolite of morphine and is linked to the liver toxicity of morphine (Nagamatsu *et al.*, 1986; Nagamatsu and Hasegawa, 1992; Yamano and colleagues, 1997). The mechanism of -induced hepatoxicity involves ability to covalently bind to hepatic glutathione (GSH). The group c non-ezymatically reacts with GSH to form GSH (Nagamatsu *et al.*, 1982). In a later published report, Nagamatsu *et al.* (1986) demonstrated that isolated rat hepatocytes incubated with morphine induced a marked decrease in GSH and resulted in cell death. These effects were correlated with the formation of , a reactive electrophilic intermediate.

b(4)

is a potential metabolite of morphine in humans. Hence, the potential of to induce liver toxicity in humans exist. While has not been identified in the urine of humans following the administration of morphine, the metabolism of morphine to has been demonstrated *in vitro*. Todaka and colleagues (2005) reported that isolated human hepatocytes metabolized morphine to in a fashion similar to that reported for rats. The reviewer concur with Todaka and colleagues conclusion that following the administration of morphine in high doses, as would be seen for the treatment of chronic pain, a significant elevation in level may occur and result in morphine-induced toxicity.

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The Sponsor did not reduce the specification for in the drug product. According to the chemist review of the stability data submitted with this submission,

levels that were increasing before in the batches reported earlier continued to increase. In new batches submitted for review; one batch showed no increase and the others showed a slight increase. A statistical analysis of these batches conducted by Dr. Arthur Shaw suggests that if the Division were to accept a specification of NMT the product would receive a month expiration date for the morphine sulfate tablets. A specification of NMT is unacceptable because there is no toxicology data available to support the safety of at this level. This information was conveyed to the chemistry review team. In his final statistical analysis of these batches, Dr. Arthur Shaw has concluded that the upper limit for should be set at and an expiration data of 18 months will support this limit. b(4)

CONCLUSION AND RECOMMENDATIONS

The Sponsor did not reduce the safety qualification of to meet the ICH Q3A safety qualification threshold. Also, the Sponsor did not provide the Agency with sufficient information to adequately qualify the safety of these impurities. Even with a maximum daily dose of 2 g, the safety threshold level of exceeds ICH Q3A safety qualification. Thus, the Sponsor should complete a minimal genetic toxicology screen (one in vitro mutagenicity study and one in vitro chromosome damage study). Given the presence of these impurities in the drug substance to date, repeat-dose toxicology studies will not be required for these impurities. However, the existing experience with these impurities does not address the genotoxic potential of the compounds. b(4)

Furthermore, the level in the morphine sulfate tablets was not reduced to meet ICH Q3B safety qualification threshold. The Sponsor did not submit any data on the toxicological profile . A review of the published literature has shown is a minor metabolite of morphine in several species and possibly humans and is a potential hepatotoxin. b(4)

Assuming a 2 gram maximum daily dose limit for the morphine sulfate tablet, the upper limit for should be set at . The chemistry review team has reported that the stability data will support an expiration date of eighteen month will support a threshold level of . An expiration date greater than eighteen months will exceed the limit and will not meet ICH qualification threshold for a total daily intake of 2 grams. b(4)

Based on the information provided to date for NDA 22-207 (Morphine Tablet), from the nonclinical pharmacology toxicology perspective, NDA 22-207 may be approved if the upper limit of is set at and not the Sponsor's proposed limit of and the specification of the impurities in the drug substance be reduced to or the Sponsor agree to conduct the following Phase 4 studies: b(4)

1. Conduct a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay)

tested up to the limit dose for the assay, for each of the following drug substance impurities that exceed ICHQ3A qualification thresholds of NMT 0.15%:

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REFERENCES:

Brunk, S.F. and Delle, M. Morphine metabolism in man. Clin. Pharmacol. Ther. 16(1): 51-57, 1974.

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Nagamatsu, K., Ohno, Y., Ikebuchi, H., Takahashi, A., Terao, T., and Takanaka, A. Morphine metabolism in isolated rat hepatocytes and its implications for hepatotoxicity. Biochem. Pharmac. 35: 3543-3548, 1986.

Nagamatsu, K, and Hasegawa, A. Covalent binding of morphine to isolated rat hepatocytes. Biochem. Pharmac. 43: 2631-2635, 1992.

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Vermeire, A. and Remon, J.P. Stability and compatibility of morphine. Int. J. Pharm. 187(1): 17-51, 1999.

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/s/

Belinda Hayes
3/13/2008 07:37:32 PM
PHARMACOLOGIST

R. Daniel Mellon
3/14/2008 10:49:47 AM
PHARMACOLOGIST
I concur

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-207**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**06/08/07**
PRODUCT:	**Morphine Sulfate Tablets**
INTENDED CLINICAL POPULATION:	**Relief of Moderate to severe acute and chronic pain**
SPONSOR:	**Roxane Laboratories, Inc.**
DOCUMENTS REVIEWED:	**Vol. 2 of 40**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**BeLinda A. Hayes, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Basham**

Date of review submission to Division File System (DFS): December 12, 2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a nonclinical pharmacology and toxicology perspective, NDA 22-207 may be approved.

B. Recommendation for nonclinical studies

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Should the sponsor not be able to either reduce the specifications for — or identify other data to support the proposed specifications, they should complete a minimal genetic toxicology screen (one in vitro mutagenicity study and one in vitro chromosome damage study). These studies may be completed post approval, as the impurities have been in approved drug products and the new specification of NMT — is being asked to comply with current specification guidelines.

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According to the chemistry review team, stability data showed that — levels in the drug product increases over time. The sponsor is proposing to set the specification at which exceeds ICH Q3B threshold for safety qualification. The chemistry review team will request that the specification be reduced as per ICH Q3B. If the sponsor is unable to reduce the specifications, they may justify the safety based on

- A repeat dose toxicology study of up to 90-days duration to support the proposed indication or
- Via reference to such data in the published literature.

C. Recommendations on labeling
Additions are indicated by underlined

The Sponsor proposed the following labeling for the nonclinical pharmacology and toxicology sections of the label. This labeling is identical to that in the Avinza (NDA 21-260) label. Information on male fertility effects reported in the literature is recommended to be included in the proposed labeling. Otherwise, there are no further suggested changes **to the Sponsor's proposed label.**

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of *in vitro* studies showed that morphine is not mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations

when incubated with murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the *in vivo* clastogenic effects reported with morphine in mice may be directly related to increases in glucocorticoid levels produced by morphine in this species.

A literature report indicated that morphine impairs fertility in rats. In a fertility study in which male rats were administered morphine subcutaneous prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects were observed. These included reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites

Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic to those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. Morphine was not a significant teratogen in the rat at exposure levels significantly beyond that normally encountered in clinical practice. In one study however decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days to mating. In two studies performed in rabbit, no evidence of teratogenicity was reported to be no greater than expected among children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Nonteratogenic Effects

Published literature has reported exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following, treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and sexual maturation, and increased mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubules shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine into adulthood.

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Roxane Laboratories, Inc. has submitted a New Drug Application (NDA) for Morphine Sulfate Tablet, 15 mg and 30 mg, for the relief of moderate to severe acute and chronic pain. Roxane Laboratories has been marketing this formulation since the 1980s under the brand name Morphine Sulfate Tablets (Immediate Release) 15 mg and 30 mg. The nonclinical development program outlined in this NDA submission relies in part on the FDA's previous findings of safety and efficacy of King Pharma's NDA (21-260) for Avinza (morphine sulfate extended-release capsules) and Baxter Healthcare's NDA (18-565) for Duramorph (morphine sulfate injection USP).

B. Pharmacologic activity

The Sponsor did not conduct formal pharmacological studies in support of this NDA. During the pre-NDA meeting on September 12, 2006, the Sponsor proposed to cross-reference the data in King Pharma's NDA for Avinza (morphine sulfate extended-release capsules) and Baxter Healthcare's NDA for Duramorph (morphine sulfate injection USP) and to reference published

literature. The Agency indicated that for a 505(b)(2) application, it would be acceptable to reference published literature.

Morphine's principal therapeutic action is analgesia. It also produces drowsiness, changes in mood, alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine function and affect rewarding behavior. Morphine exerts its primary physiological effects via activation of the μ opioid receptor.

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to this drug product. As is well known with opioid drug products, respiratory depression, a known extension of the pharmacological action of morphine, is the most prominent adverse effect of morphine that is relevant to the proposed clinical use. Clinically significant respiratory depression rarely occurs with standard morphine doses in the absence of underlying pulmonary dysfunction.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

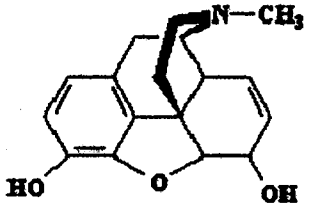
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	22-207
Review number:	1
Sequence number/date/type of submission:	000/June 8, 2007/Commerical 505(b)(2)
Information to sponsor:	Yes ( ) No (X)
Sponsor and/or agent:	Roxane Laboratories, Inc. 1809 Wilson Rd. Columbus, OH 43228
Manufacturer for drug substance:	——— b(4)
Reviewer name:	BeLinda A. Hayes, Ph.D.
Division name:	Division of Anesthesia, Analgesia and Rheumatology Products
HFD #:	170
Review completion date:	December 06, 2007

Drug:

Trade name:	N/A
Generic name:	Morphine Sulfate Tablets
Code name:	N/A
Chemical name:	Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) (salt) pentahydrate
CAS registry number:	64-31-3 (morphine sulfate)
Molecular formula/molecular weight:	$(C_{17}H_{19}NO_3)_2\ H_2SO_4 \cdot 5H_2O/758.83$
Structure:	

Morphine
$C_{17}H_{19}NO_3$



Relevant INDs/NDAs/DMFs:

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DMF	—	Morphine Sulfate USP
DMF		Morphine Sulfate USP ———

Drug class:	Opioid Agonist, Narcotic
Intended clinical population:	Relief of moderate to sever acute and chronic pain

Clinical formulation: Tablet

Morphine Sulfate Tablets will be marketed in 2 strengths, 15 mg and 30 mg for oral administration. The recommended dosage is 15 to 30 mg every 4 hours for both acute and chronic pain. The morphine tablets will be manufactured and packaged in bottles of 100 tablets and 25 tablets x 4 unit dose blisters. The components, quantitative composition, compendial and function of the ingredients for both dosage strengths are provided in the table below.

			15 mg tablets	30 mg tablets
Ingredients	**Function**	**Quality Standard**	**Amount (mg per tablet)**	**Amount (mg per tablet)**
Morphine Sulfate, USP	Active Ingredient		15.15 mg	30.3 mg
Microcrystalline Cellulose, NF		NF		
Pregelatinized Starch, NF		NF		
Corn Starch		NF		
Colloidal Silicon Dioxide, NF		NF		
Stearic Acid, NF				
Theoretical Tablet Weight	-	-	100 mg	200 mg

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There are no novel excipients in the drug product. All of the above excipients are found in approved drug or food products within approved ranges.

Impurities:

The impurity levels in the referenced DMF are the same for the currently marketed morphine products. Although most of these impurities exceed current ICH thresholds for safety qualification, they have been present in morphine products and do not appear to pose a significant safety risk. The impurities in the drug substance were reported by the drug manufactures and are identified in the table below. The identified impurities are:

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. The structures of these impurities are presented below. is a metabolite of morphine and therefore is considered to be qualified (Brunk and Delle, 1974). are well known degradation products of morphine. is an oxidation product of morphine (Misra and Mule, 1972) and a morphine metabolite in several species (Misra and Mule, 1972; Marme, 1983). It has been reported that morphine degrades in aqueous solutions to (Vermeire and Remon, 1999). The minor impurity, 10-hydroxymorphine, has been detected in morphine products for almost two decades. The compound appears to have similar binding and potency as morphine itself (Farsam et al., 1990). The impurities have been used therapeutically for years and are well characterized.

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Morphine sulfate obtained from — contains the impurity — . — that is a structural alert for mutagenicity. specification for this impurity was limited to . This specification is above the ICH Q3A qualification threshold of — The — level is being requested since there is no maximum daily dose for opioid drug products. The potential genotoxic effects of — were described in the — DMF '. Evaluation of — in the *in vitro* mammalian chromosomal aberration and the bacterial reverse mutation assays indicated that — was negative. b(4)

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Degradants:

Stability data has indicated that levels are increased over time in morphine tablets. As a result of the data, the sponsor is proposing a specification of for . This specification is above the ICH Q3B qualification threshold of 0.15%. The potential toxicity associated with repeated exposure to the degradant is unknown. Published nonclinical repeat toxicity studies were not found in the published literature. However one published *in vitro* study suggested that may be hepatotoxic. An *in vitro* study with human liver showed that morphine is metabolized to in the presence of NAD and NADP (Todaka *et al.*, 2005). The formed has **the ability to deplete liver's GSH level by binding to it and eliciting hepatotoxic effects.** Hence, the potential long-term toxicity of the accumulation of is unknown. The sponsor should limit the levels of resulting from degradation of the tablet or qualify the levels as per ICHQ3B or provide adequate safety qualification for this impurity. Although genetic toxicology studies exist for morphine (in both referenced

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DMFs), the sponsor has not provided data regarding the potential repeat-dose toxicity of this degradant.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-195 are owned by Roxane Laboratories, Inc. or are data for which Roxane Laboratories, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-195 that Roxane Laboratories, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in **the drug's approved labeling**. Any data or information described or referenced below from a previously approved application that Roxane Laboratories, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-207.

Studies reviewed within this submission:

The sponsor did **not** conduct any toxicology studies in support of this NDA.

Studies not reviewed within this submission: Many of the studies (i.e., published literature study reports) for this NDA were previously reviewed by Dr. Kathleen Haberny for NDA 21-260. The findings were incorporate-, d in this NDA review and noted in the text.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Morphine, a phenanthrene opioid, is one of the most effective analgesics and is the prototype against which all other opioids are measured. Morphine sulfate has been used for many years in the management of pain. It was first approved by the Food and Drug Administration (FDA) in September of 1984 under the trade name Duramorph® Preservative-free Injection (NDA 18-565; Baxter Healthcare) for intrathecal and epidural administration. Today, morphine sulfate is marketed in a variety of formulations, including oral solutions, immediate- and sustained-release tablets and capsules, suppositories and injectable preparations. Morphine is marketed under generic and brand name products including MS-Contin®, Oramorph SR®, Avinza®, Duramorph PF®, Depodur®, and Kadian®.

Morphine is an opioid agonist with activity at μ-, κ- and δ-opioid receptors. Activation of μ-opioid-receptors is associated with analgesia, respiratory depression, sedation,

decreased gastrointestinal motility, euphoria and physical dependence. Morphine actions at the κ-opioid receptors are associated with spinal analgesia, miosis and psychotomimetic effects.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Morphine mediates it primary pharmacodynamic effect, analgesia, thorough activation of μ-opioid receptors. Its primary pharmacodynamic effects are well known and were summarized in NDA 21-260. No additional primary pharmacodynamic studies were conducted by the Sponsor for the current NDA.

Drug activity related to proposed indication: μ-Opioid receptors are highly concentrated in regions of the central nervous system involved with the neuronal circuitry involved with the processing of nociceptive information; the periaqueductal and periventricular gray matter, ventromedial medulla and spinal cord. The pain modulating effects of morphine ensue from its direct inhibition of the ascending transmission of nociceptive information from spinal cord dorsal horn and to the activation of the pain control circuits that descend from the midbrain via the rostral ventromedial medulla to the spinal cord dorsal horn.

2.6.2.3 Secondary pharmacodynamics

Morphine secondary pharmacological effects include dysphoria, euphoria, sedation, respiratory depression, decreased gastrointestinal motility and physical dependence. These effects were described in NDA 21-260.

These pharmacodynamic effects have been extensively reviewed in the published literature.

2.6.2.4 Safety pharmacology

The Sponsor did not conduct formal safety pharmacology studies.

Neurological effects: No nonclinical safety pharmacology studies were conducted to evaluate potential central nervous system safety concerns.

Cardiovascular effects: Animal studies had shown that morphine causes hemodynamic changes. In conscious dogs, morphine initially induced coronary vasodilation followed by a sustained reduction in coronary blood flow and significant coronary vasoconstriction followed by hypotension (Vatner et al., 1975). Morphine induces the release of histamine. High doses of morphine cause the release of histamine that induces peripheral vasodilation, with significant hypotension.

In contrast to the results observed in dogs, when morphine was the sole medication administered to healthy humans, no hypotensive effects were observed; only stimulatory effects were observed. Morphine (0.07 mg/kg and 0.14 mg/kg) elicited a dose-dependent increase in mean arterial blood pressure, heart rate and oxygen consumption (Mildh *et al.*,

2000). The morphine-induced stimulation was correlated to signs of local histamine release (increase redness and itching at the injection site).

Morphine can cause hemodynamic changes and cardiovascular adverse reactions. These adverse effects include: bradycardia, sinus tachycardia, palpitations, hypotension, hypertension, orthostatic hypotension, diaphoresis, and syncope. Orthostatic hypotension is a secondary effects resulting from morphine-induced peripheral vasodilatation.

Pulmonary effects: Respiratory depression is a clinically significant effect of morphine. At high doses, morphine causes respiratory depression, pulmonary edema and respiratory arrest. Like other opioids, morphine decreases the responsivity of the brain stem respiratory center to CO_2 and depression of pontine and medullary centers via its action at the mu2 opioid receptors.

Renal effects: The Sponsor did not conduct formal safety pharmacology studies to evaluate potential renal safety concerns with morphine administration. A review of the literature did not identify any animal studies that specifically addressed morphine-related renal effects.

However, morphine does present some safety concerns in patients with HIV-associated nephropathy and renal failure. Patients with HIV-associated nephropathy are often intravenous users of heroin. Morphine is an active metabolite of heroin and has been associated with the renal interstitial fibrosis observed in heroin-associated glumerulosclerosis. *In vitro* studies have demonstrated that morphine has the potential to modulate proliferation of kidney fibroblasts (Singhal et al., 1998). Cultured rat kidney fibroblasts were exposed to morphine at concentrations in the range of 10^{-12} M to 10^{-4} M for 24 hours or 48 hours. At both incubation period, morphine at low concentration 10^{-12} M, induced proliferation of fibroblast.

Chronic use of morphine in patients with renal failure should be use with caution (Angst *et al.*, 2000). Morphine-6-glucuronide, a pharmacological active metabolite of morphine is cleared via the kidney. In patients with renal failures, it will accumulate and allow opioid side effects to persist hours after plasma concentration of morphine has peaked and morphine-6-glucuronide plasma concentration has peaked.

Gastrointestinal effects: Gastrointestinal side effects are the major adverse effects associated with acute and chronic use of morphine. Inhibition of gastrointestinal motility (i.e., propulsive peristalsis) is a long-known classical effect of morphine. In addition to this effect, like other opioid drugs, morphine exerts a wide spectrum of other effects on the mammalian intestinal function. These effects include reduction in secretions (pancreatic, biliary, and electrolyte/fluid) and increases in intestinal fluid absorption and blood flow (Brown and Miller, 1991). Morphine effects on gastrointestinal function are mediated via actions on opioid receptors within the central nervous system and through a direct action on peripherally located opioid receptors within the enteric nervous system (Parolaro *et al.*, 1977; Stewart et al., 1978; Tavani *et al.*, 1990). Mμ opioid receptors in

the brain of mice (Porreca *et al.*, 1973, 1984) and rats (Koslo *et al.*, 1985) are involved in the CNS-mediation of morphine inhibition of gastrointestinal motility.

The pharmacological action of morphine on the gastrointestinal tract is manifested clinically. These clinical effects are presented in the following table.

GI Tract Site of Action	Pharmacological Action	Clinical Effect
Stomach	Decreased gastric motility	Anorexia
	Decreased pyloric tone	Nausea and vomiting
Small Intestine	Decreased pancreatic and biliary secretion	Delayed digestion
	Reduced propulsion	Delayed absorption of medication
	Increased fluid absorption	Hard and dry stool
Large Intestine	Increased non-propulsive contractions	Spasm, abdominal cramps, and pain
	Increased fluid absorption	Hard and dry stool
	Increased anal sphincter tone	Retention of gastrointestinal contents (incomplete evacuation)

Abuse liability: Morphine is a Schedule II controlled substance and is highly addictive. Psychological and physical dependence develop quickly to morphine. Morphine elicits **euphoria by activating the brain's reward** systems; specifically its binds to opioid receptors on neurons located in the VTA and in the nucleus accumbens. Withdrawal symptoms associated with morphine addiction include drug craving, watery eyes, insomnia, diarrhea, running nose, yawning, dysphoria, chills and sweating.

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Sponsor did not submit pharmacology tabulated summary.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The Sponsor for this NDA did not conduct formal pharmacokinetics and toxicokinetics studies. The absorption, distribution, metabolism, excretion and pharmacokinetics of morphine sulfate were described in NDA 21-260. A summary of data in the NDA and information in the published literature is described here.

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

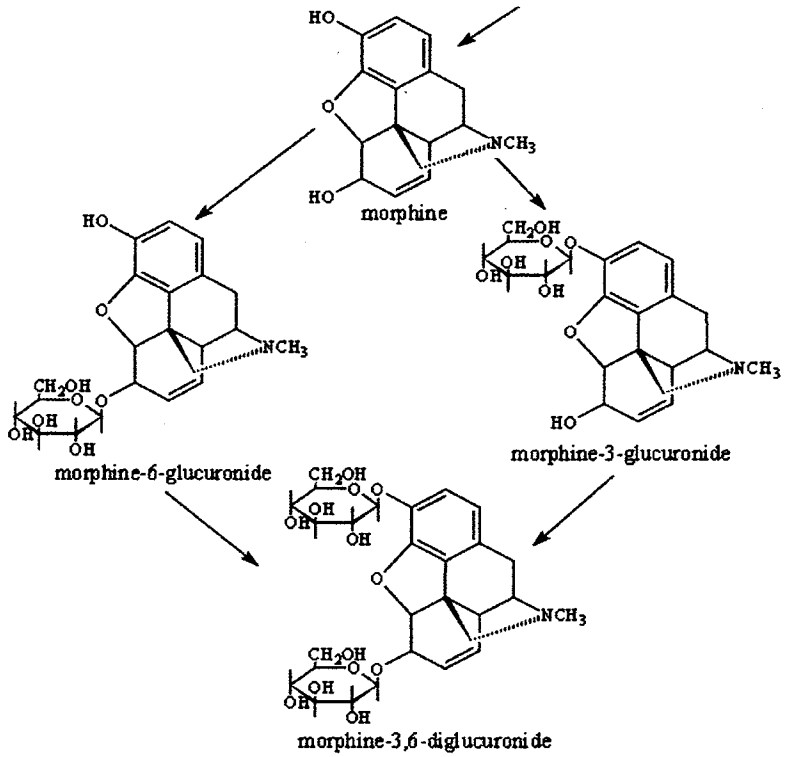
Absorption of morphine following oral administration is variable and decreased by extensive pre-systemic metabolism in both the liver and gut. The oral bioavailability of is less than 40%, approximately 20%-33%.

2.6.4.4 Distribution

Morphine is distributed to the intestinal tract, kidneys, liver, lungs, skeletal muscle, spleen and brain. Although the central nervous system is the primary site of action of morphine, only small quantities cross the blood-brain barrier. Morphine also crosses the placental membranes and has been detected in breast milk (Feilberg *et al.*, 1989; Robieux *et al.*, 1990). The volume of distribution of morphine in humans is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Muscle tissue binding has been reported to be 54%.

2.6.4.5 Metabolism

Morphine metabolism is primarily by hepatic glucuronidation by uridine diphosphate glucuronosyl transferase (UGT) enzyme, with specific affinity for the UGT2B7 and UGT1A3 isozymes, (Amstrong and Cozza, 2003; Wittwer and Kern, 2006). The isoenzyme is responsible for the formation of both major glucuronide metabolites of morphine; morphine-3-glucuronide (M3G, about 50%) and morphine-6-glucuronide (M6G, about 15%). M3G has no analgesic activity; whereas M6G has been shown to have analgesic activity but crosses the blood brain barrier poorly. The metabolism of morphine can also occur in the brain and the kidneys (Christrup, 1997). In humans, morphine is also metabolized to normorphine and normorphine-6-glucurinide (Yeh *et al.*, 1977). Normorphine is formed by hepatic microsomal oxidation. Minor metabolites that have been identified in the urine of humans following large doses of morphine chronically include codeine (3-O-methyl morphine) and morphine N-oxide. Following oral administration, approximately 5% of the morphine undergoes N-demethylation to normorphine and 10% metabolized to codeine.



2.6.4.6 Excretion

Morphine is eliminated in urine, feces and bile; renal excretion being the major route of elimination. Approximately 10% of a dose of morphine is excreted unchanged in the urine. Most of the dose of morphine is excreted in the urine as the metabolites M3G and M6G, with elimination of morphine occurring primarily as renal excretion of M3G. A small amount of the glucuronide conjugates are excreted in the bile, with minor enterohepatic recycling. Seven to 10% of administered morphine is excreted in the feces. The mean adult plasma clearance of morphine is approximately 20 to 30 mL/min/kg. The effective terminal half-life of morphine after intravenous administration is reported to be approximately 2 hours. Longer periods of plasma sampling in some studies suggest a longer terminal half-life of morphine of about 15 hours.

2.6.4.7 Pharmacokinetic drug interactions

The sponsor did not conduct nonclinical pharmacokinetic studies to evaluate potential drug interaction with morphine. Hence, no pharmacokinetic studies were submitted with the NDA. However, the known drug interaction of morphine with other drugs is well known. The known drug interactions involving morphine are pharmacodynamic. Co-administration of morphine with CNS depressants (i.e., sedatives or hypnotics, general anesthetics, tranquilizers, and alcohol) can result in additive CNS respiratory depressant effects. Agonist/antagonist analgesic (i.e., pentazocine, nalbuphine, butorphanol, and

buprenorphine) co-administered with morphine may reduce morphine's analgesic effect or may precipitate withdrawal symptoms.

2.6.4.8 Other Pharmacokinetic Studies

None were conducted by the sponsor.

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and figures to include comparative TK summary

Summary tables were not provided by sponsor.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Summary tables were not provided by sponsor.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

No toxicology studies to evaluate the toxicity potential of morphine have been conducted by the sponsor. The sponsor conducted a search of the published literature to identify single-dose and repeat-dose toxicity studies conducted from 2002 to 2007. The sponsor stated that no studies were identified in their search of the literature during this period. Review of the literature showed that nonclinical studies evaluating the toxicity potential of morphine were conducted prior to 2002. Dr. Kathleen Haberny, for NDA 21-260, reviewed the published literature and summarized the general toxicology in her review in support of that NDA. Dr. Haberny's summary was reproduced verbatim from the review.

General toxicology:

NDA 21-260 for Morphelan™ did not contain single-dose toxicology data, but relied upon the published literature. Toxicity studies have been conducted in several species. Acute toxicity associated with the single administration of high doses of morphine in dogs includes: vomiting, delirium, clonic spasms and raspy and labored breathing (Humphreys, 1988). Morphine-induced acute toxicity in rodents was associated with catalepsy, circling, stereotypical behavior, Straub tail, increased motor activity, exophthalmos, and shallow breathing (Humphreys, 1988).

Genetic toxicology:

The sponsor did not conduct any genetic toxicology studies. However, there are a limited number of genotoxicity studies assessing the mutagenic potential of morphine reported in the published literature. These studies have suggested that morphine has mutagenic

potential. Results from *in vivo* chromosomal aberration assay and *in vivo* micronucleus assay suggest that morphine is a potential clastogen.

Carcinogenicity:

The Sponsor has not performed long-term studies in animals to evaluate the carcinogenic potential of morphine sulfate. Likewise, carcinogenicity studies were not performed in support of the referenced Morphine Product of NDAs 18-565 and 21-260 at the time of approval.

Reproductive toxicology:

No formal reproductive toxicity studies were submitted with the current NDA. The sponsor is relying upon the published literature during the period of 2002 to 2007. Four published studies that contain pertinent information on the reproductive and developmental toxicity of morphine were identified.

Special toxicology:

The Sponsor did not conduct local irritation and sensitization studies in animals.

2.6.6.2 Single-dose toxicity

NDA 22-207 for Morphine Sulfate Oral Solution did not contain single-dose toxicology studies, but relied upon findings of safety in NDA 18-565 and NDA 21-260 for Duramorph and Avinza, respectively, and published literature. The NDA for both Duramorph and Avinza also lacked single dose toxicology data, and relied on prior FDA findings. FDA's prior findings were based on data in the published literature. Dr. Haberny summarized the published literature pertinent to morphine-induced toxicity following a single dose. Her summary is reproduced verbatim from the review.

Single dose The median lethal dose (LD_{50}) reported in mice is 375 and 506 mg/kg SC (Witkin *et al.*, 1961; Blane *et al.*,1967), 221 and 250 mg/kg IV (Blane *et al.*,1967; Fennessy and Fearn, 1969), and 600 and 1270 mg/kg PO (Witkin *et al.*,1961; Blane *et al.*,1967). In rats, the LD_{50} values were 170 and 572 mg/kg SC (Blane *et al.*, 1967; Finnegan *et al.*,1948), 100 and 237 mg/kg IV (Blane *et al.*,1967; Finnegan *et al.*,1948) and 461 and 905 mg/kg PO (Blane *et al.*,1967; Finnegan *et al.*,1948). The LD_{50} values in rabbits were 266 mg/kg SC and 500 mg/kg IP (Sunshine ed. 1969) and in dogs the LD_{50} was 133 mg/kg IV. The lowest reported lethal dose was 8 mg/kg IV and 190 mg/kg SC in rabbits, 500 mg/kg SC in guinea pigs, 210 mg/kg SC in dogs, 40 mg/kg SC in cats, 900 mg/kg SC in ducks, 250 mg/kg SC and 500 mg/kg PO in pigeons, 600 mg/kg SC in frogs and 3676 mcg/kg by an unreported route in humans. In the preclinical study reports, morphine was 3x-10x more toxic in newborn animals than in adults due to greater permeability of the brain to morphine in newborns (Kupferberg and Way, 1963).

The morphine-induced deaths in animals were associated with convulsions, respiratory failure and circulatory failure (Humphreys, 1988). Adverse effects of high morphine doses in dogs include vomiting, delirium, clonic spasms, and raspy and labored breathing (Humphreys, 1988). Catalepsy, circling, stereotypical behavior, Straub tail, increased motor activity, exophthalmos, and shallow breathing are observed in rodents given high doses of morphine. Histopathological examination after single doses of morphine at 125 mg/kg IP in rats have shown centrilobular and midzonal vacuolation, diffuse fatty degeneration and eosinophilic changes without necrosis in the liver during the period from 2.5 to 18 hours after dosing (Maruta *et al.*,1997).

Acute morphine toxicity in humans includes miosis, constipation, urinary retention, nausea, vomiting, hypothermia, drowsiness, dizziness, apathy, confusion, respiratory depression, hallucinations, distorted perceptions, dyspnea, sleep disturbance, hypotension, cold/clammy skin, coma and pulmonary edema.

2.6.6.3 Repeat-dose toxicity

NDA 22-207 for Morphine Sulfate Oral Solution did not contain repeat-dose toxicology studies, but relied upon findings of safety in NDA 18-565 and NDA 21-260 for Duramorph and Avinza, respectively, and published literature. The NDA for both Duramorph and Avinza also lacked repeat-dose toxicology data, and relied on prior FDA findings. **FDA's prior findings were based on data in the published literature. Dr.** Haberny summarized the published literature pertinent to morphine-induced toxicity following repeated dosing. Her summary is reproduced verbatim from the review.

Multiple dose A study by Finnegan *et al.* (1948) showed a treatment-related decrease in body weight gain, increased mortality and increased incidence of pneumonia after chronic treatment with oral morphine sulfate at 0.01%-1% (dietary) in male and female rats. Decreased body weights were also observed without other drug-related abnormalities in a study on chronic morphine administration in female rats given 25 mg/kg/d (dietary) for 124 days (Fennessy and Fearn, 1969). Drug-related morphologic changes in the kidneys of rats treated with increasing doses of morphine sulphate from 24 to 96 mg/kg/d SC or 10 mg/kg SC b.i.d. for 6 days were reported in a study by Marchand *et al.* (1969). The changes included large cytoplasmic and intercellular vacuoles, increased thickness of basement membranes, loss of microvilli, larger and clumping mitochondria, increased lysomes and changes in size, shape and density of nuclei in the proximal, distal and collecting tubules. Reduced hepatic glucuronosyl

transferase and N-demethylase have also been reported in rats treated chronically with morphine (Parke, 1968).

In dogs, subcutaneous morphine at 2 or 5 mg/kg/d for 100 days resulted in one death a the high dose on day 70, and weights loss in all of the animals (Finnegan *et al.*, 1948). In that study, the biochemical assays showed decreased red blood cell counts and hemoglobin concentrations at the high dose, spleen or lung hemorrhage at the low dose and fatty changes in liver and renal tubular epitheluim in the dog that died.

Tolerance to the analgesic effect and to many of the side effects of morphine, and dependence on the drug resulting in withdrawal signs and symptoms when morphine administration is abruptly stopped, are well known results of chronic treatment. The rapid development of tolerance results in a need for increasing doses over time to produce the same effects.

Adverse effects of chronic injected opioid abuse in humans have included abscesses, anaphylaxis, acute transverse myelitis, arrhythmias, wound botulism, cellulitis, endocarditis, fecal impaction, glomerulonephritis, hyperglycemia, hypoglycemia, osteomyelitis, postanoxic encephalopathy, tetanum, thrombophlebitis, nephropathy, hoarseness, hepatitis, pneumothorax, paraplegia, mycotic aneurysms and leukoencephalopathy (Lewis *et al.*, 1980; Wolters *et al.*, 1982).

2.6.6.4 Genetic toxicology

The sponsor has not performed genetic toxicology studies to evaluate the genetic toxicity potential of morphine. However, nine study reports on the genetic toxicology of morphine sulfate have been identified in the published literature. The results of these studies are summarized in table 1.

The limited information available on the genotoxic potential of morphine suggests that it has mutagenic potential. Morphine increased the frequency of chromosomal aberrations **in mice's bone marrow cells following a single** intraperitoneal administration in the dose range of 3.2-64 mg/kg (Swain et al., 1980). Morphine induced a dose-related increase in

the incidence of micronuclei in polychromatic erythrocytes of mice administered two doses of 3.2-32 mg/kg (ip) within 24 hours (Das and Swain, 1982) and in lymphocytes of mice administered a single dose of morphine in the dose range of 0-100 mg/kg (Sawant and Couch 1995). In contrast, *in vitro* assays, morphine failed to induce chromosomal aberrations in cultured human lymphocytes (Falek *et al.*, 1972) or micronuclei in mitogen stimulated splenocytes (Sawant and Couch, 1995). These findings suggest that metabolic activation is involved in the induction of chromosomal aberrations or micronuclei formation.

Badr and Rouh (1983) reported that morphine, at doses ≥ 10 mg/kg (ip) for 3 consecutive days, was positive in the dominant lethal test in mice; increasing the frequency of chromosomal aberrations in spermatids and in dividing spermatocytes. Implantation of morphine pellets (75 mg, sc) increased DNA fragmentation in murine thymocytes (Fuchs and Pruett, 1983).

Mutagenic effects of morphine were not observed in *Drosophila*, *Salmonella* and yeast test systems (Madden, 1979). In contrast, treated with morphine alone or in combination with a brief ethyl methane sulfonate (EMS) exposure dose-dependently increased the frequency of Comet tails of fragmented DNA in human HUT-78 cells (Shafer *et al.*, 1994). Morphine induced DNA fragmentation has been associated with apoptosis in murine thymocytes (Fuchs and Pruetts, 1993). Opiate and glucocorticoid antagonists antagonized the genotoxic effects of morphine in mice. Evidence suggests that morphine may be classified as a co-mutagen. Subcutaneous administration of morphine to rats at high doses (≥5 mg/kg) increased the ethylation of oesophageal DNA by N-nitrosodiethyl amine and may reduce the first pass clearance of N-nitrosodiethyl amine by the liver (Ribeiro-Pinto and Swann, 1997).

Table 1. Summary of published genetic toxicology study reports during the period 1972 to 1995.

Citation	Assay/Test System	№ Animals/Dose	Dose Regimen/Formulation/Route	Significant Findings
Falek *et al.*, 1972	Chromosomal Aberration/Human Leukocytes	Not applicable	*In vitro* lymphocyte culture	2-fold increase in chromatid damage among the opiate addicts. Increase SCE in opiate addicts.
Knapp and Cramer, 1976	Mutagenicity	Not applicable	*In vivo*	No evidence of induction of the sex linked recessive or dominant lethal mutation or translocation
Madden *et al.*, 1979	Human PBL	Not applicable	*In vitro*	Morphine negatively effect on DNA damage caused by UV radiation in addicts
Swain *et al.*, 1980	*In vivo* Cytogenic/mice	5/sex/group	Single Dose; 0. 3.2, 8, 16, 32, 64 mg/kg IP 17 consecutive days: 3.2 mg/kg/day IP Morphine sulfate dissolved in distilled water	At 32 mg/kg, increase in chromosomal aberration in born marrow cells. No-morphine-related effects observed following repeated dosing. Presumably due to the development of tolerance.
Das and Swain, 1982	Micronucleus mice	5/sex/group	2 doses separated by 24 hours: 0, 3.2, 8, 16, 32, 64 mg/kg IP	Dose-related increase in incidence of micronuclei in polychromatic erythrocytes at doses > 3.2 mg/kg

			Morphine sulfate dissolved in distilled water	
Badr and Rabouh, 1983	Dominant Lethal and Spermatocyte Test/Male Mouse	12 male mated with 2 female/dose group	Consecutive daily doses of 0, 10, 20, 40, 60 mg/kg IP Morphine sulfate dissolved in distilled water	Increase in number of dominant lethal, particularly early spermatids and types and frequencies of chromosomal aberration in dividing spermatocytes at all dose levels.
Fuchs and Pruett, 1993	In vivo and In vitro DNA Fragmentation in Thymocytes/Mice	2-4 females	75 mg SC time release pellet morphine released for 12-48 hours	DNA fragmentation noted in thymocytes following implantation of morphine. *In vivo*, DNA fragmentation blocked by opiate and glucocorticoid antagonists; **suggesting that morphine effect's** are partially mediated through effect on hypothalamic-pituitary-adrenal axis. *In vitro*, no DNA fragmentation observed in thymocytes following morphine exposure.
Shafer *et al.*, 1994	Mutagenicity/Human HUT 78 ells and HRPT mutant cells	Not applicable	*In vitro*	Morphine alone increased DNA fragmentation at concentrations ≥5 x 10^9 M. Morphine increased the mutation frequency of the mutagen ethylmethanesulfonate over that of the mutagen alone.
Sawant and Couch, 1995	*In vivo* and *in vitro* Micronuclei Assay.Mice	Female C57 black and DBA strain of mice/№ unknown	Single IP doses of 0-100 mg/kg Single IV doses: 20 mg/kg Morphine sulfate dissolved in phosphate-buffered saline	Dose- and time-related increase in micronucleated splenocytes and lymphocytes. Morphine-induced effect was blocked by adrenalectomy; suggesting increase in corticosteroid plasma level mediate genotoxic response. Morphine added to lymphocytes of cyclophosphamide treated animals at ≥107M increased number of micronuclei in binucleated cells following in vitro stimulation with mitogen.

2.6.6.5 Carcinogenicity

The sponsor had not performed long-term studies in animals to evaluate the carcinogenic potential of morphine. Likewise, carcinogenicity studies were not performed in support of the referenced morphine products of NDA 18-565 and NDA 21-260 at the time of approval. Although carcinogenicity data are not available for any morphine drug product, the policy in the Office of New Drugs is to only request such data for 505(b)(2) applications when the proposed drug product either significantly expands the patient population to be exposed, the duration of exposure, or the route of exposure compared to

previously approved drug products. Based on that policy, carcinogenicity studies will not be required for this NDA application.

There are several published reports of studies evaluating the carcinogenic potential of morphine in rats and dogs. No microscopic evidences of pre-neoplastic or neoplastic changes in repeated dose toxicity studies at doses up to 25 mg/kg/day (dietary) for 124 days in rats (Finnegan *et al.*, 1948; Fennesay and Fearn, 1969) or in dogs at doses up to 5 mg/kg/day (sc) for 100 days (Finnegan *et al.*, 1948). It has been reported that morphine inhibits tumor necrosis factor and the growth of several human cancer cell lines and BALB/3T3 cells (Sueoka *et al.*, 1996). In a subsequent study, Sueoka and colleagues (1998) found that morphine metabolite morphine-6-glucuronide inhibit inhibits neuroblastoma and PC-9 (peripheral neuronal cell line) cell line growth in vitro.

In the published literature, evidence of indirect involvement of morphine in tumorigenesis was reported. Ribeiro-Pinto and Swann (1997) reported that subcutaneous morphine at doses of 5 mg/kg and higher (sc) increased ethylation of oesophageal DNA. Immunosuppression has been observed with morphine administration in several animal species (Liu *et al.*, 1992; Fuchs and Pruett, 1993; Levier *et al.*, 1994). Theoretically, immunosuppression can contribute to an increase risk in carcinogenesis. Morphine's immunosuppressive effects have not been observed in clinical studies when morphine was administered at therapeutic doses.

There is evidence for indirect involvement of morphine in tumorigenesis. Morphine administered subcutaneous at doses of 5 mg/kg and higher increased the ethylation of esophageal DNA induced by nitrosodiethylamine in rats (Ribeiro-Pinto and Swann, 1977). Morphine treatment has also been reported to stimulate angiogenesis and promote tumor growth of a human breast tumor xenograph model in mice (Gupta *et al*, 2002).

Immunosuppression by morphine has been observed in several animal species (Liu *et al.*, 1992; Fuchs and Pruett, 1993; LeVier *et al.*, 1994). Theoretically, this immunosuppressant effect can contribute to an increase risk in carcinogenesis.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Reproductive and developmental toxicity studies with morphine were described in NDA 18-565 and NDA 21-260. NDA 18-565 for Duramorph® (for acute pain) and NDA 21-260 for Avinza® (for chronic pain) did not contain reproductive toxicology data, but references information in the published literature. The information included in Duramorph® and Avinza® labels appear to be based on the information in the published literature during the years between 1968 and 1997. Results of reproductive toxicology studies on embryo-fetal development reported in the literature were summarized by Dr. Kathleen Haberny for NDA 21-260; and is reproduced in table 2: below.

Table 2: Dr. Kathleen Haberny's Summary of Published reproductive toxicology Studies During the Period 1968 to 1997.

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Citation	Species #Treated/Dose Group	Dose (mg/kg/d), Route, Formulation, Dosing Period	Developmental Endpoints	Significant Findings
Lintern-Moore *et al.*, 1979	Rat (immature) 6/timepoint	50 mg/kg/d IP, in saline, 1 or 7 days	Body, pituitary, ovarian, uterine and adrenal weights, histopathology	Altered ovarian follicular development, ↓number of follicles after single dose, ↓initiation of follicular growth and number of follicles after 7 days of administration
James et al., 1980	Rat (male) 15/group	50 mg/kg/d SC in sterile water, for 4 and 9 weeks, or 13 week recovery	Serum LH, FSH, and testosterone, testes, seminal vesicles, prostate and pituitary weights and histopath	↓serum LH and testosterone, secondary sex organ weights, modified secretory activity of pituitary gonadotrophic cells, ↓spermatogenic cell populations (particularly early spermatids), all effects reversed after 13 weeks
Harpel & Gautieri, 1968	Mouse 5-32/group	0, 100-500 SC Morphine sulfate in distilled water, Gestation days 8 or 9	Embryo-Fetal: viability, implantation sites, resorptions, body weights, lengths, gross&skeletal observations	Clinical signs, ↓maternal food consumption: all doses Day 8: ↓fetal body wt. (>200 mg/kg) Exencephaly (>300 mg/kg) Axial skeletal fusions & ↓crown-rump length (>400 mg/kg) Day 9: Axial skeletal fusions & ↓fetal body wt (>100 mg/kg) ↑partial fetal resorptions & ↓crown-rump length (>400 mg/kg) ↓maternal body wt (500 mg/kg)
Iuliucci & Gautieri, 1971	Mouse # not provided	0, 200, 300, 400 IP, Gestation days 8 or 9	Embryo-Fetal: viability, resorptions, body wts, sex ratios, gross & skeletal malformations	Clinical signs in all morphine dose groups, deaths at 400 mg/kg. Exencephaly, axial skeletal fusions in >1 dose grp after treatment on days 8 or 9, ↓fetal body wt at 300 mg/kg, no effects on litter size, resorptions, sex ratios.
Ciociola & Gautieri, 1982	Mouse # not provided	0, 0.15, 1.5, 15 SC infusion, morphine sulfate in saline, gestations days 7-10 daily	Embryo-Fetal: viability, resorptions, body wts, sex ratios, gross & skeletal malformations	↓ fetal body wt, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae and xiphoid in morphine treated grps, inversely dose-proportional (perhaps due to tolerance at higher doses)
Glick *et al.*, 1977	Rat 4/group	0, 0.4 g/L, morphine sulfate in drinking water, gestation days 0-21 daily	Embryo-Fetal: Sex ratios, body wts Postnatal: self-administration behavior	Faster acquisition of morphine self-administration behavior in offspring of morphine treated dams. No embryo-fetal effects.
Eriksson & Ronnback, 1989	Rat 5/group	0, 12.5, 25, 50, 100 PO (fluid diet), gestation day 5 through postpartum day 2	Embryo-Fetal: Viability, body wts, litter size Postnatal: nociceptive responses	↓fetal viability, body wts, and postnatal viability, and ↑sensitivity to morphine-induced analgesia at >12.5 mg/kg/d, no surviving offspring at >25 mg/kg/d
Zagon & McLaughlin, 1977a	Rat 12-19/group	0, 80 IP, morphine sulfate dissolved in	Embryo-Fetal: Viability, body, whole	Morphine-induced clinical signs and ↓body wts in dams, ↓litter size, viability, neonatal mortality, fetal neonatal body wts, absolute

		saline, b.i.d. 5 d prior to mating through gestation & lactation	brain, cerebellum wts Postnatal: brain length, cerebrum & cerebellar widths	brain and cerebellar wts at birth and during neonatal period, ↑relative brain and cerebellar wts at postnatal day 60, reduced brain lengths and cerebral & cerebellar widths, cyanotic and hypothermic infants
Zagon & McLaughlin, 1977b	Rat 12-19/group	0, 80 IP, morphine sulfate dissolved in saline, b.i.d. 5 d prior to mating through gestation & lactation	Embryo-Fetal: Viability, body wts, gross malformations	Morphine-induced maternal clinical signs and ↓body wt, ↓litter size, viability, neonatal mortality, fetal & neonatal body wts
Siddiqui *et al.*, 1995	Rat 10-23/group	Doses gradually incr up to 40 IP, morphine sulfate dissolved in saline, several weeks prior to mating through mating, gestation and 10 d into postpartum pd	Embryo-Fetal: gestational length, litter size, incidence of stillbirths, cannibalism, body wts, gross malformations Postnatal: hormonal/neuro chemical levels, histopathology (testes)	↓maternal body wt gain, ↑gestation length & # stillbirths/litter, ↓litter size, birth wt & postnatal body wt gain, ↓plasma/testicular levels of luteinizing hormone and testosterone, ↓testes wt (adult), seminiferous tubule shrinkage, germinal cell aplasia, ↓spermatogenesis, ↑hypothalamic norepinephrine
Siddiqui *et al.*, 1997	Rat 6-16/group	Doses gradually incr up to 40 IP, morphine sulfate dissolved in saline, several weeks prior to mating through mating, gestation and 10 d into postpartum pd	Embryo-Fetal: gestational length, viability, litter size, incidence of stillbirths, body wts, Postnatal: ovarian function, reproductive behavior & indices, neurochemical analyses	Abnormal estrus cycles in adult ♀s, ↑ gestational length, ↑ #stillbirths, ↓ body wts at birth and body wt gain during development, delayed sexual maturation in ♀ offspring, mating behavior altered at adulthood, ↓ plasma estradiol, ovarian estradiol, progesterone, hypothalamic norepinephrine in offspring of morphine treated rats
Johannesson & Becker, 1972	Rat 6-9/group	0, 10, 20 SC, morphine sulfate dissolved in distilled water, gestation days 2-5, 7-9, 11-13 or 17-20 daily	Embryo-Fetal: viability, implantation sites, body wts, lengths, gross & skeletal observations	Maternal mortality in 6 animals, ↓ growth rate, ↑ response to nociceptive stimulus in offspring of morphine treated rats
Sobrian, 1977	Rat 9-15/group	40 SC, morphine sulfate dissolved in saline, 5 d prior to mating and gestation days 0-15	Embryo-fetal: viability, sex ratios, body wts, gross malformations Postnatal: motor activity	↓ viability, neonatal mortality in morphine grp, ↓ fetal body wts, ↑ postnatal spontaneous motor activity
Kirby, 1982	Rat # not provided	0, 20 SC, morphine sulfate dissolved in saline, every 4 h, gestation days 12-21	Embryo-Fetal: viability, litter size, body wts, length&volume of 1st thoracic spinal cord segment	↓ maternal food consumption and body wt, ↓ body wt of offspring at birth, ↑ mortality in offspring, ↓ growth of spinal cord components in offspring
Vathy *et al.*, 1983	Rat	20 SC, morphine	Embryo-Fetal:	↑ inter-litter variability for vaginal opening, ↑

	5-6/group	sulfate dissolved in saline, b.i.d. gestation days 5-12	body wts Postnatal: vaginal opening, mating behavior, hypothalamic-preoptic area cytosolic estrogen receptor levels	neonatal body wts, ↓ adult feminine sexual behavior in offspring
Fujinaga & Mazze, 1988	Rat 15-30/group	0, 10, 35, 70 SC infusion, morphine sulfate dissolved in saline, continuous on gestation days 5-17	Embryo-Fetal: viability, sex ratios, resorptions, implantations, body wts, gross & skeletal malformations	Maternal morphine plasma levels: 197 (LD) to 676 (HD) ng/ml, fetal plasma levels 60-292 ng/ml (gestation day 20) Normal maternal blood gasses. ↓pregnancy rates, slightly enlarged cerebral ventricles, ↑ postnatal mortality, ↓ postnatal body wt, Suggests teratogenicity in previous studies due to respiratory depression
Vathy & Katay, 1992	Rat 13-14/group	0, 10, 20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Postnatal: sexual behavior, brain catecholamine content	↑ male and ↓ female hypothalamic norepinephrine and altered sexual behavior
Koyuncuoglu & Arlcioglu, 1993	Rat 8/group	0, 10 SC, morphine sulfate dissolved in saline, t.i.d., gestation days 16-21	Embryo-Fetal: body wts Postnatal: morphine dependence	Abstinence clinical signs more pronounced upon morphine withdrawal and naloxone treatment in offspring of morphine treated rats
Ramsey *et al.*, 1993	Rat 21-23/group	0, 20 SC and Oral (drinking water), morphine HCl in water, gestation days 7, 8, 9 (SC b.i.d.), gestation days 10-21 (PO, daily)	Embryo-Fetal: viability, litter size, sex ratios Postnatal: body wts, cocaine and heroin self-administration behavior	No maternal toxicity Enhanced self-administration behavior in offspring
Vathy *et al.*, 1994	Rat 5-6/group	0, 10-20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Embryo-Fetal: body wts Postnatal: neurochemical analyses	Altered norepinephrine content and turnover in sexually dimorphic manner
Vathy *et al.*, 1995	Rat 5-6/group	0, 10-20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Embryo-Fetal: viability, litter size, sex ratios Postnatal: neurochemical analyses	No effects on maternal body wt, fetal viability, litter size, sex ratios Altered development of norepinephrine and dopamine neurotransmitter systems in hypothalamus, preoptic area, striatum, cerebellum in sexually dimorphic manner
Gagin & Shavit, 1996	Rat # not provided	Up to 12 SC, morphine in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: body wts, gross malformations Postnatal: nociceptive responses and sweetness preference	↓ maternal food consumption, body wt at birth Enhanced analgesic responses after morphine challenge postnatally, ↑ preference for saccharin solution
Hol *et al.*, 1996	Rat 10/group	0, 10 SC, morphine HCl dissolved in saline, gestation days 8-21 daily	Postnatal: behavior	↑ Pinning (play behavior) and social grooming in offspring, less social avoidance in adulthood

Niesink *et al.*, 1996	Rat 10/group	0, 10 SC, morphine HCl dissolved in saline, gestation days 8-21 daily	Embryo-Fetal: viability, litter size Postnatal: body wt, various behavioral endpoints	No maternal toxicity, no postnatal effects on sensorimotor development Elevated social play, no other behavior affected
Gagin *et al.*, 1997a	Rat 10/group	Up to 48 SC, morphine, slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: viability, litter size, body wt, gross malformations Postnatal: sexual behavior	↓ maternal food consumption, normal copulatory behavior but partial feminization (female patterns of receptivity) in males exposed prenatally
Gagin *et al.*, 1977b	Rat # not provided	Up to 48 SC, morphine dissolved in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: viability, litter size, body wt, gross malformations Postnatal: sexual behavior	↓ maternal food consumption, enhanced morphine reinforcing effect in adulthood in offspring
Shavit *et al.*, 1998	Rat # not provided	Up to 48 SC, morphine dissolved in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Postnatal: immune function, nociceptive function, behavior	↓ cytotoxic activity of NK cells in offspring, ↓ LPS-induced fever, ↓ hyperalgesia after LPS administration, altered open-field activity, suggests long-term impairment of host-defense mechanisms
Geber & Schramm, 1975	Hamster 20-120/group	0, 35, 88, 157, 222, 244, 300, 322 SC, morphine sulfate dissolved in unknown vehicle, gestation day 8	Embryo-Fetal: viability, implantation sites, resorptions, body wts, lengths, gross & skeletal observations	Congenital malformations (exencephaly and/or cranioschisis) at >88 mg/kg/d
Johnston *et al.*, 1996	Hamster # not provided	0, 10 IP, DuraMorph® aqueous suspension, 4d prior to mating through pregnancy and lactation, daily	Postnatal: sexual behavior	Altered sexual behavior in male offspring
Hunter *et al.*, 1997	Guinea pig 6-8/group	0, 1.5, 5, 15 SC, morphine dissolved in saline, gestation day 32 until parturition, daily	Fetal: gestation duration, viability, litter size, sex ratios Postnatal: respiratory parameters, locomotor activity, body temperature	↓ maternal body wt at >1.5 mg/kg/d ↓ birth wts, neonatal minute ventilation and central respiratory drive in early postnatal pd at >5 mg/kg/d ↑ locomotor activity in early postnatal pd at >15 mg/kg/d
Roloff *et al.*, 1975	Rabbit 11-31/group	0, 10, 20, 40 SC, q.i.d. gestation days 6-14	Embryo-Fetal: viability, litter size, body wt, lung volume, amniotic fluid composition	↓ maternal body wt in all morphine grps ↑ abortion rate dose-related ↓ fetal body wt at all doses No effects on lung volume, amniotic fluid composition, litter size, intrauterine death or % pregnancies with dead fetuses
Raye *et al.*, 1977	Rabbit # not provided	0, 50, 100 SC, morphine sulfate in unspecified diluent, 7d prior to mating through mating and gestation, daily	Embryo-Fetal: viability, body wts, crown-rump lengths, organ weights, gross malformations	↓ maternal body wt and food consumption in all morphine grps ↓ fetal body wt , crown-rump lengths, lung weights and ↑ liver & kidney wts at >50 mg/kg/d, ↑ heart and interscapular fat pad wts at 100 mg/kg/d

As indicated in table 2, the reproductive toxicology of morphine has been evaluated in rats, mice, hamsters, guinea pigs, and rabbits. Results of studies in the published literature suggest that morphine treatment in mice is embryotoxic (Harpel and Gautieri, 1968; Iuliucci and Gautieri, 1971; Ciociola and Gautieri, 1982). Morphine administered subcutaneously produced exencephaly at doses ≥300 mg/kg given on gestation day 8 and axial fusions at doses of 100 mg/kg and higher on gestation day 9 in mice (Harpel and Gautieri, 1968). Iuliucci and Gautieri (1971) reported similar findings following intraperitoneal administration of morphine. Exencephaly and axial skeletal fusions were observed in morphine treated mice at doses of 200-400 mg/kg (ip) on gestation days 8 or 9. Continuous subcutaneous infusion of **morphine sulfate at 0.15 – 15 mg/kg/day on** gestation days 7 through 10 produced fetal exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid (Ciociola and Gautieri, 1982). As summarized in table 2, other embryotoxic effects observed in mice included decreased crown-rump length, decreased fetal body weights, and increase partial fetal resorption.

Reproductive toxicology studies in rats evaluated the effects of morphine following oral, subcutaneous and intraperitoneal administration. Oral (fluid diet) morphine sulfate administered to rats from gestation day 5 through postpartum day 2 resulted in a decrease in fetal viability, body weights and postnatal viability (Eriksson and Ronnback, 1989). Also an increase in sensitivity to morphine induce analgesia was observed at doses of 12.5 mg/kg/day and greater. At doses≥ 25 mg/kg/day, there were no surviving offspring.

Daily perinatal exposure (gestation days 0-21) of morphine sulfate in the maternal drinking water at 0.4 g/L resulted in faster acquisition of morphine self-administration behavior in offspring of morphine-treated dams (Glick, 2977). No embryo-fetal effects were observed.

The published literature reports of four studies on reproductive toxicology of intraperitoneal morphine in rats showed that morphine treatment prior to mating, through mating and gestation and lactation resulted in increased gestational length, increase number of stillbirths, decreased litter size, decreased fetal viability, decreased birth weight, and increased neonatal mortality (Zagon and Mclaughlin, 1977a; Zagon and McLaughlin, 1977b; Siddiqui *et al.*, 1995; and Siddiqui *et al.*, 1997).

As indicated in table 2, sixteen published reports evaluated the reproductive toxicology of subcutaneously administered morphine in rats (Johannesson and Becker, 1973; Sovrian, 1977; Kirby, 1982; Vathy *et al.*, 1983; Fujinaga and Mazze, 1988; Vathy and Katay, 1992; Vathy *et al.*, 1994; Vathy et al., 1995; Gagin and Shavit, 1996; Hol *et al.*, 1996; Niesink *et al.*, 1996; Gagin *et al.*, 1997 and 1997b; Shavit *et al.*, 1998). In these studies, morphine was administered at doses ranging from 10 to 70 mg/kg/day by subcutaneous injection or perfusion pumps during various gestation periods of organogenesis (e.g. gestation days 5-12, 11-18, etc.) to dosing from pre-mating through gestation day 15. Subcutaneous morphine treatment during gestational periods of organogenesis resulted in the following treatment-related embryo toxicity in one or more of these studies: increased pre- and post-natal mortality, inter-litter variability for vaginal opening, incidences of

enlarged cerebral ventricles, increased hypothalamic norepinephrine in males, decreased body weights, growth of spinal cord components, female hypothalamic norepinephrine, and immune function.

An early study by Sobrian (1977) showed that morphine administered to pregnant rats at 40 mg/kg/day from 4 days prior to mating through gestation day 15 resulted in decreased fetal viability and body weights, and increased neonatal mortality and postnatal spontaneous motor activity. Fujinaga and Mazze (1988) reported that morphine infused continuously on gestation day 5 through 17 resulted in decreased pregnancy rates, slightly enlarged cerebral ventricles, increased postnatal mortality and decreased postnatal body weight.

Two studies conducted in rabbits during gestation days 6-14 (Roloff *et al.*, 1975) and 7 days prior to mating through mating and gestation (Raye *et al.*, 1977) suggested that morphine was embryotoxic. At doses in the range of 10 to 100 mg/kg, morphine caused a dose-dependent increase in abortion rate, decrease in fetal weight, and decreased crown-rump lengths.

For this NDA, the sponsor is relying upon the published literature during the period of 2002 to 2007. The sponsor identified four published studies that contain pertinent information on the reproductive and developmental toxicity of morphine. These studies are summarized in table 3. Results in three of these studies are consistent with those observed in earlier reports that morphine elicits embryotoxic effects. Oral administration of morphine (0.01-0.1 mg/mL) during pregnancy resulted in neural tube defects, reduction in weight and length of embryo (Nasiraei-Moghadam *et al.*, 2005). Subcutaneous morphine (30 mg/kg/day) administered to males for two consecutive weeks prior to mating affected males sexual behavior and the fertilization/conception processes (Cicero *et al.*, 2002). Relative to the control males, the weight of the prostrate and seminal vesicles of chronically treated morphine males wee significantly lower. Females mated with treated morphine males had a significant increase (40%) in pseudopregnancies relative to 6% in the control females. Also, gravid females had significantly fewer implantation sites.

Table 3: Summary of published scientific studies during the period 2002 to 2007.

Citation	Species	Methods	Developmental Endpoints	Findings/Conclusion
Cicero *et al.*, 2002	Rats (Sprague-Dawley)	Male rats were dosed with morphine (n=99) or saline (n=51) for 14 days. Day 1: 0 or 10 mg/kg were administered (sc) 2x day (9-hrs apart) Dose of morphine was increased daily by 5 mg/kg increments per injection until a maximum of 30 mg/kg (2x/day) was achieved. The rats continued at 30 mg/kg (2x/day) until day 14. Day 14: The dose of morphine was reduced to 20 mg/kg (2x/day) for the breeding period. Day 15 & 16: Breeding period	Male Fertility Parameters: testes, seminal vesicles, and prostate weight and histopath; Sperm motility, sperm counts, & sperm morphology Female Fertility: pseudopregnancy, # of implantation sites, ovaries and uterus weight Fetal Outcome: Fetal resorption, signs of abnormalities	Chronic paternal morphine exposure significantly affected fertility. Compared to control, the weight of the prostrate and seminal vesicles were a significantly lower. Compared to control (6%), females mated with chronically treated morphine males had a significant increase (40%) in pseudopregnancies. Compared to control, gravid females mated with chronically treated morphine males had fewer implantation sites. The results suggest that chronic morphine treatment caused a defect in sexual behavior or caused a complete failure of the fertilization or conception processes.
Nasiraei-Moghadam *et al.*, 2005	Female Rats (Wistar)	Mated females were orally administered 0, 0.01, 0.05 or 0.1 mg/mL of morphine in drinking water daily from embryonic day 0 (E0) to E9.5. **Embryonic Day 9.5 – rats were** anesthetized and embryos were surgically removed.	Fetal Outcome: embryo weight, antero-posterior axis length, neural tube development	Morphine-related effects on embryo weight. Dose-related decrease in embryo weight. Embryos exposed to morphine in utero embryo showed significant effects on neural tube development and the thickness of the neuron-ectoderm layer was substantially lower than that of the control. Embryos exposed to 0.05 and 0.1 mg/mL morphine presented with a neural groove instead of a neural tube. Results suggest that exposure to morphine during early days of pregnancy could lead to a defect or delay in neural tube development.
Byrnes, 2005	Female Rats (Sprague Dawley)	Female rats (30 days of age) were dosed with increasing dose regimen of morphine sulfate (s.c.) or saline. Group Size: 12. Day 1: 2,5 mg/kg b.i.d. Subsequent days, the dose of morphine was increased by 2.5 mg/kg. By day 20 of treatment, the rats were receiving 2 doses of 50 mg/kg (b.i.d).	Maternal: Body weight Pups Outcome: birth weight and behavioral changes	Compared to the control females, a significant decrease in body weight was observed in the morphine-treated dams (84.8 g vs. 102.5 g). No morphine-related effects on pups body weight or body gain in post partum period. Adult female offspring of the morphine-treated dams exposed to morphine during puberty exhibited behavioral changes; a decrease in

		Day 20: dosing was stopped and Day 30: Females were mated.		exploration of novel environment was observed. In contrast, male offspring of morphine-treated dams exploratory behavior was comparable to the control males. Female offspring also demonstrated a more rapid induction of sensitization. Male offspring demonstrated significant enhancement in the expression of morphine sensitization. Results suggest that chronic morphine exposure during adolescence can have significant trans-generational effects on adult offspring.
Che *et al.*, 2005	Chick	Embryonic Days E12-E19 (hatch day is E21): morphine 920 mg/kg/day) was injected into the airspace of the eggs. Groups: morphine, saline and untreated groups. (n=40/group)	Chicks: body weight, behavioral (memory as measured in the one-trial passive avoidance learning paradigm)	No significance difference in hatch weights of chicks. Morphine-exposed chicks hatched earlier than the untreated and saline treated chicks; however the difference was marginal. Hatch rate was lower in chicks exposed to morphine and saline. Chicks exposed to morphine had significantly impaired long-term memory as assessed in the passive avoidance learning paradigm. The avoidance ratio was significantly reduced.

2.6.6.7 Local tolerance

Local irritation and sensitization studies were not conducted.

2.6.6.8 Special toxicology studies

Special toxicology studies were not conducted.

2.6.6.9 Discussion and Conclusions

No new toxicology studies were submitted in support of NDA 22-207. The toxicity profile of morphine has been described in the published literature. Based upon extensive human experience with morphine, additional repeat-dose toxicology studies were not required for this 505(b)(2) submission.

General Toxicology: Single Dose Studies. The Sponsor conducted no additional single-dose toxicology studies. Also, no new single-dose studies were identified in the published literature search performed by the Sponsor. The two referenced NDAs, 21-260

and 18-565, also lacked single-dose toxicology data; only referencing data found in the published literature. The FDA's prior findings of safety are based on findings in the published literature and will support the safety of NDA 22-207.

General Toxicology: Repeat Dose Studies. No additional repeat-dose toxicity studies were conducted by the Sponsor to support NDA 22-207. Also, no new repeat-dose toxicology studies were identified in the published literature search performed by the Sponsor. The two referenced NDAs, 21-260 and 18-565, also lacked repeat-dose toxicology data; only referencing data found in the published literature. Hence, the FDA's prior findings of safety are based on findings in the published literature and will be used to support the safety of NDA 22-207.

Genetic Toxicology. No genetic toxicology study report was submitted with NDA 22-207. The sponsor relied on the published literature and the product label for the referenced NDAs (18-565 and 21-260). Also, no new genetic toxicology study reports were identified in the published literature search performed by the Sponsor. The two referenced NDAs, lacked genetic toxicology data and referenced data found in the published literature. Hence, the FDA's prior findings on genotoxicity are based on findings in the published literature and are also used to support NDA 22-207.

Carcinogenicity. No carcinogenicity study report was submitted with NDA 22-207. The sponsor relied on the published literature and the product label for the referenced NDAs (18-565 and 21-260). Also, no new carcinogenicity study reports were identified in the published literature search performed by the Sponsor. The two referenced NDAs, also lacked carcinogenicity data; only referencing data found in the published literature prior to 2002. Hence, the FDA's prior findings on carcinogenicity are based on findings in the published literature and are used to support NDA 22-207.

Reproductive Toxicology. No additional reproductive toxicity studies were conducted by the Sponsor to support NDA 22-207. However, the sponsor did identify five study reports in the published literature and submitted them to support NDA 22-207.

2.6.6.10 Tables and Figures
N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY
N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The proposed drug product does not present with any unique toxicology concerns compared to the already approved drug products and based on current practice in OND, no further studies are required to support this NDA application.

Unresolved toxicology issues (if any): According to the morphine drug substance contains the following impurities: reported that the impurities are at a level of NMT which exceeds ICH Q3A safety qualification threshold. On December 5, 2007, the sponsor was been requested to either reduce the specifications to NMT or provide adequate safety qualification as per ICH Q3A. Adequate qualification should include: b(4)

- **Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g.,** one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- **Repeat dose toxicology of appropriate** duration to support the proposed indication.

If the Sponsor is unable to reduce the specifications, they may justify the safety based on the above toxicology data or via reference to such data in the published literature.

According to the chemistry review team, stability data showed that levels in the drug product increases over time. The sponsor is proposing to set the specification at which exceeds ICH Q3B safety qualification. The chemistry review team will request that the specification be reduced as per ICH Q3B. If the sponsor is unable to reduce the specifications, they may justify the safety based on b(4)

- A repeat dose toxicology study of up to 90 days to support the proposed indication or
- Via reference to such data in the published literature.

Recommendations: From the nonclinical pharmacology and toxicology issues perspective, the NDA is approvable pending the resolution of the unresolved toxicology issues. Discussion is ongoing between the **Agency's chemistry review team and the** NDA sponsor to determine is the levels in the drug product can be reduced or if if the shelf life of the product can be reduced. If this issue can not be resolved prior **to the NDA's PDUFA date, the sponsor will be** required to provide toxicology data to support the safety of morphinone in their drug product.

Suggested labeling:

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of *in vitro* studies showed that morphine is not mutagenic in the *Drosophilia melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the *in vivo*

clastogenic effects reported with morphine in murine lymphocytes and spermatids. Some of the *in vivo* clastogenic effects reported with morphine in mice may be directly related to increases in glucocorticoid levels produced by morphine in this species.

A literature report indicated that morphine impairs fertility in rats. In a fertility study in which male rats were administered morphine subcutaneous prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects were observed. These included reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites

Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic to those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. Morphine was not a significant teratogen in the rat at exposure levels significantly beyond that normally encountered in clinical practice. In one study however decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days to mating. In two studies performed in rabbit, no evidence of teratogenicity was reported to be no greater than expected among children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Nonteratogenic Effects

Published literature has reported exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following, treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and

sexual maturation, and increased mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubules shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine into adulthood.

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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APPENDIX/ATTACHMENTS

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/s/

Belinda Hayes
12/12/2007 03:58:21 PM
PHARMACOLOGIST

R. Daniel Mellon
12/12/2007 05:05:59 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY TOXICOLOGY REVIEW AND EVALUATION
Addendum to Primary Review (February 12, 2008)

NDA NUMBER:	22-195
PRODUCT:	Morphine Sulfate Oral Solution
FORMULATION:	Oral Solution
INDICATION:	Relief of moderate to severe acute and chronic pain
SPONSOR:	Roxane Laboratories, Inc.
TYPE OF SUBMISSION:	Amendment
DATE RECEIVED:	20-Dec-2007
PHARM/TOX REVIEWER:	BeLinda A. Hayes, Ph.D.
PHARM/TOX SUPERVISOR:	R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR:	Bob A. Rappaport, M.D.
PROJECT MANAGER:	Lisa Basham

BACKGROUND

In 2007, the Sponsor submitted NDA 21-195 for morphine sulfate oral solution (10 and 20 mg/mL) under 505(b)(2) regulations.

During the review of NDAs 22-195, the Agency became aware of several impurity issues. Review of stability data revealed that the morphine sulfate drug substance contained several impurities that exceeded ICH Q3A specifications. These concerns were conveyed to the Sponsor via an email on December 5, 2007 and during the December 14, 2007 teleconference. The requests conveyed to the Sponsor were:

According to , the morphine drug substance contains the following impurities: b(4)

reported that they are at a level of NMT which exceeds ICH Q3A safety qualification threshold. You should either reduce the specifications to NMT or provide adequate safety qualification as per ICH Q3A. Adequate qualification should include:

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Repeat dose toxicology of appropriate duration to support the proposed indication.

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Based upon their own literature search, the Sponsor concluded that there were inadequate data in the published literature to clearly demonstrate that the — impurities were human metabolites. b(4)

SUMMARY:

In their amendment to the NDA, the Sponsor did not reduce the specifications of — for morphine sulfate oral solution to NMT or provide adequate safety qualification to support their proposed specifications. The articles submitted for review did not provide any toxicology data that support the safety of these impurities. These articles verified the reviewer initial assessment. That is: b(4)

b(4)

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However, the Sponsor did provide a clinical justification for applying a higher qualification threshold of NMT 0.15% (the ICH specification for a drug whose maximum daily dose would be less than 2 g/day). Although opioid products do not have maximum daily dose, due to the development of tolerance to the opioid, the Sponsor believes setting a maximum daily dose of 2 gram for the morphine sulfate oral solution is appropriate based on published literature which details clinical use of immediate release formulations of morphine in treating chronic pain conditions. Evaluation of the Sponsor's rationale and proposal to set a maximum feasible daily dose of 2 gm has been discussed with the medical review team. Given the large number of liquid dosages required to reach a daily dose of 2 grams, the Division accepts the proposal to set the impurity qualification thresholds based on a NMT 2 gram/day dose. However, given a 2 g maximum daily dose limit for immediate release morphine products, the proposed specifications for the drug substance still will not meet ICH qualification threshold level of NMT 0.15% for drug substance impurities. As indicated in the table below, a maximum daily dose of up to 2 g should meet the specification qualification of NMT 0.15%.

Drug Substance (Q3A)	
Maximum Daily Dose	**Identification**
≤ 2 g	0.15%
> 2 g	
Drug Product (Q3B)	
10 mg – 100 mg	
>100 mg - 2 g	
> 2g	0.15%

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CONCLUSION AND RECOMMENDATIONS

The Sponsor did not reduce the specifications to below the ICH Q3A safety qualification threshold. Also, the Sponsor did not provide the Agency with sufficient information to adequately qualify the

b(4)

safety of these impurities. Even with a maximum daily dose of 2 g, the safety threshold level of — exceeds ICH Q3A safety qualification. Thus, the Sponsor should complete a minimal genetic toxicology screen (one in vitro mutagenicity study and one in vitro chromosome damage study). Given the presence of these impurities in the drug substance to date, repeat-dose toxicology studies will not be required for these impurities. However, the existing experience with these impurities does not address the genotoxic potential of the compounds. These studies may be completed post approval, as the impurities have been in approved drug products and the new specification of NMT 0.15% is being asked to comply with current ICH specification guidelines. b(4)

Based upon the information provided to date for NDA 22-195 (Morphine Oral Solution), from the nonclinical pharmacology toxicology perspective, NDA 22-195 may be approved with the Phase 4 study requirements listed below:

Recommendation for nonclinical studies

The following nonclinical studies should be conducted as a Phase 4 commitment:

1. Conduct a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) tested up to the limit dose for the assay, for each of the following drug substance impurities that exceed ICHQ3A qualification thresholds of NMT 0.15%:

b(4)

REFERENCES:

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b(4)

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Vermeire, A. and Remon, J.P. Stability and compatibility of morphine. Int. J. Pharm. 187(1): 17-51, 1999.

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Belinda Hayes
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R. Daniel Mellon
3/14/2008 10:48:41 AM
PHARMACOLOGIST
I concur.

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-195**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**05/17/07**
PRODUCT:	**Morphine Sulfate Oral Solution**
INTENDED CLINICAL POPULATION:	**Relief of Moderate to severe acute and chronic pain**
SPONSOR:	**Roxane Laboratories, Inc.**
DOCUMENTS REVIEWED:	**Vol. 2 of 42**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**BeLinda A. Hayes, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Basham**

Date of review submission to Division File System (DFS): December 11, 2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a nonclinical pharmacology and toxicology perspective, NDA 22-195 may be approved.

B. Recommendation for nonclinical studies

Should the sponsor not be able to either reduce the specifications for or identify other data to support the proposed specifications, they should complete a minimal genetic toxicology screen (one in vitro mutagenicity study and one in vitro chromosome damage study). These studies may be completed post approval, as the impurities have been in approved drug products and the new specification of NMT is being asked to comply with current specification guidelines. b(4)

C. Recommendations on labeling
Additions are indicated by underlined

The Sponsor proposed the following labeling for the nonclinical pharmacology and toxicology sections of the label. This labeling is identical to that in the Avinza (NDA 21-260) label. Information on male fertility effects reported in the literature are recommended to be included in the proposed labeling. Otherwise, there are no further suggested changes **to the Sponsor's proposed label.**

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of *in vitro* studies showed that morphine is not mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the *in vivo* clastogenic effects reported with morphine in mice may be directly related to increases in glucocorticoid levels produced by morphine in this species.

A literature report indicated that morphine impairs fertility in rats. In a fertility study in which male rats were administered morphine subcutaneous prior to

mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects were observed. These included reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites

Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic to those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. Morphine was not a significant teratogen in the rat at exposure levels significantly beyond that normally encountered in clinical practice. In one study however decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days to mating. In two studies performed in rabbit, no evidence of teratogenicity was reported to be no greater than expected among children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Nonteratogenic Effects

Published literature has reported exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following, treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and sexual maturation, and increased mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubules shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Behavioral

abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine into adulthood.

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Roxane Laboratories, Inc. has submitted a New Drug Application (NDA) for Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL, for the relief of moderate to severe acute and chronic pain. Roxane Laboratories has been marketing this formulation since the 1980s under the brand name Morphine Sulfate (immediate Release) Oral Solution, 10 mg/5 mL and 20 mg/5 mL. The nonclinical development program outlined in this NDA submission relies in part on the FDA's previous findings of safety and efficacy of King Pharma's NDA (21-260) for Avinza (morphine sulfate extended-release capsules) and Baxter Healthcare's NDA (18-565) for Duramorph (morphine sulfate injection USP).

B. Pharmacologic activity

The Sponsor did not conduct formal pharmacological studies in support of this NDA. During the pre-NDA meeting on September 12, 2006, the Sponsor proposed to cross-reference the data in King Pharma's NDA for Avinza (morphine sulfate extended-release capsules) and Baxter Healthcare's NDA for Duramorph (morphine sulfate injection USP) and to reference published literature. The Agency indicated that for a 505(b)(2) application, it would be acceptable to reference published literature.

Morphine's principal therapeutic action is analgesia. It also produces drowsiness, changes in mood, alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine function and affect rewarding behavior. Morphine exerts its primary physiological effects via activation of the μ opioid receptor.

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to this drug product. As is well known with opioid drug products, respiratory depression, a known extension of the pharmacological action of morphine, is the most prominent adverse effect

of morphine that is relevant to the proposed clinical use. Clinically significant respiratory depression rarely occurs with standard morphine doses in the absence of underlying pulmonary dysfunction.

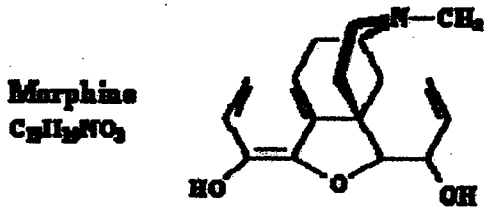
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	22-195
Review number:	1
Sequence number/date/type of submission:	000/May 17, 2007/Commerical 505(b)(2)
Information to sponsor:	Yes ( ) No (X)
Sponsor and/or agent:	Roxane Laboratories, Inc. 1809 Wilson Rd. Columbus, OH 43228
Manufacturer for drug substance:	[redacted] b(4)
Reviewer name:	BeLinda A. Hayes, Ph.D.
Division name:	Division of Anesthesia, Analgesia and Rheumatology Products
HFD #:	170
Review completion date:	November 12, 2007

Drug:

Trade name:	N/A
Generic name:	Morphine Sulfate Oral Solution
Code name:	N/A
Chemical name:	Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) (salt) pentahydrate
CAS registry number:	64-31-3 (morphine sulfate)
Molecular formula/molecular weight:	$(C_{17}H_{19}NO_3)_2\ H_2SO_4 \cdot 5H_2O$/758.83
Structure:	



Relevant INDs/NDAs/DMFs:

DMF	[redacted]	Morphine Sulfate USP
DMF		Morphine Sulfate USP [redacted] b(4)

Drug class: Opioid Agonist, Narcotic

Intended clinical population: Relief of moderate to sever acute and chronic pain

Clinical formulation: Solution

Morphine Sulfate Oral Solution will be marketed in 2 strengths, 10 mg/5 mL and 20 mg/5 mL for oral administration. The recommended dosage is 10 to 20 mg every 4 hours for both acute and chronic pain. The lower strength will be packaged in polyethylene bottles with child resistant closures containing 100 and 500 mL of formulation or 30 mL aluminum laminate unit dose cups containing 5 or 10 mL of formulation. The higher strength will be packaged in polyethylene bottles with child resistant closures containing 100 and 500 mL of formulations. The components, quantitative composition, compendial and function of the ingredients for both dosage strengths are provided in the table below.

Ingredients	Function	Quality Standard	10 mg/5 mL Amount (per 5 mL)	20 mg/5 mL Amount (per 5 mL)
Morphine Sulfate, USP	Active Ingredient		10 mg	20 mg
Sorbitol USP		USP		
Glycerin, USP		USP		
Citric Acid, USP		USP		
Sodium Benzoate, NF		NF		
Disodium Edetate, USP		USP		
FD & C Green (Fast Green)				
Water,		USP		
Methylparaben, NF		NF		
Propylparaben, NF		NF		

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There are no novel excipients in the drug product. All of the above excipients are found in approved drug or food products within approved ranges.

Impurities:

The impurity levels in the referenced DMF are the same for the currently marketed morphine products. Although most of these impurities exceed current ICH thresholds for safety qualification, they have been present in morphine products and do not appear to pose a significant safety risk. The impurities in the drug substance were reported by the drug manufactures and are identified in the table below. The identified impurities are:

. The structures of these impurities are presented below.
is a metabolite of morphine and therefore is considered to be qualified (Brunk and Delle, 1974). are well known degradant products of morphine. is an oxidation product of morphine (Misra and Mule, 1972) and a morphine metabolite in several species (Misra and Mule, 1972; Marme, 1983). It has been reported that morphine degrades in aqueous solutions to

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and to a lesser extent to (Vermeire and Remon, 1999). The minor impurity, 10-hydroxymorphine, has been detected in morphine products for almost two decades. The compound appears to have similar binding and potency as morphine itself (Farsam et al., 1990). The impurities have been used therapeutically for years and are well characterized. b(4)

Morphine sulfate obtained contains the impurity . that is a structural alert for mutagenicity. specification for this impurity was limited to . This specification is above the ICH Q3A qualification threshold of . The level is being requested since there is no maximum daily dose for opioid drug products. The potential genotoxic effects of were described in the DMF . Evaluation of in the *in vitro* mammalian chromosomal aberration and the bacterial reverse mutation assays indicated that was negative. b(4)

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Leachables:

On September 7, 2007, the Agency requested that the Sponsor demonstrate the safety of their drug product in terms of potential leachables from the bottle or the unit dose cap container. On November 7, 200, the Sponsor submitted data from two studies to evaluate the potential leachables. The chemistry review team has reviewed the data and concluded that the sponsor has provided sufficient information/data to allay any concerns for leachables, as per the recommendations in the Agency container and closure system guidance.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-195 are owned by Roxane Laboratories, Inc. or are data for which Roxane Laboratories, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-195 that Roxane Laboratories, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in **the drug's approved labeling. Any data or** information described or referenced below from a previously approved application that Roxane Laboratories, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-195.

Studies reviewed within this submission:

The sponsor did **not** conduct any toxicology studies in support of this NDA.

Studies not reviewed within this submission: Many of the studies (i.e., published literature study reports) for this NDA were previously reviewed by Dr. Kathleen Haberny for NDA 21-260. The findings were incorporate-, d in this NDA review and noted in the text.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Morphine, a phenanthrene opioid, is one of the most effective analgesics and is the prototype against which all other opioids are measured. Morphine sulfate has been used for many years in the management of pain. It was first approved by the Food and Drug Administration (FDA) in September of 1984 under the trade name Duramorph® Preservative-free Injection (NDA 18-565; Baxter Healthcare) for intrathecal and epidural administration. Today, morphine sulfate is marketed in a variety of formulations, including oral solutions, immediate- and sustained-release tablets and capsules, suppositories and injectable preparations. Morphine is marketed under generic and brand name products including MS-Contin®, Oramorph SR®, Avinza®, Duramorph PF®, Depodur®, and Kadian®.

Morphine is an opioid agonist with activity at μ-, κ and δ-opioid receptors. Activation of μ-opioid-receptors is associated with analgesia, respiratory depression, sedation, decreased gastrointestinal motility, euphoria and physical dependence. Morphine actions at the κ-opioid receptors are associated with spinal analgesia, miosis and psychotomimetic effects.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Morphine mediates it primary pharmacodynamic effect, analgesia, thorough activation of μ-opioid receptors. Its primary pharmacodynamic effects are well known and were summarized in NDA 21-260. No additional primary pharmacodynamic studies were conducted by the Sponsor for the current NDA.

Drug activity related to proposed indication: μ-Opioid receptors are highly concentrated in regions of the central nervous system involved with the neuronal circuitry involved with the processing of nociceptive information; the periaqueductal and periventricular gray matter, ventromedial medulla and spinal cord. The pain modulating effects of morphine ensue from its direct inhibition of the ascending transmission of nociceptive information from spinal cord dorsal horn and to the activation of the pain control circuits that descend from the midbrain via the rostral ventromedial medulla to the spinal cord dorsal horn.

2.6.2.3 Secondary pharmacodynamics

Morphine secondary pharmacological effects include dysphoria, euphoria, sedation, respiratory depression, decreased gastrointestinal motility and physical dependence. These effects were described in NDA 21-260.

These pharmacodynamic effects have been extensively reviewed in the published literature.

2.6.2.4 Safety pharmacology

The Sponsor did not conduct formal safety pharmacology studies.

Neurological effects: No new nonclinical safety pharmacology studies were conducted to evaluate potential central nervous system safety concerns.

Cardiovascular effects: Animal studies had shown that morphine causes hemodynamic changes. In conscious dogs, morphine initially induced coronary vasodilation followed by a sustained reduction in coronary blood flow and significant coronary vasoconstriction followed by hypotension (Vatner et al., 1975). Morphine induces the release of histamine. High doses of morphine cause the release of histamine that induces peripheral vasodilation, with significant hypotension.

In contrast to the results observed in dogs, when morphine was the sole medication administered to healthy humans, no hypotensive effects were observed; only stimulatory effects were observed. Morphine (0.07 mg/kg and 0.14 mg/kg) elicited a dose-dependent increase in mean arterial blood pressure, heart rate and oxygen consumption (Mildh *et al.*, 2000). The morphine-induced stimulation was correlated to signs of local histamine release (increase redness and itching at the injection site).

Morphine can cause hemodynamic changes and cardiovascular adverse reactions.

These adverse effects include: bradycardia, sinus tachycardia, palpitations, hypotension, hypertension, orthostatic hypotension, diaphoresis, and syncope. Orthostatic hypotension is a secondary effects resulting from morphine-induced peripheral vasodilatation.

Pulmonary effects: Respiratory depression is a clinically significant effect of morphine. At high doses, morphine causes respiratory depression, pulmonary edema and respiratory arrest. Like other opioids, morphine decreases the responsivity of the brain stem respiratory center to CO_2 and depression of pontine and medullary centers via its action at the mu2 opioid receptors.

Renal effects: The Sponsor did not conduct formal safety pharmacology studies to evaluate potential renal safety concerns with morphine administration. A review of the literature did not identify any animal studies that specifically addressed morphine-related renal effects.

However, morphine does present some safety concerns in patients with HIV-associated nephropathy and renal failure. Patients with HIV-associated nephropathy are often intravenous users of heroin. Morphine is an active metabolite of heroin and has been associated with the renal interstitial fibrosis observed in heroin-associated glomerulosclerosis. *In vitro* studies have demonstrated that morphine has the potential to modulate proliferation of kidney fibroblasts (Singhal et al., 1998). Cultured rat kidney fibroblasts were exposed to morphine at concentrations in the range of 10^{-12} M to 10^{-4} M for 24 hours or 48 hours. At both incubation period, morphine at low concentration 10^{-12} M, induced proliferation of fibroblast.

Chronic use of morphine in patients with renal failure should be use with caution (Angst *et al.*, 2000). Morphine-6-glucuronide, a pharmacological active metabolite of morphine is cleared via the kidney. In patients with renal failures, it will accumulate and allow opioid side effects to persist hours after plasma concentration of morphine has peaked and morphine-6-glucuronide plasma concentration has peaked.

Gastrointestinal effects: Gastrointestinal side effects are the major adverse effects associated with acute and chronic use of morphine. Inhibition of gastrointestinal motility (i.e., propulsive peristalsis) is a long-known classical effect of morphine. In addition to this effect, like other opioid drugs, morphine exerts a wide spectrum of other effects on the mammalian intestinal function. These effects include reduction in secretions (pancreatic, biliary, and electrolyte/fluid) and increases in intestinal fluid absorption and blood flow (Brown and Miller, 1991). Morphine effects on gastrointestinal function are mediated via actions on opioid receptors within the central nervous system and through a direct action on peripherally located opioid receptors within the enteric nervous system (Parolaro *et al.*, 1977; Stewart et al., 1978; Tavani *et al.*, 1990). Mμ opioid receptors in the brain of mice (Porreca *et al.*, 1973, 1984) and rats (Koslo *et al.*, 1985) are involved in the CNS-mediation of morphine inhibition of gastrointestinal motility.

The pharmacological action of morphine on the gastrointestinal tract is manifested clinically. These clinical effects are presented in the following table.

GI Tract Site of Action	Pharmacological Action	Clinical Effect
Stomach	Decreased gastric motility	Anorexia
	Decreased pyloric tone	Nausea and vomiting
Small Intestine	Decreased pancreatic and biliary secretion	Delayed digestion
	Reduced propulsion	Delayed absorption of medication
	Increased fluid absorption	Hard and dry stool
Large Intestine	Increased non-propulsive contractions	Spasm, abdominal cramps, and pain
	Increased fluid absorption	Hard and dry stool
	Increased anal sphincter tone	Retention of gastrointestinal contents (incomplete evacuation)

Abuse liability: Morphine is a Schedule II controlled substance and is highly addictive. Psychological and physical dependence develop quickly to morphine. Morphine elicits euphoria by activating the brain's reward systems; specifically its binds to opioid receptors on neurons located in the VTA and in the nucleus accumbens. Withdrawal symptoms associated with morphine addiction include drug craving, watery eyes, insomnia, diarrhea, running nose, yawning, dysphoria, chills and sweating.

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Sponsor did not submit pharmacology tabulated summary.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The Sponsor for this NDA did not conduct formal pharmacokinetics and toxicokinetics studies. The absorption, distribution, metabolism, excretion and pharmacokinetics of morphine sulfate were described in NDA 21-260. A summary of data in the NDA and information in the published literature is described here.

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

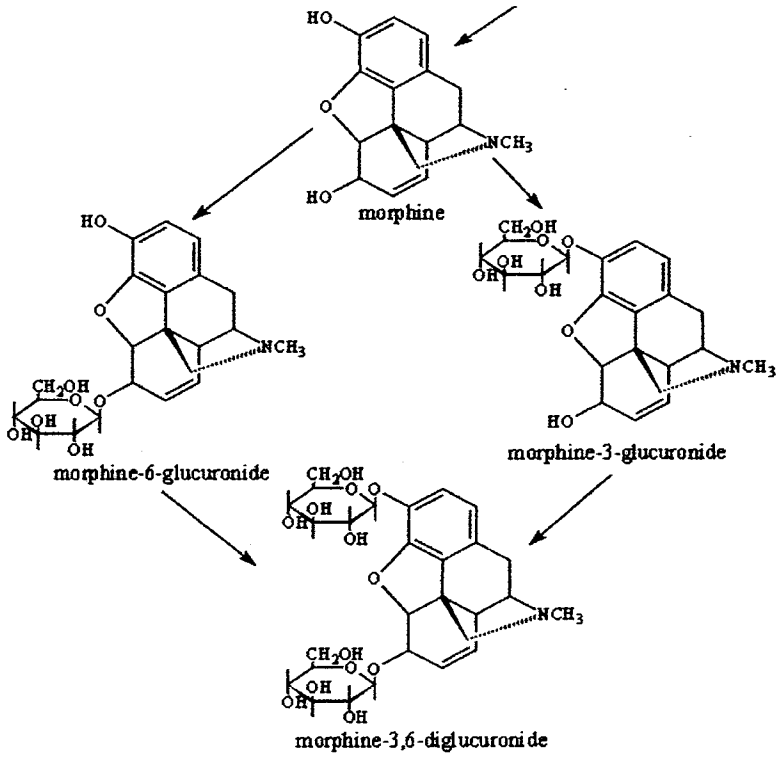
Absorption of morphine following oral administration is variable and decreased by extensive pre-systemic metabolism in both the liver and gut. The oral bioavailability of is less than 40%, approximately 20%-33%.

2.6.4.4 Distribution

Morphine is distributed to the intestinal tract, kidneys, liver, lungs, skeletal muscle, spleen and brain. Although the central nervous system is the primary site of action of morphine, only small quantities cross the blood-brain barrier. Morphine also crosses the placental membranes and has been detected in breast milk (Feilberg *et al.*, 1989; Robieux *et al.*, 1990). The volume of distribution of morphine in humans is approximately 3 to 4 L/kg. Morphine is 30 to 35% reversibly bound to plasma proteins. Muscle tissue binding has been reported to be 54%.

2.6.4.5 Metabolism

Morphine metabolism is primarily by hepatic glucuronidation by uridine diphosphate glucuronosyl transferase (UGT) enzyme, with specific affinity for the UGT2B7 and UGT1A3 isozymes, (Amstrong and Cozza, 2003; Wittwer and Kern, 2006). The isoenzyme is responsible for the formation of both major glucuronide metabolites of morphine; morphine-3-glucuronide (M3G, about 50%) and morphine-6-glucuronide (M6G, about 15%). M3G has no analgesic activity; whereas M6G has been shown to have analgesic activity but crosses the blood brain barrier poorly. The metabolism of morphine can also occur in the brain and the kidneys (Christrup, 1997). In humans, morphine is also metabolized to normorphine and normorphine-6-glucurinide (Yeh *et al.*, 1977). Normorphine is formed by hepatic microsomal oxidation. Minor metabolites that have been identified in the urine of humans following large doses of morphine chronically include codeine (3-O-methyl morphine) and morphine N-oxide. Following oral administration, approximately 5% of the morphine undergoes N-demethylation to normorphine and 10% metabolized to codeine.



2.6.4.6 Excretion

Morphine is eliminated in urine, feces and bile; renal excretion being the major route of elimination. Approximately 10% of a dose of morphine is excreted unchanged in the urine. Most of the dose of morphine is excreted in the urine as the metabolites M3G and M6G, with elimination of morphine occurring primarily as renal excretion of M3G. A small amount of the glucuronide conjugates are excreted in the bile, with minor enterohepatic recycling. Seven to 10% of administered morphine is excreted in the feces. The mean adult plasma clearance of morphine is approximately 20 to 30 mL/min/kg. The effective terminal half-life of morphine after intravenous administration is reported to be approximately 2 hours. Longer periods of plasma sampling in some studies suggest a longer terminal half-life of morphine of about 15 hours.

2.6.4.7 Pharmacokinetic drug interactions

The sponsor did not conduct nonclinical pharmacokinetic studies to evaluate potential drug interaction with morphine. Hence, no pharmacokinetic studies were submitted with the NDA. However, the known drug interaction of morphine with other drugs is well known. The known drug interactions involving morphine are pharmacodynamic. Co-administration of morphine with CNS depressants (i.e., sedatives or hypnotics, general anesthetics, tranquilizers, and alcohol) can result in additive CNS respiratory depressant effects. Agonist/antagonist analgesic (i.e., pentazocine, nalbuphine, butorphanol, and

buprenorphine) co-administered with morphine may reduce morphine's analgesic effect or may precipitate withdrawal symptoms.

2.6.4.8 Other Pharmacokinetic Studies

None were conducted by the sponsor.

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and figures to include comparative TK summary

Summary tables were not provided by sponsor.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Summary tables were not provided by sponsor.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

No toxicology studies to evaluate the toxicity potential of morphine have been conducted by the sponsor. The sponsor conducted a search of the published literature to identify single-dose and repeat-dose toxicity studies conducted from 2002 to 2007. The sponsor stated that no studies were identified in their search of the literature during this period. Review of the literature showed that nonclinical studies evaluating the toxicity potential of morphine were conducted prior to 2002. Dr. Kathleen Haberny, for NDA 21-260, reviewed the published literature and summarized the general toxicology in her review in support of that NDA. Dr. Haberny's summary was reproduced verbatim from the review.

General toxicology:

NDA 21-260 for Morphelan™ did not contain single-dose toxicology data, but relied upon the published literature. Toxicity studies have been conducted in several species. Acute toxicity associated with the single administration of high doses of morphine in dogs includes: vomiting, delirium, clonic spasms and raspy and labored breathing (Humphreys, 1988). Morphine-induced acute toxicity in rodents was associated with catalepsy, circling, stereotypical behavior, Straub tail, increased motor activity, exophthalmos, and shallow breathing (Humphreys, 1988).

Genetic toxicology:

The sponsor did not conduct any genetic toxicology studies. However, there are a limited number of genotoxicity studies assessing the mutagenic potential of morphine reported in the published literature. These studies have suggested that morphine has mutagenic

potential. Results from *in vivo* chromosomal aberration assay and *in vivo* micronucleus assay suggest that morphine is a potential clastogen.

Carcinogenicity:

The Sponsor has not performed long-term studies in animals to evaluate the carcinogenic potential of morphine sulfate. Likewise, carcinogenicity studies were not performed in support of the referenced Morphine Product of NDAs 18-565 and 21-260 at the time of approval.

Reproductive toxicology:

No formal reproductive toxicity studies were submitted with the current NDA. The sponsor is relying upon the published literature during the period of 2002 to 2007. Four published studies that contain pertinent information on the reproductive and developmental toxicity of morphine were identified.

Special toxicology:

The Sponsor did not conduct local irritation and sensitization studies in animals.

2.6.6.2 Single-dose toxicity

NDA 22-195 for Morphine Sulfate Oral Solution did not contain single-dose toxicology studies, but relied upon findings of safety in NDA 18-565 and NDA 21-260 for Duramorph and Avinza, respectively, and published literature. The NDA for both Duramorph and Avinza also lacked single dose toxicology data, and relied on prior FDA findings. FDA's prior findings were based on data in the published literature. Dr. Haberny summarized the published literature pertinent to morphine-induced toxicity following a single dose. Her summary is reproduced verbatim from the review.

Single dose The median lethal dose (LD_{50}) reported in mice is 375 and 506 mg/kg SC (Witkin *et al.*, 1961; Blane *et al.*,1967), 221 and 250 mg/kg IV (Blane *et al.*,1967; Fennessy and Fearn, 1969), and 600 and 1270 mg/kg PO (Witkin *et al.*,1961; Blane *et al.*,1967). In rats, the LD_{50} values were 170 and 572 mg/kg SC (Blane *et al.*, 1967; Finnegan *et al.*,1948), 100 and 237 mg/kg IV (Blane *et al.*,1967; Finnegan *et al.*,1948) and 461 and 905 mg/kg PO (Blane *et al.*,1967; Finnegan *et al.*,1948). The LD_{50} values in rabbits were 266 mg/kg SC and 500 mg/kg IP (Sunshine ed. 1969) and in dogs the LD_{50} was 133 mg/kg IV. The lowest reported lethal dose was 8 mg/kg IV and 190 mg/kg SC in rabbits, 500 mg/kg SC in guinea pigs, 210 mg/kg SC in dogs, 40 mg/kg SC in cats, 900 mg/kg SC in ducks, 250 mg/kg SC and 500 mg/kg PO in pigeons, 600 mg/kg SC in frogs and 3676 mcg/kg by an unreported route in humans. In the preclinical study reports, morphine was 3x-10x more toxic in newborn animals than in adults due to greater permeability of the brain to morphine in newborns (Kupferberg and Way, 1963).

The morphine-induced deaths in animals were associated with convulsions, respiratory failure and circulatory failure (Humphreys, 1988). Adverse effects of high morphine doses in dogs include vomiting, delirium, clonic spasms, and raspy and labored breathing (Humphreys, 1988). Catalepsy, circling, stereotypical behavior, Straub tail, increased motor activity, exophthalmos, and shallow breathing are observed in rodents given high doses of morphine. Histopathological examination after single doses of morphine at 125 mg/kg IP in rats have shown centrilobular and midzonal vacuolation, diffuse fatty degeneration and eosinophilic changes without necrosis in the liver during the period from 2.5 to 18 hours after dosing (Maruta *et al.*,1997).

Acute morphine toxicity in humans includes miosis, constipation, urinary retention, nausea, vomiting, hypothermia, drowsiness, dizziness, apathy, confusion, respiratory depression, hallucinations, distorted perceptions, dyspnea, sleep disturbance, hypotension, cold/clammy skin, coma and pulmonary edema.

2.6.6.3 Repeat-dose toxicity

NDA 22-195 for Morphine Sulfate Oral Solution did not contain repeat-dose toxicology studies, but relied upon findings of safety in NDA 18-565 and NDA 21-260 for Duramorph and Avinza, respectively, and published literature. The NDA for both Duramorph and Avinza also lacked repeat-dose toxicology data, and relied on prior FDA findings. **FDA's prior findings were based on** data in the published literature. Dr. Haberny summarized the published literature pertinent to morphine-induced toxicity following repeated dosing. Her summary is reproduced verbatim from the review.

Multiple dose A study by Finnegan *et al.* (1948) showed a treatment-related decrease in body weight gain, increased mortality and increased incidence of pneumonia after chronic treatment with oral morphine sulfate at 0.01%-1% (dietary) in male and female rats. Decreased body weights were also observed without other drug-related abnormalities in a study on chronic morphine administration in female rats given 25 mg/kg/d (dietary) for 124 days (Fennessy and Fearn, 1969). Drug-related morphologic changes in the kidneys of rats treated with increasing doses of morphine sulphate from 24 to 96 mg/kg/d SC or 10 mg/kg SC b.i.d. for 6 days were reported in a study by Marchand *et al.* (1969). The changes included large cytoplasmic and intercellular vacuoles, increased thickness of basement membranes, loss of microvilli, larger and clumping mitochondria, increased lysomes and changes in size, shape and density of nuclei in the proximal, distal and collecting tubules. Reduced hepatic glucuronosyl transferase and N-demethylase have also been reported in rats treated chronically with morphine (Parke, 1968).

In dogs, subcutaneous morphine at 2 or 5 mg/kg/d for 100 days resulted in one death a the high dose on day 70, and weights loss in all of the animals (Finnegan *et al.*,1948). In that study, the biochemical assays showed decreased red blood cell counts and hemoglobin concentrations at the high dose, spleen or lung hemorrhage at the low dose and fatty changes in liver and renal tubular epitheluim in the dog that died.

Tolerance to the analgesic effect and to many of the side effects of morphine, and dependence on the drug resulting in withdrawal signs and symptoms when morphine administration is abruptly stopped, are well known results of chronic treatment. The rapid development of tolerance results in a need for increasing doses over time to produce the same effects.

Adverse effects of chronic injected opioid abuse in humans have included abscesses, anaphylaxis, acute transverse myelitis, arrhythmias, wound botulism, cellulitis, endocarditis, fecal impaction, glomerulonephritis, hyperglycemia, hypoglycemia, osteomyelitis, postanoxic encephalopathy, tetanum, thrombophlebitis, nephropathy, hoarseness, hepatitis, pneumothorax, paraplegia, mycotic aneurysms and leukoencephalopathy (Lewis *et al.*,1980; Wolters *et al.*,1982).

2.6.6.4 Genetic toxicology

The sponsor has not performed genetic toxicology studies to evaluate the genetic toxicity potential of morphine. However, nine study reports on the genetic toxicology of morphine sulfate have been identified in the published literature. The results of these studies are summarized in table 1.

The limited information available on the genotoxic potential of morphine suggests that it has mutagenic potential. Morphine increased the frequency of chromosomal aberrations **in mice's bone marrow cells following a single** intraperitoneal administration in the dose range of 3.2-64 mg/kg (Swain et al., 1980). Morphine induced a dose-related increase in

the incidence of micronuclei in polychromatic erythrocytes of mice administered two doses of 3.2-32 mg/kg (ip) within 24 hours (Das and Swain, 1982) and in lymphocytes of mice administered a single dose of morphine in the dose range of 0-100 mg/kg (Sawant and Couch 1995). In contrast, *in vitro* assays, morphine failed to induce chromosomal aberrations in cultured human lymphocytes (Falek *et al.*, 1972) or micronuclei in mitogen stimulated splenocytes (Sawant and Couch, 1995). These findings suggest that metabolic activation is involved in the induction of chromosomal aberrations or micronuclei formation.

Badr and Rouh (1983) reported that morphine, at doses ≥ 10 mg/kg (ip) for 3 consecutive days, was positive in the dominant lethal test in mice; increasing the frequency of chromosomal aberrations in spermatids and in dividing spermatocytes. Implantation of morphine pellets (75 mg, sc) increased DNA fragmentation in murine thymocytes (Fuchs and Pruett, 1983).

Mutagenic effects of morphine were not observed in *Drosophila*, *Salmonella* and yeast test systems (Madden, 1979). In contrast, treated with morphine alone or in combination with a brief ethyl methane sulfonate (EMS) exposure dose-dependently increased the frequency of Comet tails of fragmented DNA in human HUT-78 cells (Shafer *et al.*, 1994). Morphine induced DNA fragmentation has been associated with apoptosis in murine thymocytes (Fuchs and Pruetts, 1993). Opiate and glucocorticoid antagonists antagonized the genotoxic effects of morphine in mice. Evidence suggests that morphine may be classified as a co-mutagen. Subcutaneous administration of morphine to rats at high doses (≥5 mg/kg) increased the ethylation of oesophageal DNA by N-nitrosodiethyl amine and may reduce the first pass clearance of N-nitrosodiethyl amine by the liver (Ribeiro-Pinto and Swann, 1997).

Table 1. Summary of published genetic toxicology study reports during the period 1972 to 1995.

Citation	Assay/Test System	№ Animals/Dose	Dose Regimen/Formulation/Route	Significant Findings
Falek *et al.*, 1972	Chromosomal Aberration/Human Leukocytes	Not applicable	*In vitro* lymphocyte culture	2-fold increase in chromatid damage among the opiate addicts. Increase SCE in opiate addicts.
Knapp and Cramer, 1976	*Drosophila*/Mutagenicity	Not applicable	*In vivo*	No evidence of induction of the sex linked recessive or dominant lethal mutation or translocation
Madden *et al.*, 1979	Human PBL	Not applicable	*In vitro*	Morphine negatively effect on DNA damage caused by UV radiation in addicts
Swain *et al.*, 1980	*In vivo* Cytogenic/mice	5/sex/group	Single Dose; 0. 3.2, 8, 16, 32, 64 mg/kg IP 17 consecutive days: 3.2 mg/kg/day IP Morphine sulfate dissolved in distilled water	At 32 mg/kg, increase in chromosomal aberration in born marrow cells. No-morphine-related effects observed following repeated dosing. Presumably due to the development of tolerance.
Das and Swain, 1982	Micronucleus mice	5/sex/group	2 doses separated by 24 hours: 0, 3.2, 8, 16, 32, 64 mg/kg IP	Dose-related increase in incidence of micronuclei in polychromatic

			Morphine sulfate dissolved in distilled water	erythrocytes at doses > 3.2 mg/kg
Badr and Rabouh, 1983	Dominant Lethal and Spermatocyte Test/Male Mouse	12 male mated with 2 female/dose group	Consecutive daily doses of 0, 10, 20, 40, 60 mg/kg IP Morphine sulfate dissolved in distilled water	Increase in number of dominant lethal, particularly early spermatids and types and frequencies of chromosomal aberration in dividing spermatocytes at all dose levels.
Fuchs and Pruett, 1993	In vivo and In vitro DNA Fragmentation in Thymocytes/Mice	2-4 females	75 mg SC time release pellet morphine released for 12-48 hours	DNA fragmentation noted in thymocytes following implantation of morphine. *In vivo*, DNA fragmentation blocked by opiate and glucocorticoid antagonists; suggesting that morphine effect's are partially mediated through effect on hypothalamic-pituitary-adrenal axis. *In vitro*, no DNA fragmentation observed in thymocytes following morphine exposure.
Shafer *et al.*, 1994	Mutagenicity/Human HUT 78 ells and HRPT mutant cells	Not applicable	*In vitro*	Morphine alone increased DNA fragmentation at concentrations ≥5 x 10^{9}M. Morphine increased the mutation frequency of the mutagen ethylmethanesulfonate over that of the mutagen alone.
Sawant and Couch, 1995	*In vivo* and *in vitro* Micronuclei Assay.Mice	Female C57 black and DBA strain of mice/№ unknown	Single IP doses of 0-100 mg/kg Single IV doses: 20 mg/kg Morphine sulfate dissolved in phosphate-buffered saline	Dose- and time-related increase in micronucleated splenocytes and lymphocytes. Morphine-induced effect was blocked by adrenalectomy; suggesting increase in corticosteroid plasma level mediates genotoxic response. Morphine added to lymphocytes of cyclophosphamide treated animals at ≥107M increased number of micronuclei in binucleated cells following in vitro stimulation with mitogen.

2.6.6.5 Carcinogenicity

The sponsor had not performed long-term studies in animals to evaluate the carcinogenic potential of morphine. Likewise, carcinogenicity studies were not performed in support of the referenced morphine products of NDA 18-565 and NDA 21-260 at the time of approval. Although carcinogenicity data are not available for any morphine drug product, the policy in the Office of New Drugs is to only request such data for 505(b)(2) applications when the proposed drug product either significantly expands the patient population to be exposed, the duration of exposure, or the route of exposure compared to previously approved drug products. Based on that policy, carcinogenicity studies will not be required for this NDA application.

There are several published reports of studies evaluating the carcinogenic potential of morphine in rats and dogs. No microscopic evidences of pre-neoplastic or neoplastic changes in repeated dose toxicity studies at doses up to 25 mg/kg/day (dietary) for 124 days in rats (Finnegan *et al.*, 1948; Fennesay and Fearn, 1969) or in dogs at doses up to 5 mg/kg/day (sc) for 100 days (Finnegan *et al.*, 1948). It has been reported that morphine inhibits tumor necrosis factor and the growth of several human cancer cell lines and BALB/3T3 cells (Sueoka *et al.*, 1996). In a subsequent study, Sueoka and colleagues (1998) found that morphine metabolite morphine-6-glucuronide inhibit inhibits neuroblastoma and PC-9 (peripheral neuronal cell line) cell line growth in vitro.

In the published literature, evidence of indirect involvement of morphine in tumorigenesis was reported. Ribeiro-Pinto and Swann (1997) reported that subcutaneous morphine at doses of 5 mg/kg and higher (sc) increased ethylation of oesophageal DNA. Immunosuppression has been observed with morphine administration in several animal species (Liu *et al.*, 1992; Fuchs and Pruett, 1993; Levier *et al.*, 1994). Theoretically, immunosuppression can contribute to an increase risk in carcinogenesis. Morphine's immunosuppressive effects have not been observed in clinical studies when morphine was administered at therapeutic doses.

There is evidence for indirect involvement of morphine in tumorigenesis. Morphine administered subcutaneous at doses of 5 mg/kg and higher increased the ethylation of esophageal DNA induced by nitrosodiethylamine in rats (Ribeiro-Pinto and Swann, 1977). Morphine treatment has also been reported to stimulate angiogenesis and promote tumor growth of a human breast tumor xenograph model in mice (Gupta et all, 2002).

Immunosuppression by morphine has been observed in several animal species (Liu *et al.*, 1992; Fuchs and Pruett, 1993; LeVier *et al.*, 1994). Theoretically, this immunosuppressant effect can contribute to an increase risk in carcinogenesis.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Reproductive and developmental toxicity studies with morphine were described in NDA 18-565 and NDA 21-260. NDA 18-565 for Duramorph® (for acute pain) and NDA 21-260 for Avinza® (for chronic pain) did not contain reproductive toxicology data, but references information in the published literature. The information included in Duramorph® and Avinza® labels appear to be based on the information in the published literature during the years between 1968 and 1997. Results of reproductive toxicology studies on embryo-fetal development reported in the literature were summarized by Dr. Kathleen Haberny for NDA 21-260; and is reproduced in table 2: below.

Table 2: Dr. Kathleen Haberny's Summary of Published reproductive toxicology Studies During the Period 1968 to 1997.

Citation	Species #Treated/Dose Group	Dose (mg/kg/d), Route, Formulation, Dosing Period	Developmental Endpoints	Significant Findings
Lintern-Moore *et al.*, 1979	Rat (immature) 6/timepoint	50 mg/kg/d IP, in saline, 1 or 7 days	Body, pituitary, ovarian, uterine and adrenal weights, histopathology	Altered ovarian follicular development, ↓number of follicles after single dose, ↓initiation of follicular growth and number of follicles after 7 days of administration
James et al., 1980	Rat (male) 15/group	50 mg/kg/d SC in sterile water, for 4 and 9 weeks, or 13 week recovery	Serum LH, FSH, and testosterone, testes, seminal vesicles, prostate and pituitary weights and histopath	↓serum LH and testosterone, secondary sex organ weights, modified secretory activity of pituitary gonadotrophic cells, ↓spermatogenic cell populations (particularly early spermatids), all effects reversed after 13 weeks
Harpel & Gautieri, 1968	Mouse 5-32/group	0, 100-500 SC Morphine sulfate in distilled water, Gestation days 8 or 9	Embryo-Fetal: viability, implantation sites, resorptions, body weights, lengths, gross&skeletal observations	Clinical signs, ↓maternal food consumption: all doses Day 8: ↓fetal body wt. (>200 mg/kg) Exencephaly (>300 mg/kg) Axial skeletal fusions & ↓crown-rump length (>400 mg/kg) Day 9: Axial skeletal fusions & ↓fetal body wt (>100 mg/kg) ↑partial fetal resorptions & ↓crown-rump length (>400 mg/kg) ↓maternal body wt (500 mg/kg)
Iulucci & Gautieri, 1971	Mouse # not provided	0, 200, 300, 400 IP, Gestation days 8 or 9	Embryo-Fetal: viability, resorptions, body wts, sex ratios, gross & skeletal malformations	Clinical signs in all morphine dose groups, deaths at 400 mg/kg. Exencephaly, axial skeletal fusions in >1 dose grp after treatment on days 8 or 9, ↓fetal body wt at 300 mg/kg, no effects on litter size, resorptions, sex ratios.
Ciociola & Gautieri, 1982	Mouse # not provided	0, 0.15, 1.5, 15 SC infusion, morphine sulfate in saline, gestations days 7-10 daily	Embryo-Fetal: viability, resorptions, body wts, sex ratios, gross & skeletal malformations	↓ fetal body wt, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae and xiphoid in morphine treated grps, inversely dose-proportional (perhaps due to tolerance at higher doses)
Glick *et al.*, 1977	Rat 4/group	0, 0.4 g/L, morphine sulfate in drinking water, gestation days 0-21 daily	Embryo-Fetal: Sex ratios, body wts Postnatal: self-administration behavior	Faster acquisition of morphine self-administration behavior in offspring of morphine treated dams. No embryo-fetal effects.
Eriksson & Ronnback, 1989	Rat 5/group	0, 12.5, 25, 50, 100 PO (fluid diet), gestation day 5 through postpartum day 2	Embryo-Fetal: Viability, body wts, litter size Postnatal: nociceptive responses	↓fetal viability, body wts, and postnatal viability, and ↑sensitivity to morphine-induced analgesia at >12.5 mg/kg/d, no surviving offspring at >25 mg/kg/d
Zagon & McLaughlin, 1977a	Rat 12-19/group	0, 80 IP, morphine sulfate dissolved in	Embryo-Fetal: Viability, body, whole	Morphine-induced clinical signs and ↓body wts in dams, ↓litter size, viability, neonatal mortality, fetal neonatal body wts, absolute

		saline, b.i.d. 5 d prior to mating through gestation & lactation	brain, cerebellum wts Postnatal: brain length, cerebrum & cerebellar widths	brain and cerebellar wts at birth and during neonatal period, ↑relative brain and cerebellar wts at postnatal day 60, reduced brain lengths and cerebral & cerebellar widths, cyanotic and hypothermic infants
Zagon & McLaughlin, 1977b	Rat 12-19/group	0, 80 IP, morphine sulfate dissolved in saline, b.i.d. 5 d prior to mating through gestation & lactation	Embryo-Fetal: Viability, body wts, gross malformations	Morphine-induced maternal clinical signs and ↓body wt, ↓litter size, viability, neonatal mortality, fetal & neonatal body wts
Siddiqui *et al.*, 1995	Rat 10-23/group	Doses gradually incr up to 40 IP, morphine sulfate dissolved in saline, several weeks prior to mating through mating, gestation and 10 d into postpartum pd	Embryo-Fetal: gestational length, litter size, incidence of stillbirths, cannibalism, body wts, gross malformations Postnatal: hormonal/neuro chemical levels, histopathology (testes)	↓maternal body wt gain, ↑gestation length & # stillbirths/litter, ↓litter size, birth wt & postnatal body wt gain, ↓plasma/testicular levels of luteinizing hormone and testosterone, ↓testes wt (adult), seminiferous tubule shrinkage, germinal cell aplasia, ↓spermatogenesis, ↑hypothalamic norepinephrine
Siddiqui *et al.*, 1997	Rat 6-16/group	Doses gradually incr up to 40 IP, morphine sulfate dissolved in saline, several weeks prior to mating through mating, gestation and 10 d into postpartum pd	Embryo-Fetal: gestational length, viability, litter size, incidence of stillbirths, body wts, Postnatal: ovarian function, reproductive behavior & indices, neurochemical analyses	Abnormal estrus cycles in adult ♀s, ↑ gestational length, ↑ #stillbirths, ↓ body wts at birth and body wt gain during development, delayed sexual maturation in ♀ offspring, mating behavior altered at adulthood, ↓ plasma estradiol, ovarian estradiol, progesterone, hypothalamic norepinephrine in offspring of morphine treated rats
Johannesson & Becker, 1972	Rat 6-9/group	0, 10, 20 SC, morphine sulfate dissolved in distilled water, gestation days 2-5, 7-9, 11-13 or 17-20 daily	Embryo-Fetal: viability, implantation sites, body wts, lengths, gross & skeletal observations	Maternal mortality in 6 animals, ↓ growth rate, ↑ response to nociceptive stimulus in offspring of morphine treated rats
Sobrian, 1977	Rat 9-15/group	40 SC, morphine sulfate dissolved in saline, 5 d prior to mating and gestation days 0-15	Embryo-fetal: viability, sex ratios, body wts, gross malformations Postnatal: motor activity	↓ viability, neonatal mortality in morphine grp, ↓ fetal body wts, ↑ postnatal spontaneous motor activity
Kirby, 1982	Rat # not provided	0, 20 SC, morphine sulfate dissolved in saline, every 4 h, gestation days 12-21	Embryo-Fetal: viability, litter size, body wts, length&volume of 1st thoracic spinal cord segment	↓ maternal food consumption and body wt, ↓ body wt of offspring at birth, ↑ mortality in offspring, ↓ growth of spinal cord components in offspring
Vathy *et al.*, 1983	Rat	20 SC, morphine	Embryo-Fetal:	↑ inter-litter variability for vaginal opening, ↑

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	5-6/group	sulfate dissolved in saline, b.i.d. gestation days 5-12	body wts Postnatal: vaginal opening, mating behavior, hypothalamic-preoptic area cytosolic estrogen receptor levels	neonatal body wts, ↓ adult feminine sexual behavior in offspring
Fujinaga & Mazze, 1988	Rat 15-30/group	0, 10, 35, 70 SC infusion, morphine sulfate dissolved in saline, continuous on gestation days 5-17	Embryo-Fetal: viability, sex ratios, resorptions, implantations, body wts, gross & skeletal malformations	Maternal morphine plasma levels: 197 (LD) to 676 (HD) ng/ml, fetal plasma levels 60-292 ng/ml (gestation day 20) Normal maternal blood gasses. ↓pregnancy rates, slightly enlarged cerebral ventricles, ↑ postnatal mortality, ↓ postnatal body wt, Suggests teratogenicity in previous studies due to respiratory depression
Vathy & Katay, 1992	Rat 13-14/group	0, 10, 20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Postnatal: sexual behavior, brain catecholamine content	↑ male and ↓ female hypothalamic norepinephrine and altered sexual behavior
Koyuncuoglu & Aricioglu, 1993	Rat 8/group	0, 10 SC, morphine sulfate dissolved in saline, t.i.d., gestation days 16-21	Embryo-Fetal: body wts Postnatal: morphine dependence	Abstinence clinical signs more pronounced upon morphine withdrawal and naloxone treatment in offspring of morphine treated rats
Ramsey *et al.*, 1993	Rat 21-23/group	0, 20 SC and Oral (drinking water), morphine HCl in water, gestation days 7, 8, 9 (SC b.i.d.), gestation days 10-21 (PO, daily)	Embryo-Fetal: viability, litter size, sex ratios Postnatal: body wts, cocaine and heroin self-administration behavior	No maternal toxicity Enhanced self-administration behavior in offspring
Vathy *et al.*, 1994	Rat 5-6/group	0, 10-20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Embryo-Fetal: body wts Postnatal: neurochemical analyses	Altered norepinephrine content and turnover in sexually dimorphic manner
Vathy *et al.*, 1995	Rat 5-6/group	0, 10-20 SC, morphine sulfate dissolved in saline, b.i.d., gestation days 11-18	Embryo-Fetal: viability, litter size, sex ratios Postnatal: neurochemical analyses	No effects on maternal body wt, fetal viability, litter size, sex ratios Altered development of norepinephrine and dopamine neurotransmitter systems in hypothalamus, preoptic area, striatum, cerebellum in sexually dimorphic manner
Gagin & Shavit, 1996	Rat # not provided	Up to 12 SC, morphine in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: body wts, gross malformations Postnatal: nociceptive responses and sweetness preference	↓ maternal food consumption, body wt at birth Enhanced analgesic responses after morphine challenge postnatally, ↑ preference for saccharin solution
Hol *et al.*, 1996	Rat 10/group	0, 10 SC, morphine HCl dissolved in saline, gestation days 8-21 daily	Postnatal: behavior	↑ Pinning (play behavior) and social grooming in offspring, less social avoidance in adulthood

Niesink *et al.*, 1996	Rat 10/group	0, 10 SC, morphine HCl dissolved in saline, gestation days 8-21 daily	Embryo-Fetal: viability, litter size Postnatal: body wt, various behavioral endpoints	No maternal toxicity, no postnatal effects on sensorimotor development Elevated social play, no other behavior affected
Gagin *et al.*, 1997a	Rat 10/group	Up to 48 SC, morphine, slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: viability, litter size, body wt, gross malformations Postnatal: sexual behavior	↓ maternal food consumption, normal copulatory behavior but partial feminization (female patterns of receptivity) in males exposed prenatally
Gagin *et al.*, 1977b	Rat # not provided	Up to 48 SC, morphine dissolved in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Embryo-Fetal: viability, litter size, body wt, gross malformations Postnatal: sexual behavior	↓ maternal food consumption, enhanced morphine reinforcing effect in adulthood in offspring
Shavit *et al.*, 1998	Rat # not provided	Up to 48 SC, morphine dissolved in slow-release emulsion containing saline and Arlacel-A, gestation days 12-18 daily	Postnatal: immune function, nociceptive function, behavior	↓ cytotoxic activity of NK cells in offspring, ↓ LPS-induced fever, ↓ hyperalgesia after LPS administration, altered open-field activity, suggests long-term impairment of host-defense mechanisms
Geber & Schramm, 1975	Hamster 20-120/group	0, 35, 88, 157, 222, 244, 300, 322 SC, morphine sulfate dissolved in unknown vehicle, gestation day 8	Embryo-Fetal: viability, implantation sites, resorptions, body wts, lengths, gross & skeletal observations	Congenital malformations (exencephaly and/or cranioschisis) at >88 mg/kg/d
Johnston *et al.*, 1996	Hamster # not provided	0, 10 IP, DuraMorph® aqueous suspension, 4d prior to mating through pregnancy and lactation, daily	Postnatal: sexual behavior	Altered sexual behavior in male offspring
Hunter *et al.*, 1997	Guinea pig 6-8/group	0, 1.5, 5, 15 SC, morphine dissolved in saline, gestation day 32 until parturition, daily	Fetal: gestation duration, viability, litter size, sex ratios Postnatal: respiratory parameters, locomotor activity, body temperature	↓ maternal body wt at >1.5 mg/kg/d ↓ birth wts, neonatal minute ventilation and central respiratory drive in early postnatal pd at >5 mg/kg/d ↑ locomotor activity in early postnatal pd at >15 mg/kg/d
Roloff *et al.*, 1975	Rabbit 11-31/group	0, 10, 20, 40 SC, q.i.d. gestation days 6-14	Embryo-Fetal: viability, litter size, body wt, lung volume, amniotic fluid composition	↓ maternal body wt in all morphine grps ↑ abortion rate dose-related ↓ fetal body wt at all doses No effects on lung volume, amniotic fluid composition, litter size, intrauterine death or % pregnancies with dead fetuses
Raye *et al.*, 1977	Rabbit # not provided	0, 50, 100 SC, morphine sulfate in unspecified diluent, 7d prior to mating through mating and gestation, daily	Embryo-Fetal: viability, body wts, crown-rump lengths, organ weights, gross malformations	↓ maternal body wt and food consumption in all morphine grps ↓ fetal body wt , crown-rump lengths, lung weights and ↑ liver & kidney wts at >50 mg/kg/d, ↑ heart and interscapular fat pad wts at 100 mg/kg/d

As indicated in table 2, the reproductive toxicology of morphine has been evaluated in rats, mice, hamsters, guinea pigs, and rabbits. Results of studies in the published literature suggest that morphine treatment in mice is embryotoxic (Harpel and Gautieri, 1968; Iuliucci and Gautieri, 1971; Ciociola and Gautieri, 1982). Morphine administered subcutaneously produced exencephaly at doses ≥300 mg/kg given on gestation day 8 and axial fusions at doses of 100 mg/kg and higher on gestation day 9 in mice (Harpel and Gautieri, 1968). Iuliucci and Gautieri (1971) reported similar findings following intraperitoneal administration of morphine. Exencephaly and axial skeletal fusions were observed in morphine treated mice at doses of 200-400 mg/kg (ip) on gestation days 8 or 9. Continuous subcutaneous infusion of morphine sulfate at **0.15 – 15 mg/kg/day on** gestation days 7 through 10 produced fetal exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid (Ciociola and Gautieri, 1982). As summarized in table 2, other embryotoxic effects observed in mice included decreased crown-rump length, decreased fetal body weights, and increase partial fetal resorption.

Reproductive toxicology studies in rats evaluated the effects of morphine following oral, subcutaneous and intraperitoneal administration. Oral (fluid diet) morphine sulfate administered to rats from gestation day 5 through postpartum day 2 resulted in a decrease in fetal viability, body weights and postnatal viability (Eriksson and Ronnback, 1989). Also an increase in sensitivity to morphine induce analgesia was observed at doses of 12.5 mg/kg/day and greater. At doses≥ 25 mg/kg/day, there were no surviving offspring.

Daily perinatal exposure (gestation days 0-21) of morphine sulfate in the maternal drinking water at 0.4 g/L resulted in faster acquisition of morphine self-administration behavior in offspring of morphine-treated dams (Glick, 2977). No embryo-fetal effects were observed.

The published literature reports of four studies on reproductive toxicology of intraperitoneal morphine in rats showed that morphine treatment prior to mating, through mating and gestation and lactation resulted in increased gestational length, increase number of stillbirths, decreased litter size, decreased fetal viability, decreased birth weight, and increased neonatal mortality (Zagon and Mclaughlin, 1977a; Zagon and McLaughlin, 1977b; Siddiqui *et al.*, 1995; and Siddiqui *et al.*, 1997).

As indicated in table 2, sixteen published reports evaluated the reproductive toxicology of subcutaneously administered morphine in rats (Johannesson and Becker, 1973; Sovrian, 1977; Kirby, 1982; Vathy *et al.*, 1983; Fujinaga and Mazze, 1988; Vathy and Katay, 1992; Vathy *et al.*, 1994; Vathy et al., 1995; Gagin and Shavit, 1996; Hol *et al.*, 1996; Niesink *et al.*, 1996; Gagin *et al.*, 1997 and 1997b; Shavit *et al.*, 1998). In these studies, morphine was administered at doses ranging from 10 to 70 mg/kg/day by subcutaneous injection or perfusion pumps during various gestation periods of organogenesis (e.g. gestation days 5-12, 11-18, etc.) to dosing from pre-mating through gestation day 15. Subcutaneous morphine treatment during gestational periods of organogenesis resulted in the following treatment-related embryo toxicity in one or more of these studies: increased pre- and post-natal mortality, inter-litter variability for vaginal opening, incidences of

enlarged cerebral ventricles, increased hypothalamic norepinephrine in males, decreased body weights, growth of spinal cord components, female hypothalamic norepinephrine, and immune function.

An early study by Sobrian (1977) showed that morphine administered to pregnant rats at 40 mg/kg/day from 4 days prior to mating through gestation day 15 resulted in decreased fetal viability and body weights, and increased neonatal mortality and postnatal spontaneous motor activity. Fujinaga and Mazze (1988) reported that morphine infused continuously on gestation day 5 through 17 resulted in decreased pregnancy rates, slightly enlarged cerebral ventricles, increased postnatal mortality and decreased postnatal body weight.

Two studies conducted in rabbits during gestation days 6-14 (Roloff *et al.*, 1975) and 7 days prior to mating through mating and gestation (Raye *et al.*, 1977) suggested that morphine was embryotoxic. At doses in the range of 10 to 100 mg/kg, morphine caused a dose-dependent increase in abortion rate, decrease in fetal weight, and decreased crown-rump lengths.

For this NDA, the sponsor is relying upon the published literature during the period of 2002 to 2007. The sponsor identified four published studies that contain pertinent information on the reproductive and developmental toxicity of morphine. These studies are summarized in table 3. Results in three of these studies are consistent with those observed in earlier reports that morphine elicits embryotoxic effects. Oral administration of morphine (0.01-0.1 mg/mL) during pregnancy resulted in neural tube defects, reduction in weight and length of embryo (Nasiraei-Moghadam *et al.*, 2005). Subcutaneous morphine (30 mg/kg/day) administered to males for two consecutive weeks prior to mating affected males sexual behavior and the fertilization/conception processes (Cicero *et al.*, 2002). Relative to the control males, the weight of the prostrate and seminal vesicles of chronically treated morphine males wee significantly lower. Females mated with treated morphine males had a significant increase (40%) in pseudopregnancies relative to 6% in the control females. Also, gravid females had significantly fewer implantation sites.

Table 3: Summary of published scientific studies during the period 2002 to 2007.

Citation	Species	Methods	Developmental Endpoints	Findings/Conclusion
Cicero *et al.*, 2002	Rats (Sprague-Dawley)	Male rats were dosed with morphine (n=99) or saline (n=51) for 14 days. Day 1: 0 or 10 mg/kg were administered (sc) 2x day (9-hrs apart) Dose of morphine was increased daily by 5 mg/kg increments per injection until a maximum of 30 mg/kg (2x/day) was achieved. The rats continued at 30 mg/kg (2x/day) until day 14. Day 14: The dose of morphine was reduced to 20 mg/kg (2x/day) for the breeding period. Day 15 & 16: Breeding period	Male Fertility Parameters: testes, seminal vesicles, and prostate weight and histopath; Sperm motility, sperm counts, & sperm morphology Female Fertility: pseudopregnancy, # of implantation sites, ovaries and uterus weight Fetal Outcome: Fetal resorption, signs of abnormalities	Chronic paternal morphine exposure significantly affected fertility. Compared to control, the weights of the prostrate and seminal vesicles were a significantly lower. Compared to control (6%), females mated with chronically treated morphine males had a significant increase (40%) in pseudopregnancies. Compared to control, gravid females mated with chronically treated morphine males had fewer implantation sites. The results suggest that chronic morphine treatment caused a defect in sexual behavior or caused a complete failure of the fertilization or conception processes.
Nasiraei-Moghadam *et al.*, 2005	Female Rats (Wistar)	Mated females were orally administered 0, 0.01, 0.05 or 0.1 mg/mL of morphine in drinking water daily from embryonic day 0 (E0) to E9.5. **Embryonic Day 9.5 – rats were** anesthetized and embryos were surgically removed.	Fetal Outcome: embryo weight, antero-posterior axis length, neural tube development	Morphine-related effects on embryo weight. Dose-related decrease in embryo weight. Embryos exposed to morphine in utero embryo showed significant effects on neural tube development and the thickness of the neuron-ectoderm layer was substantially lower than that of the control. Embryos exposed to 0.05 and 0.1 mg/mL morphine presented with a neural groove instead of a neural tube. Results suggest that exposure to morphine during early days of pregnancy could lead to a defect or delay in neural tube development.
Byrnes, 2005	Female Rats (Sprague Dawley)	Female rats (30 days of age) were dosed with increasing dose regimen of morphine sulfate (s.c.) or saline. Group Size: 12. Day 1: 2,5 mg/kg b.i.d. Subsequent days, the dose of morphine was increased by 2.5 mg/kg. By day 20 of treatment, the rats were receiving 2 doses of 50	Maternal: Body weight Pups Outcome: birth weight and behavioral changes	Compared to the control females, a significant decrease in body weight was observed in the morphine-treated dams (84.8 g vs. 102.5 g). No morphine-related effects on pups body weight or body gain in post partum period. Adult female offspring of the morphine-treated dams exposed to morphine during puberty exhibited

		mg/kg (b.i.d). Day 20: dosing was stopped and Day 30: Females were mated.		behavioral changes; a decrease in exploration of novel environment was observed. In contrast, male offspring of morphine-treated dams exploratory behavior was comparable to the control males. Female offspring also demonstrated a more rapid induction of sensitization. Male offspring demonstrated significant enhancement in the expression of morphine sensitization. Results suggest that chronic morphine exposure during adolescence can have significant trans-generational effects on adult offspring.
Che *et al.*, 2005	Chick	Embryonic Days E12-E19 (hatch day is E21): morphine 920 mg/kg/day) was injected into the airspace of the eggs. Groups: morphine, saline and untreated groups. (n=40/group)	Chicks: body weight, behavioral (memory as measured in the one-trial passive avoidance learning paradigm)	No significance difference in hatch weights of chicks. Morphine-exposed chicks hatched earlier than the untreated and saline treated chicks; however the difference was marginal. Hatch rate was lower in chicks exposed to morphine and saline. Chicks exposed to morphine had significantly impaired long-term memory as assessed in the passive avoidance learning paradigm. The avoidance ratio was significantly reduced.

2.6.6.7 Local tolerance

Local irritation and sensitization studies were not conducted.

2.6.6.8 Special toxicology studies

Special toxicology studies were not conducted.

2.6.6.9 Discussion and Conclusions

No new toxicology studies were submitted in support of NDA 22-195. The toxicity profile of morphine has been described in the published literature. Based upon extensive human experience with morphine, additional repeat-dose toxicology studies were not required for this 505(b)(2) submission.

General Toxicology: Single Dose Studies. The Sponsor conducted no additional single-dose toxicology studies. Also, no new single-dose studies were identified in the

published literature search performed by the Sponsor. The two referenced NDAs, 21-260 and 18-565, also lacked single-dose toxicology data; referencing data found in the published literature. The FDA's prior findings of safety are based on findings in the published literature and will support the safety of NDA 22-195.

General Toxicology: Repeat Dose Studies. No additional repeat-dose toxicity studies were conducted by the Sponsor to support NDA 22-195. Also, no new repeat-dose toxicology studies were identified in the published literature search performed by the Sponsor. The two referenced NDAs, 21-260 and 18-565, also lacked repeat-dose toxicology data; referencing data found in the published literature. Hence, the FDA's prior findings of safety are based on findings in the published literature and will be used to support the safety of NDA 22-195.

Genetic Toxicology. No genetic toxicology study report was submitted with NDA 22-195. The sponsor relied on the published literature and the product label for the referenced NDAs (18-565 and 21-260). Also, no new genetic toxicology study reports were identified in the published literature search performed by the Sponsor. The two referenced NDAs, lacked genetic toxicology data and referenced data found in the published literature. Hence, the FDA's prior findings on genotoxicity are based on findings in the published literature and are also used to support NDA 22-195.

Carcinogenicity. No carcinogenicity study report was submitted with NDA 22-195. The sponsor relied on the published literature and the product label for the referenced NDAs (18-565 and 21-260). Also, no new carcinogenicity study reports were identified in the published literature search performed by the Sponsor. The two referenced NDAs, also lacked carcinogenicity data; referencing data found in the published literature prior to 2002. Hence, the FDA's prior findings on carcinogenicity are based on findings in the published literature and are used to support NDA 22-195.

Reproductive Toxicology. No additional reproductive toxicity studies were conducted by the Sponsor to support NDA 22-195. However, the sponsor did identify five study reports in the published literature and submitted them to support NDA 22-195.

2.6.6.10 Tables and Figures

N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The proposed drug product does not present with any unique toxicology concerns compared to the already approved drug products and based on current practice in OND, no further studies are required to support this NDA application.

Unresolved toxicology issues (if any): According the b(4)
morphine drug substance contains the following impurities:
reported that
they are at a level of NMT which exceeds ICH Q3A safety qualification threshold. The sponsor has been requested to either reduce the specifications to NMT or provide adequate safety qualification as per ICH Q3A. Adequate qualification should include:

- **Minimal genetic toxicology** screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- **Repeat dose toxicology of appropriate** duration to support the proposed indication.

If the sponsor is unable to reduce the specifications, they may justify the safety based on the above toxicology data or via reference to such data in the published literature.

Recommendations: From the nonclinical pharmacology and toxicology issues perspective, the NDA may be approved.

Suggested labeling:

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of *in vitro* studies showed that morphine is not mutagenic in the *Drosophilia melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the *in vivo* clastogenic effects reported with morphine in murine lymphocytes and spermatids. Some of the *in vivo* clastogenic effects reported with morphine in mice may be directly related to increases in glucocorticoid levels produced by morphine in this species.

A literature report indicated that morphine impairs fertility in rats. In a fertility study in which male rats were administered morphine subcutaneous prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects were observed. These included reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites

Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic to those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. Morphine was not a significant teratogen in the rat at exposure levels significantly beyond that normally encountered in clinical practice. In one study however decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days to mating. In two studies performed in rabbit, no evidence of teratogenicity was reported to be no greater than expected among children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Nonteratogenic Effects

Published literature has reported exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following, treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and sexual maturation, and increased mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubules shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine into adulthood.

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit

withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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APPENDIX/ATTACHMENTS

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/s/

Belinda Hayes
12/11/2007 03:13:35 PM
PHARMACOLOGIST

R. Daniel Mellon
12/11/2007 03:54:42 PM
PHARMACOLOGIST
I concur.