

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202515Orig1s000**

**PHARMACOLOGY REVIEW(S)**



FDA Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia and Addiction Products  
10903 New Hampshire Avenue, Silver Spring, MD 20993

**MEMO TO FILE**

**PHARMACOLOGY TOXICOLOGY**

**NDA number:** 202515  
**Serial #; date:** SDN 10, Received and submit dates: July 14, 2011  
**Drug:** Morphine Sulfate USP  
**Indication:** moderate to severe chronic pain  
**Sponsor:** Hospira, Inc.  
**Date of Memo:** October 25, 2011

**Reviewer name:** Elizabeth A. Bolan, Ph.D.  
**Division name:** Division of Anesthesia, Analgesia and Addiction Products  
**HFD #:** 170

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**Background:**

Specifications of three drug product impurities, (b) (4) in the Hospira Morphine Sulfate USP product (NDA 202515) exceed ICH Q3B(R2) thresholds and qualification of these impurities is necessary. Safety qualification of the impurities was deemed acceptable to be completed as a post-marketing requirement (PMR) since the drug product is already a marketed product and the drug product impurities have been previously reported as morphine degradants in the literature. To qualify the impurities, the Applicant will conduct a minimal genetic toxicology screen with (b) (4) and a 13-week repeat-dose toxicology study with (b) (4) and (b) (4) (refer to PMR for details).

The Applicant has submitted a brief summary of the study design for the 13-week toxicology study and has requested feedback from the Division. This memo serves to provide advice to the Applicant regarding the design of the study.

**Evaluation:**

The summary of the study design briefly describes a 13-week toxicology study in rat intended for qualification of three drug product impurities. The study will be conducted under GLP. The three impurities to be tested, (b) (4), will be "combined/mixed" for dosing at two dose levels with once daily IV

**NDA 202515**  
Morphine Sulfate USP  
Hospira, Inc.

administration. The dose levels are described as 1x HED and 3x HED. Standard toxicology parameters will be measured (body weight, clinical pathology, hematology, etc.) including organ weights and histopathology (full set of standard tissues). Toxicokinetic evaluation will not be conducted.

The study design appears to be acceptable for a repeat-dose toxicology study to qualify the three impurities. Combining the three impurities is an acceptable approach, however, if toxicity is observed, it will not be possible to determine which individual impurity is responsible for the observed toxicity. The proposed dose levels of 1x HED and 3x HED are acceptable provided the HED is based on a maximum daily dose of 722 mg/day of morphine. Since the study utilizes intravenous administration, toxicokinetic evaluation will be not be necessary.

**Comments to Sponsor:**

We have the following comments on your study design of the 13-week toxicity study in rats for the morphine impurities.

1. The use of a mixture of the three impurities is acceptable.
2. The proposed dose levels (1x HED and 3x HED) are acceptable provided adequate coverage is demonstrated at the maximum daily dose of 722 mg for morphine.

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/s/  
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ELIZABETH BOLAN  
10/26/2011

RICHARD D MELLON  
10/26/2011



FDA Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia and Addiction Products  
10903 New Hampshire Avenue, Silver Spring, MD 20993

**MEMO TO FILE**

**ADDENDUM TO PHARMACOLOGY TOXICOLOGY NDA REVIEW**

**NDA number:** 202515  
**Serial #; date:** EDR NDA Original-1, Received and submit dates: 1/14/11 and SDN 10, Received and submit dates: 7/14/11

**Drug:** Morphine Sulfate Injection USP  
**Indication:** Management of pain not responsive to non-narcotic analgesics  
**Applicant:** Hospira, Inc.  
**Date of Memo:** October 13, 2011

**Reviewer name:** Elizabeth A. Bolan, Ph.D.  
**Division name:** Division of Anesthesia, Analgesia and Addiction Products  
**HFD #:** 170

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**Recommendation:** From a nonclinical pharmacology toxicology perspective, the NDA may be approved with three PMRs discussed in this memorandum pending agreement on the labeling recommendations.

**Background:** This memo is an addendum to the pharmacology toxicology review of NDA 202515 for Morphine Sulfate Injection USP. It serves to document changes made to the Applicant's proposed label and the adequacy of the Applicant's response to the pharmacology toxicology Discipline Review letter sent on June 20, 2011.

The table below contains the draft labeling submitted by the Applicant, the proposed changes from the reviewer and the rationale for the reviewer's proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

| <i>Applicant's proposed labeling</i> | <i>Reviewer's proposed changes</i> | <i>Rationale for changes</i> |
|--------------------------------------|------------------------------------|------------------------------|
|--------------------------------------|------------------------------------|------------------------------|

| <i>Applicant's proposed labeling</i>                                                                                                                                                                                                                                                                      | <i>Reviewer's proposed changes</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <i>Rationale for changes</i>                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>INDICATIONS AND USAGE</b><br>Morphine sulfate is indicated for the management of pain not responsive to non-narcotic analgesics. (1)                                                                                                                                                                   | <b>INDICATIONS AND USAGE</b><br>Morphine sulfate is <b>an opioid agonist</b> indicated for the management of pain not responsive to non-narcotic analgesics. (1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | The Established Pharmacologic Class for morphine was added.                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>USE IN SPECIFIC POPULATIONS</b>                                                                                                                                                                                                                                                                        | <b>USE IN SPECIFIC POPULATIONS</b> <ul style="list-style-type: none"> <li>• <b>Pregnancy: Based on animal data, may cause fetal harm. (8.1)</b></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | As per the Maternal Health Team labeling initiative, nonclinical pregnancy information with a reference to section 8.1 was added to the Highlights section.                                                                                                                                                                                                                                                                                     |
| <b>8.1 Pregnancy</b><br>Teratogenic Effects – Pregnancy Category C<br><div style="background-color: #cccccc; height: 150px; width: 100%; margin-top: 10px;">(b) (4)</div><br>Nonteratogenic Effects<br><div style="background-color: #cccccc; height: 50px; width: 100%; margin-top: 10px;">(b) (4)</div> | <b>8.1 Pregnancy</b><br><b>Teratogenic Effects (Pregnancy Category C)</b><br>No formal studies to assess the teratogenic effects of morphine in animals have been conducted. It is also not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Morphine should only be given to a pregnant woman only if clearly needed.<br><br>In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy (Heinonen OP, et al., 1977). 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 (Czeizel, et al., 1988). | <div style="background-color: #cccccc; height: 100px; width: 100%; margin-top: 10px;">(b) (4)</div><br>The introductory paragraph was added as per the CFR for Category C drugs.<br><br>As per the Maternal Health Team labeling initiative, human data were placed first.<br><br>Literature reports describing effects of morphine on human and animal development were summarized. The references in parentheses will be removed in the final |

| <i>Applicant's proposed labeling</i> | <i>Reviewer's proposed changes</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <i>Rationale for changes</i>                                                                                                                                              |
|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      | <p>Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities (Geber and Schramm, 1975; Harpel, Jr. and Gautieri, 1968; Iuliucci and Gautieri, 1971; Ciociola and Gautieri, 1983). With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of 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 (Ciociola and Gautieri, 1983). In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis (Geber and Schramm, 1975). In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed. No maternal toxicity was observed in this study, however, increased mortality and growth retardation were seen in the offspring (Fujinaga and Mazze, 1988). In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg (Roloff, et al., 1975; Raye JR, et al., 1977).</p> <p><b>Nonteratogenic Effects</b><br/>Controlled studies of chronic <i>in utero</i> morphine exposure in pregnant women</p> | <p>label. The human data from the literature can be found in other morphine product labels and the citations listed here are to document the source of the statement.</p> |

| <i><b>Applicant's proposed labeling</b></i> | <i><b>Reviewer's proposed changes</b></i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <i><b>Rationale for changes</b></i> |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
|                                             | <p>have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms (Cobrinik RW, et al., 1959), reversible reduction in brain volume, small size, decreased ventilatory response to CO<sub>2</sub> 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.</p> <p>Published literature has reported that 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 (Zagon and McLaughlin, 1977a; Zagon and McLaughlin, 1977b), embryo-fetal viability (Siddiqui, et al., 1995; Zagon and McLaughlin, 1977a; Zagon and McLaughlin, 1977b), fetal and neonatal body weights (Siddiqui, et al., 1995; Zagon and McLaughlin, 1977a; Zagon and McLaughlin, 1977b), absolute brain and cerebellar weights (Zagon and McLaughlin, 1977b), delayed motor and sexual maturation (Siddiqui, et al., 1997), and increased neonatal mortality (Zagon and McLaughlin, 1977a; Zagon and McLaughlin, 1977b), cyanosis and hypothermia (Zagon and McLaughlin, 1977b). Decreased fertility in female offspring (Siddiqui, et al., 1997), and decreased plasma and testicular levels of</p> |                                     |

| <i>Applicant's proposed labeling</i>                                                   | <i>Reviewer's proposed changes</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <i>Rationale for changes</i>                                                                                                                                                                             |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                        | <p>luteinizing hormone and testosterone (Siddiqui, et al., 1995), decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed (Siddiqui, et al., 1995). Decreased litter size and viability were observed in the offspring of male rats administered morphine (25 mg/kg, ip) for 1 day prior to mating (Cicero TJ, et al., 1995). Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal (Koyuncuoglu and Aricioglu, 1993), and altered responsiveness to morphine persisting into adulthood (Johannesson and Becker, 1972).</p>                                                                                                                                                 |                                                                                                                                                                                                          |
| <p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p>(b) (4)</p> | <p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p><u><b>Carcinogenesis</b></u></p> <p>Studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.</p> <p><u><b>Mutagenesis</b></u></p> <p>No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic <i>in vitro</i> increasing DNA fragmentation in human T-cells (Shafer, et al., 1994). Morphine was reported mutagenic in the <i>in vivo</i> mouse micronucleus assay (Swain, et al., 1980; Das and Swain, 1982) and positive for the induction of chromosomal aberrations in mouse spermatids (Badr and Rabouh, 1983) and murine lymphocytes (Swain, et al., 1980). Mechanistic studies suggest that the <i>in vivo</i> clastogenic effects reported with</p> | <p>(b) (4)</p> <p>Literature reports describing effects of morphine on mutagenicity, clastogenicity and fertility were summarized. The references in parentheses will be removed in the final label.</p> |

| <i>Applicant's proposed labeling</i> | <i>Reviewer's proposed changes</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <i>Rationale for changes</i> |
|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
|                                      | <p>morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species (Fuchs and Pruett, 1993; Couch and Sawant, 1995; Sawant, et al., 2001). In contrast to the above positive findings, <i>in vitro</i> studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes (Falek, et al., 1972) or translocations or lethal mutations in <i>Drosophila</i> (Knaap and Kramers, 1976).</p> <p><b><u>Impairment of Fertility</u></b></p> <p>No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine (Cicero TJ, et al., 2002; Cicero TJ, et al., 1995; Cicero TJ, et al., 1991). One study in which male rats were administered morphine sulfate subcutaneously 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 including reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites were seen (Cicero TJ, et al., 2002). Studies from the literature have also reported changes in hormonal levels (i.e. testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine (James, et al., 1980; Siddiqui, et al., 1995). These changes may be associated with the reported effects on fertility in the rat.</p> |                              |

On June 20, 2011 the Division sent a pharmacology toxicology Discipline Review letter to the Applicant with the following comments:

**FDA Comment 1:**

Your drug substance acceptance specification of (b) (4) for (b) (4) exceeds the ICH Q3A(R2) qualification threshold. We recommend that you consult with your DMF holder and tighten your acceptance specification to NMT 0.15% in order to comply with ICH Q3A(R2) guidelines.

**FDA Comment 2:**

The drug product specifications for (b) (4) exceed the ICH Q3B(R2) qualification threshold of NMT 0.2%. Your literature-based justification is not adequate to support the safety of your proposed drug product specifications. However, the genetic toxicology studies with (b) (4) are acceptable and no further genetic toxicology qualification of (b) (4) will be required.

The impurities/degradants must either be reduced to below ICH Q3B(R2) qualification threshold of NMT 0.2% or adequately qualified via toxicology studies. Adequate qualification must include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) for (b) (4), tested up to the limit dose for the assay.
- b. Repeat dose toxicology studies of 90 days duration with (b) (4).

The Applicant replied on July 14, 2011. To address Comment 1, the Applicant changed the drug substance acceptance specification from NMT (b) (4) to NMT (b) (4) for the (b) (4) impurity. The NMT (b) (4) specification meets ICH Q3A(R2) thresholds for qualification and is considered acceptable.

To address Comment 2, the Applicant committed to conducting two *in vitro* genetic toxicology studies (e.g., one point mutation assay and one chromosome aberration assay) for (b) (4) as well as a 13-week repeat-dose toxicology study with (b) (4). The Applicant stated that the results will be provided to the Agency within nine months of the date of approval. These studies will be considered a post marketing requirement (PMR). The reason these studies are suitable to be completed post marketing is that the drug product is already a currently marketed product and these drug product degradants have been previously reported as morphine drug product degradants in the literature.

The Applicant's replies to both comments are acceptable from a pharmacology toxicology perspective. From a nonclinical pharmacology toxicology perspective, the NDA may be approved with the PMRs pending agreement on the labeling.

#### Reference List

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Zagon IS and McLaughlin PJ (1977b) Morphine and brain growth retardation in the rat. *Pharmacology* **15**:276-282.

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/s/  
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ELIZABETH BOLAN

10/14/2011

RICHARD D MELLON

10/14/2011

I concur with Dr. Bolan's recommendations.

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 202515  
Supporting document/s: EDR NDA Original-1  
Applicant's letter date: 1/14/11  
CDER stamp date: Received date: 1/14/11; Submit date: 1/14/11  
Product: Morphine Sulfate Injection USP  
Indication: Management of pain not responsive to non-narcotic analgesics  
Applicant: Hospira, Inc.  
Review Division: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)  
Reviewer: Elizabeth A. Bolan, Ph.D.  
Supervisor/Team Leader: R. Daniel Mellon, Ph.D.  
Division Director: Bob Rappaport, M.D.  
Project Manager: Kimberly Compton

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

Hospira has submitted NDA 202515 for Morphine Sulfate Injection USP which is currently a marketed, unapproved product. This NDA covers several different packaging configurations of a sterile, aqueous, preservative-free morphine sulfate solution intended for (b) (4) intravenous (IV) injection. The Carpuject and iSecure syringes are single-use pre-filled syringes intended for (b) (4) IV administration. (b) (4)

(b) (4) This application was submitted via the 505(b)(2) pathway and the Applicant is relying on the Agency's findings of safety and efficacy and the pharmacology, pharmacokinetics, and toxicology information in the labels of Duramorph (for the IV products; Baxter; NDA 18565) (b) (4)

## 1.2 Brief Discussion of Nonclinical Findings

The pharmacology and toxicology of morphine have been well characterized and no studies with morphine were submitted by the Applicant or required to support this NDA. A literature review is being conducted by the reviewer in order to update the nonclinical sections of the product label (specifically reproductive and developmental toxicology and genetic toxicology). The reader is referred to the addendum to this review for specific labeling recommendations.

All excipients in the drug product are below levels found in drugs previously approved for parenteral use and are considered acceptable for NDA 202515. There are no concerns with extractables or leachables from the syringe plunger and vial stopper materials for this product.

The drug substance and drug product impurity/degradant (b) (4) and the drug product degradants (b) (4) all exceed ICH Q3A/B(R2) qualification thresholds. The Applicant submitted a literature-based justification to support the safety of the increased specifications. The justification was deemed unacceptable and it will be communicated to the Applicant that the drug product specifications must either be reduced or adequate toxicologic qualification will be necessary. The Applicant will be asked to tighten their drug substance acceptance specification for (b) (4) to be in accordance with the specification in the morphine sulfate drug substance DMF (DMF (b) (4)). The specification for (b) (4) in DMF (b) (4) meets ICH Q3A(R2) thresholds for qualification. For the impurities in the drug product, adequate qualification would include the minimal genetic toxicology screen (two *in vitro* genetic toxicology studies) with (b) (4), tested up to the limit dose for the assay as well as repeat dose toxicology studies of 90 days duration with (b) (4) and (b) (4). An Ames Test and an *in vitro* chromosomal aberration assay showing that (b) (4) is not genotoxic was submitted and (b) (4) can be considered qualified for genotoxic potential.

### 1.3 Recommendations

#### 1.3.1 Approvability

From a nonclinical pharmacology/toxicology perspective adequate safety data has not been provided to support approval of this NDA; therefore, a complete response is recommended at this time.

#### 1.3.2 Additional Non Clinical Recommendations

The following deficiencies should be communicated to the Applicant in a Discipline Review Letter:

1. Your drug substance acceptance specification of (b) (4) for (b) (4) exceeds the ICH Q3A(R2) qualification threshold. We recommend that you consult with your DMF holder and tighten your acceptance specification to NMT 0.15% in order to comply with ICH Q3A(R2) guidelines.
2. The drug product specifications for (b) (4) exceed the ICH Q3B(R2) qualification threshold of NMT 0.2%. After formal review, it has been determined that your literature-based justification is not adequate to support the safety of your proposed drug product specifications. However, the genetic toxicology studies with (b) (4) are acceptable and no further genetic toxicology qualification of (b) (4) will be required.

The impurities/degradants must either be reduced to below ICH Q3B(R2) qualification threshold of NMT 0.2% or adequately qualified via toxicology studies. Adequate qualification would include:

- Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) for (b) (4), tested up to the limit dose for the assay.
- Repeat dose toxicology studies of 90 days duration with (b) (4)

#### 1.3.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the proposed changes from the reviewer and the rationale for the reviewer's proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

| <b><i>Applicant's proposed labeling</i></b>                                                                                                                                                                                                         | <b><i>Reviewer's proposed changes</i></b>                        | <b><i>Rationale for changes</i></b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>8.1 Pregnancy</b><br><i>Teratogenic Effects – Pregnancy Category C</i><br><div style="background-color: #cccccc; height: 350px; width: 100%; position: relative;"> <span style="position: absolute; top: 5px; right: 5px;">(b) (4)</span> </div> | Changes pending completion of review of the morphine literature. | <div style="background-color: #cccccc; height: 40px; width: 100%; position: relative;"> <span style="position: absolute; top: 5px; right: 5px;">(b) (4)</span> </div> <p>Publically available literature reports describing the nonclinical toxicology of morphine appear in labels of other morphine products. A comprehensive literature review of the nonclinical reproductive and developmental toxicology, genetic toxicology and carcinogenicity data with morphine is being conducted. An addendum to this review with the proposed changes will be submitted at a later date.</p> |
| <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b><br><div style="background-color: #cccccc; height: 150px; width: 100%; position: relative;"> <span style="position: absolute; top: 5px; right: 5px;">(b) (4)</span> </div>          | Changes pending completion of review of the morphine literature. | <div style="background-color: #cccccc; height: 40px; width: 100%; position: relative;"> <span style="position: absolute; top: 5px; right: 5px;">(b) (4)</span> </div> <p>As noted above, publically available literature reports will be summarized and included in the label.</p>                                                                                                                                                                                                                                                                                                        |

## 2 Drug Information

### 2.1 Drug

CAS Registry Number

6211-15-0

Generic Name

Morphine Sulfate

Code Name

N/A

Chemical Name

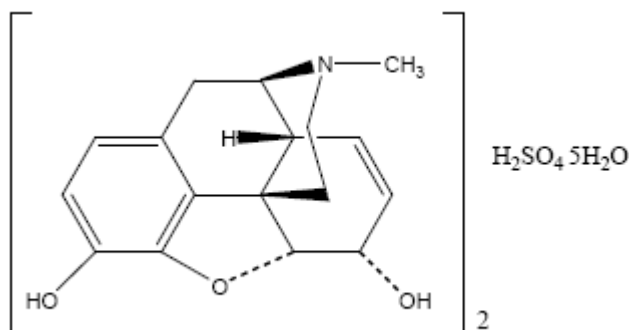
7, 8-didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate (2:1) (salt), pentahydrate

Molecular Formula/Molecular Weight

(C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub> · H<sub>2</sub>SO<sub>4</sub> · 5 H<sub>2</sub>O; MW= 758.83

Structure or Biochemical Description

**Figure 1 Structure of Morphine Sulfate**



Pharmacologic Class

Opioid Agonist (FDA Established Pharmacologic Class)

### Relevant INDs, NDAs, BLAs and DMFs

**Table 1 Relevant NDAs, INDs, and DMFs**

| <i>IND/NDA/DMF</i> | <i>Subject</i>                 | <i>Sponsor</i> | <i>Comments</i> |
|--------------------|--------------------------------|----------------|-----------------|
| IND 105936         | Morphine Sulfate Injection USP | Hospira, Inc.  | Active IND      |

|           |           |                   |                     |
|-----------|-----------|-------------------|---------------------|
| NDA 18565 | Duramorph | Baxter Healthcare | 505(b)(2) reference |
| (b) (4)   |           |                   |                     |

### Drug Formulation

NDA 202515 covers several different packaging configurations of a sterile, aqueous, preservative-free morphine sulfate solution intended for (b) (4) intravenous (IV) injection. The different packaging configurations and strengths are outlined in Table 2. The Carpuject and iSecure syringes are single-use pre-filled syringes intended for (b) (4) IV administration. (b) (4)

The formulation for all of the packaging configurations contains the active ingredient morphine sulfate in water for injection with EDTA, citric acid and sodium chloride. The amounts of each excipient per mL of the final formulation are outlined in Table 3. The levels of all excipients when this product is used at the Applicant's proposed maximum daily dose of morphine (722 mg/day) are below levels found in products for parenteral use previously approved by FDA. All excipients are found in the FDA Inactive Ingredients Guide (IIG). The levels of all excipients in the products covered by NDA 202515 are considered acceptable from the pharmacology/toxicology perspective.

**Table 2 Morphine Sulfate Injection USP Products**

| <b><i>Morphine concentration<br/>(total morphine content)</i></b> | <b><i>Fill volume,<br/>mL</i></b> | <b><i>Route</i></b> | <b><i>Container</i></b> |
|-------------------------------------------------------------------|-----------------------------------|---------------------|-------------------------|
| 2, 4, 8, 10, 15 mg/mL                                             | 1                                 | (b) (4) IV          | 2 mL Carpuject Syringe  |
| 2, 4, 8, 10, 15 mg/mL                                             | 1                                 | (b) (4) IV          | 1 mL iSecure Syringe    |
| (b) (4)                                                           |                                   |                     |                         |

**Table 3 Formulation of Morphine Sulfate Injection USP**

| <b><i>Excipient</i></b> | <b><i>Per mL,<br/>mg</i></b> | <b><i>Acceptable?<br/>(basis)</i></b> |
|-------------------------|------------------------------|---------------------------------------|
| EDTA                    | 0.2                          | Yes (IIG)                             |

|                 |         |           |
|-----------------|---------|-----------|
| Citric Acid     | 0.4     | Yes (IIG) |
| Sodium Chloride | (b) (4) | Yes (IIG) |

\*Amounts of NaCl range from (b) (4) for the various products  
IIG: FDA Inactive Ingredients Guide

## 2.4 Comments on Novel Excipients

There are no novel excipients.

## 2.5 Comments on Impurities/Degradants of Concern

The following comments regarding impurity specifications exceeding ICH Q3A/B(R2) guidelines were communicated to the Applicant in the 74-day letter:

**We note that there are several specifications for drug product impurities that exceed thresholds set by the ICH Q3B guideline. Upon preliminary review, the literature references that you submitted do not appear to support the safety of your proposed specifications. Specifically, the references do not quantify levels of the morphine metabolites (b) (4). The literature references provided to toxicologically qualify (b) (4) do not contain an adequate histopathologic assessment. If upon formal review your justification for the safety of these impurities is not deemed adequate by current toxicology standards these impurities/degradants must either be reduced to below ICHQ3A/B qualification thresholds or adequately qualified via toxicology studies.**

– Adequate qualification generally would include:

- Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with (b) (4), tested up to the limit dose for the assay.
- Repeat dose toxicology studies of 90 days duration with (b) (4)

### **Impurities in the morphine drug substance**

The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for a MDD of drug substance  $\leq 2$  g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant has proposed that the maximum daily dose of morphine for these products will be 722 mg. The Applicant states that 722 mg/day is the same MDD as their approved Morphine Sulfate Injection (NDA 19916). This value was derived from the dosing section of the product labeling for NDA 19916 and proposed for this product as well. Specifically, the FDA-approved drug product labeling for 19916 notes that an initial bolus of up to 5 mg has been used in clinical trials in opioid-tolerant patients with maximal dosing rates up to 30 mg/hr (3 mg every 6

minutes) being common for tolerant patients. Using this information, the upper range of dosing commonly used for opioid tolerant patients, as per the label, could be derived as follows: 5 mg bolus + (3 mg x 9 doses remaining in the first hour) + (30 mg/hr x 23 hours) = 722 mg/day. No further clinical use data was provided to justify the proposed dose of 722 mg/day. However, the label states that greater rates may be needed in selected patients. Indeed, the published literature has reported that, although rare, a few patients may require 1000 to 4500 mg parenteral morphine per hour (Foley KM, 1993). However, the clinicians in DAAAP consider 722 mg/day an acceptable maximum daily dose of morphine for these products. For a total daily intake of 722 mg of morphine, a specification of 0.15% would yield 1.08 mg of a given impurity. Although at the MDD of 722 mg the specification of 0.15% for impurities in the drug substance would slightly exceed the threshold of 1 mg/day it will be considered acceptable.

The morphine sulfate drug substance will be obtained from (b) (4); DMF (b) (4). The Applicant has set the specifications for impurities in the drug substance at (b) (4) with the exception of (b) (4) which are discussed below (Table 4).

(b) (4)

The following comment will be communicated to the applicant in a Discipline Review Letter:

**Your drug substance acceptance specification of (b) (4) for (b) (4) exceeds ICH Q3A(R2) qualification thresholds. We recommend that**

**you consult with your DMF holder and tighten your acceptance specification in order to comply with ICH Q3A(R2) guidelines.**

(b) (4)

**Table 4 Drug Substance Acceptance Specifications**

| <i>Impurity</i> | <i>Specification</i> | <i>acceptable?</i>        |
|-----------------|----------------------|---------------------------|
| (b) (4)         |                      | Yes                       |
|                 |                      | Yes                       |
|                 |                      | <b>No</b>                 |
|                 |                      | Yes: qualified by (b) (4) |
|                 |                      | Yes                       |
|                 |                      | Yes: approved drug        |
|                 |                      | Yes                       |

\*structural alert for mutagenicity

**Impurities in the drug product**

The qualification threshold according to the ICH Q3B(R2) guidance for impurities/degradants in the drug product for a MDD of drug substance >100 mg – 2 g (MDD of MOR is 722 g) is 0.2% or 3 mg TDI, whichever is lower. For a total daily intake

of 722 mg of morphine, a specification of 0.2% would yield 1.44 mg of a given impurity. The specifications for (b) (4) exceed the 0.2% threshold (Table 5). For these impurities/degradants, the Applicant has submitted literature references in order to justify their proposed specifications. The discussion of the adequacy of the justification is below.

**Table 5 Drug Product Specifications**

| <i>Impurity/degradant</i> | <i>Specification</i> | <i>acceptable?</i>        |
|---------------------------|----------------------|---------------------------|
| (b) (4)                   | (b) (4)              | No                        |
|                           |                      | No                        |
|                           |                      | Yes: qualified my (b) (4) |
|                           |                      | No                        |

\*structural alert for mutagenicity

The literature reports listed below were submitted by the Applicant in support of the justification of the specifications in excess of ICH Q3A/B(R2) thresholds for qualification. A literature search was also conducted by the reviewer in order to identify any additional information.

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

The drug product specifications for (b) (4) exceed the ICH Q3B(R2) qualification threshold. After formal review, it has been determined that your literature-based justification does not support the safety of your proposed drug product specifications. The genetic toxicology studies with (b) (4) are acceptable and no further genetic toxicology qualification of (b) (4) will be required.

The impurities/degradants must either be reduced to below the ICH Q3B(R2) qualification threshold of NMT 0.2% or adequately qualified via toxicology studies.

- Adequate qualification generally would include:
  - Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with (b) (4), tested up to the limit dose for the assay.
  - Repeat dose toxicology studies of 90 days duration with (b) (4)

### **Extractable/Leachables**

The Carpuject and iSecure configurations use a (b) (4) Gray plunger (DMF (b) (4)). MFs has been referenced by many NDAs for injectable products approved by FDA and no safety concerns with leachables have arisen.

Extractable studies were conducted with the rubber material used in the stoppers and plungers. The Applicant submitted a summary of an extractable study with the registration stability batches under accelerated conditions. Potential extractables from the (b) (4) Gray stopper and the (b) (4) Gray plungers were assessed.

(b) (4) The level of this extractable (b) (4) was very low. To put the level into perspective, the ICH Q3B(R2) *reporting* threshold for impurities in the drug product for a MDD of the drug substance <1 g is 0.1%. Because of the low level, this extractable is not considered to be of toxicologic concern. No other appreciable peaks were observed. Although leachable studies were not conducted with the (b) (4) Gray plungers or the (b) (4) Gray stoppers, the DMFs for both materials have been referenced by many products and no safety signals have arisen. The Agency's previous finding of safety for these materials will be relied on in order to support their safety.

## 2.6 Proposed Clinical Population and Dosing Regimen

The indication sought for Morphine Sulfate Injection USP is management of pain not responsive to non-narcotic analgesics. This is considered to be a chronic indication. The Carpuject and iSecure syringes are intended to be used for (b) (4) IV administration (b) (4)

## 2.7 Regulatory Background

The parenteral formulations of Morphine Sulfate Injection USP are currently marketed, unapproved drug products. A PIND meeting was held on October 28, 2009 with Hospira (PIND 105936). General nonclinical comments including comments on 505(b)(2) issues, excipients, impurities, extractables and leachables were provided to the Applicant.

## 3 Studies Submitted

No studies with morphine sulfate were submitted with the NDA. Two genetic toxicology studies with the drug product degradant (b) (4) were submitted. These studies have been previously reviewed by FDA (see section 3.3 below).

### 3.3 Previous Reviews Referenced

The Applicant has submitted study reports for an Ames Test (Study # AB14GP.503.BTL) and an *in vitro* chromosomal aberration assay (Study # AB14GP.331.BTL) with the drug product degradant (b) (4). These studies have been previously reviewed by R. Daniel Mellon, Ph.D. for NDA 19-916, Morphine Sulfate Injection USP, Preservative-Free 1 mg/mL (March 30, 2006) which is also owned by the Applicant.

## 4 Pharmacology

No new pharmacology studies were submitted by the Applicant. The following summary of morphine pharmacology was modified from a general morphine pharmacology review by Dr. BeLinda Hayes. Dr. Hayes' summary is denoted by indented text.

### 4.1 Primary Pharmacology

Morphine, a phenanthrene opioid, is the prototype against which all other opioids are measured. Morphine sulfate was first approved by the Food and Drug Administration in September of 1984 under the trade name Duramorph® Preservative-free Injection (NDA 18565; Baxter Healthcare) for intrathecal and epidural administration.

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

### 4.2 Secondary Pharmacology

Morphine's secondary pharmacological effects include dysphoria, euphoria, sedation, respiratory depression, decreased gastrointestinal motility and physical dependence. These pharmacodynamic effects have been extensively reviewed in the published literature.

### 4.3 Safety Pharmacology

Cardiovascular effects: Animal studies have 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 SF, 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 LH, et al., 2000).

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<sub>2</sub> and depression of pontine and medullary centers via its action at the mu<sub>2</sub> opioid receptors.

Renal effects: 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 PC, et al., 1998). Cultured rat kidney fibroblasts were exposed to morphine at concentrations in the range of 10<sup>-12</sup> M to 10<sup>-4</sup> M for 24 hours or 48 hours. At both incubation periods, low concentrations of morphine (10<sup>-12</sup> M) induced proliferation of fibroblasts.

Chronic use of morphine in patients with renal failure should be used with caution (Angst MS, et al., 2000). Morphine-6-glucuronide (M6G), a pharmacologically active metabolite of morphine is cleared via the kidney. In patients with renal failure, M6G will accumulate and allow opioid side effects to persist hours after plasma concentration of morphine 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 well-known effect of morphine. In addition to this effect, like other opioid drugs, morphine exerts a wide spectrum of other effects on mammalian intestinal function. These effects include reduction in secretions (pancreatic, biliary, and electrolyte/fluid) and increases in intestinal fluid absorption and blood flow (Brown RD and Miller R, 1989). 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 D, et al., 1977; Stewart JJ, et al., 1978; Tavani A, et al., 1990). Mu opioid receptors in the brain of mice (Porreca F, et al., 1983; Porreca F and Burks TF, 1983) and rats (Koslo RJ, 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 it binds to opioid receptors on neurons located in the ventral tegmental area 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.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### **Absorption**

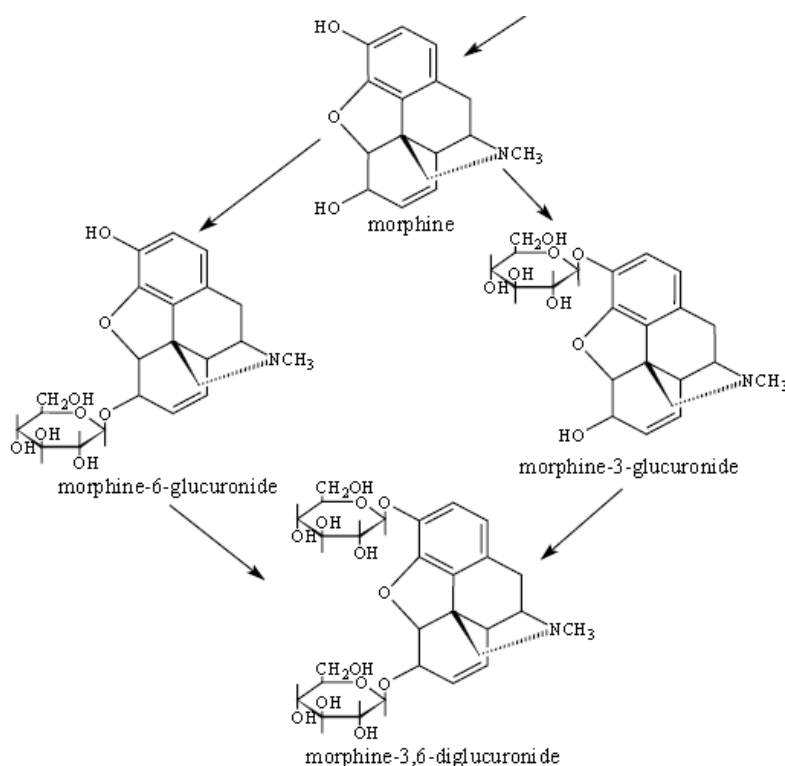
Absorption of morphine following oral administration is variable and decreased by extensive pre-systemic metabolism in both the liver and gut. Morphine is distributed to the intestinal tract, kidneys, liver, lungs, skeletal muscle, spleen and brain. Although the central nervous system is the primary 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 VL, et al., 1989; Robieux I, 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%.

### **Metabolism**

Morphine metabolism is primarily by hepatic glucuronidation by uridine diphosphate glucuronosyl transferase (UGT) enzyme, with specific affinity for the UGT2B7 and UGT1A3 isozymes, (Armstrong SC and Cozza KL, 2003; Witter E and Kern SE, 2006). The isoenzyme is responsible for the formation of both major glucuronide metabolites of morphine; morphine-3-glucuronide (M3G, about 50%) and M6G (about 15%). M3G has no

analgesic activity; whereas M6G has been shown to have analgesic activity but crosses the blood brain barrier poorly. Metabolism of morphine can also occur in the brain and the kidneys (Christrup LL, 1997). In humans, morphine is also metabolized to normorphine and normorphine-6-glucuronide (Yeh SY, et al., 1977). Normorphine is formed by hepatic microsomal oxidation. Minor metabolites including codeine have been identified in the urine of humans following large doses of chronically administered morphine. Following oral administration, approximately 5% of the morphine undergoes N-demethylation to normorphine and 10% metabolized to codeine.

**Figure 2 Major Metabolic Pathways of Morphine**



### **Excretion**

Morphine is eliminated in urine, feces and bile; with renal excretion being the major route of elimination. Approximately 10% of a dose of morphine is excreted unchanged in the urine. The majority 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 is 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.

**Reviewer's note (EAB):** (b) (4) has described the first evidence of (b) (4) formation in human tissue. In an *in vitro* human liver preparation, conversion of morphine to (b) (4) was shown to be NADP dependent and localized mainly to (b) (4). (b) (4) contains a structural alert for mutagenicity. Data to suggest that (b) (4) is not genotoxic are included in the DMF for the morphine drug substance.

#### **2.6.4.7 Pharmacokinetic drug interactions**

The known drug interactions involving morphine are pharmacodynamic. Coadministration 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.

## **6 General Toxicology**

No new studies were submitted by the Applicant.

## **7 Genetic Toxicology**

No new studies were submitted by the Applicant with (b) (4). The specification for the (b) (4) degradant (b) (4) exceeds ICH Q3B(R2) thresholds for qualification. The Applicant has submitted study reports for an Ames Test (Study # AB14GP.503.BTL) and an *in vitro* chromosomal aberration assay (Study # AB14GP 331.BTL) with (b) (4). These studies have been previously reviewed by R. Daniel Mellon, Ph.D. (see review for NDA 19916 Morphine Sulfate Injection USP, Preservative-Free 1 mg/mL, Hospira; dated March 30, 2006). The studies were found to be adequate and (b) (4) was determined to be negative in both studies. No further genetic toxicology qualification of (b) (4) will be required.

## **8 Carcinogenicity**

No new studies were submitted by the Applicant. There are no carcinogenicity data for morphine in the published literature.

## **9 Reproductive and Developmental Toxicology**

No new studies were submitted by the Applicant.

## **10 Special Toxicology Studies**

No new studies were submitted by the Applicant.

## 11 Integrated Summary and Safety Evaluation

No nonclinical data with morphine sulfate were submitted with this NDA. The Applicant has submitted a literature-based justification for the safety of the drug product specifications in excess of ICH Q3B(R2) thresholds for qualification. It is concluded that the submitted literature references as well as results from an independent literature search conducted by this reviewer do not support the safety of the proposed specifications for (b) (4) in the drug product. The Applicant has submitted an acceptable genetic toxicology battery showing that (b) (4) is not genotoxic under the conditions of the assays conducted and can be considered qualified for genotoxic potential. The drug product specifications for (b) (4) will need to be reduced or qualification will be necessary.

All excipients in the drug product are below levels found in drugs previously approved for parenteral use. There are no concerns with extractables or leachables from the syringe plunger and vial stopper materials for this product.

As of the date of this review, the Applicant has not provided adequate safety qualification for the drug product degradants, (b) (4). The drug product specifications must be either reduced to NMT 0.2% or adequate safety qualification must be provided.

## 12 Appendix/Attachments

## Reference List

Angst MS, Buhner M and Lotsch J (2000) Insidious intoxication after morphine treatment in renal failure: delayed onset of morphine-6-glucuronide action. *Anesthesiology* **92**:1473-1476.

Armstrong SC and Cozza KL (2003) Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part II. *Psychosomatics* **44**:515-520.

Brown RD and Miller R (1989) Neurohormonal control of fluid and electrolyte transport in intestinal mucosa, in *Handbook of Physiology* (Field M and Frizzell RA eds) Oxford University Press, New York.

Christrup LL (1997) Morphine metabolites. *Acta Anaesthesiol Scand* **41**:116-122.

Eder E, Hoffman C, Bastian H, Deininger C and Scheckenbach S (1990) Molecular mechanisms of DNA damage initiated by alpha, beta-unsaturated carbonyl compounds as criteria for genotoxicity and mutagenicity. *Environ Health Perspect* **88**:99-106.

Eder E, Scheckenbach S, Deininger C and Hoffman C (1993) The possible role of alpha, beta-unsaturated carbonyl compounds in mutagenesis and carcinogenesis. *Toxicol Lett* **67**:87-103.

(b) (4)

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(b) (4)

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/s/  
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ELIZABETH BOLAN  
06/16/2011

RICHARD D MELLON  
06/16/2011  
I concur.

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:** 202-515    **Applicant:** Hospira, Inc.

**Stamp Date:** January 14, 2011

**Drug Name:** Morphine Sulfate NDA/BLA Type: 505(b)(2)  
**Injection USP**

On initial overview of the NDA/BLA application for filing:

|   | Content Parameter                                                                                                                                                                                                                                                                                                                | Yes | No | Comment                                                                          |
|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|----------------------------------------------------------------------------------|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?                                                                                                                                                      | X   |    |                                                                                  |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?                                                                                                                                                                                                                   | X   |    |                                                                                  |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin?                                                                                                                                                                                                                                             | X   |    |                                                                                  |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?        |     |    | N/A<br>No studies were required or requested and none were submitted.            |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). |     |    | N/A<br>No toxicology studies were required and none were submitted.              |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?                                                                                                                 |     |    | N/A<br>No animal studies were required and none were submitted.                  |
| 7 | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?                                                                                                      |     |    | N/A<br>No pharmacology/toxicology studies were required and none were submitted. |
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?                                                                                                                                                                                                                | X   |    |                                                                                  |

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement

Reference ID: A616024

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

|    | Content Parameter                                                                                                                                                                                                           | Yes | No | Comment                                                                                 |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|-----------------------------------------------------------------------------------------|
| 9  | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57? |     | X  | The proposed label will need to be updated. This is not a filing issue.                 |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)                                                                                                                                   | X   |    | Literature references were submitted in order to justify proposed levels of impurities. |
| 11 | Has the applicant addressed any abuse potential issues in the submission?                                                                                                                                                   |     |    | Refer to Controlled Substances Staff review                                             |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?                                                                                                                                 |     |    | N/A                                                                                     |

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?** \_\_\_ Yes \_\_\_

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**We note that there are several specifications for drug product impurities that exceed thresholds set by the ICH Q3B guideline. Upon preliminary review, the literature references that you submitted do not appear to support the safety of your proposed specifications. Specifically, the references do not quantify levels of the morphine metabolites (b) (4) and (b) (4). The literature references provided to toxicologically qualify (b) (4) do not contain an adequate histopathologic assessment. If upon formal review your justification for the safety of these impurities is not deemed adequate by current toxicology standards these impurities/degradants must either be reduced to below ICHQ3A/B qualification thresholds or adequately qualified via toxicology studies.**

– Adequate qualification generally would include:

- **Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with (b) (4) and (b) (4) tested up to the limit dose for the assay.**
- **Repeat dose toxicology studies of 90 days duration with (b) (4)**

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

|                           |          |
|---------------------------|----------|
| Elizabeth A. Bolan, Ph.D. | 3/9/2011 |
| Reviewing Pharmacologist  | Date     |
| R. Daniel Mellon, Ph.D.   | 3/9/2011 |
| Team Leader/Supervisor    | Date     |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH BOLAN  
03/09/2011

RICHARD D MELLON  
03/09/2011